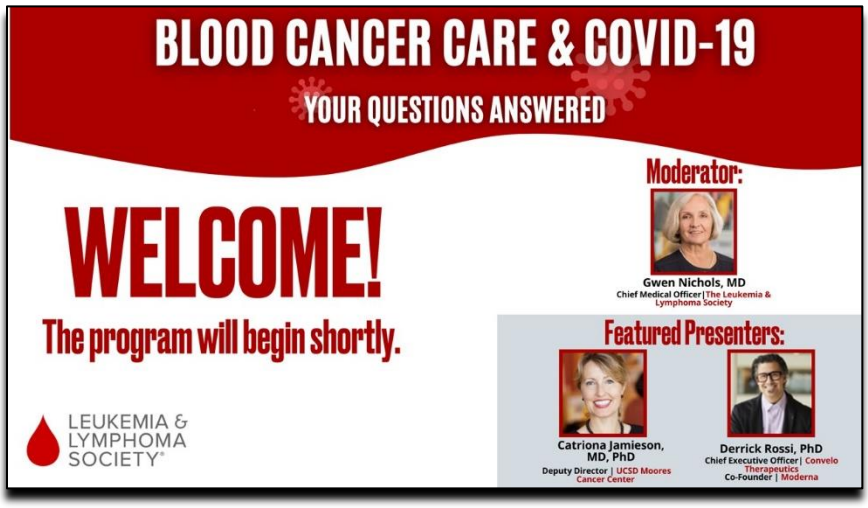


Slide 1- Blood Cancer Care and COVID-19: Your Questions Answered

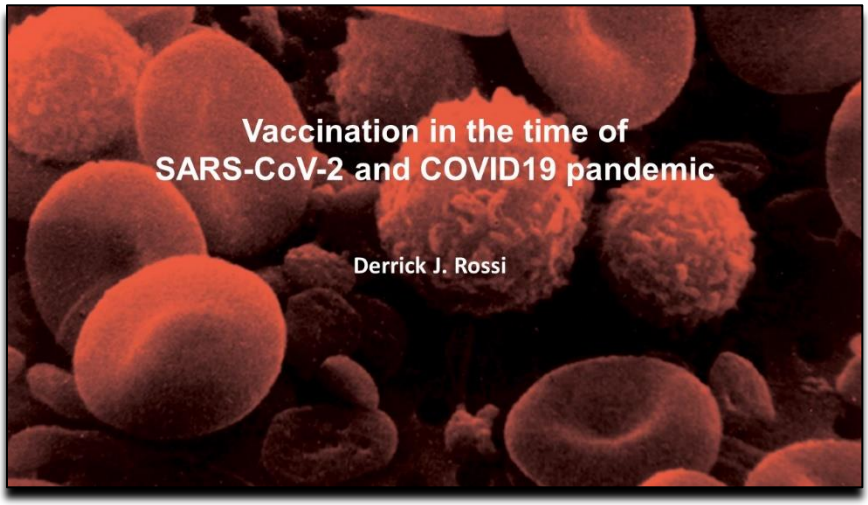
Operator
Greetings and welcome to ***Blood Cancer Care and COVID-19: Your Questions Answered***, a live web education program. At this time all participants are in a listen only mode. It is now my pleasure to introduce your moderator, Lauren Hall. Thank you, Miss Hall, you may begin.

Lauren Hall
Thank you and welcome. I want to take this time to thank everyone for participating in today's program. We have nearly 2500 people registered. Many of you have unanswered questions and concerns about the impact of the COVID-19 pandemic on the Blood Cancer Community, including risk factors, treatment implications, available vaccines and where to find the best information.

At LLS and in your treatment centers, there are many healthcare professionals that are working diligently to make sure that your needs are addressed. You've already been through adjusting to a new normal after hearing that you or your loved one was diagnosed with cancer, and now you're having to adjust once again. As the uncertainty continues, LLS wants to help in providing you with support. All of our support services and information regarding COVID-19 are available on our website at LLS.org/Coronavirus. And if you want to speak to us directly, please call our Information Specialists at 1-800-955-4572. Let us be here for you.

Slide 2- Our Presenters

And I'm now pleased to introduce the speakers for today's program. We're welcoming Dr. Catriona Jamieson, the Deputy Director of the UCSD Morris Cancer Center, and the Director of the Sanford Stem Cell Clinical Center. And, co-founder of Moderna and the current CEO of Convelo Therapeutics. On behalf of The Leukemia and Lymphoma Society, thank you, Dr. Jamieson, and Dr. Rossi for volunteering your time and expertise. And I'm now privileged to turn the program over to you, Dr. Rossi.



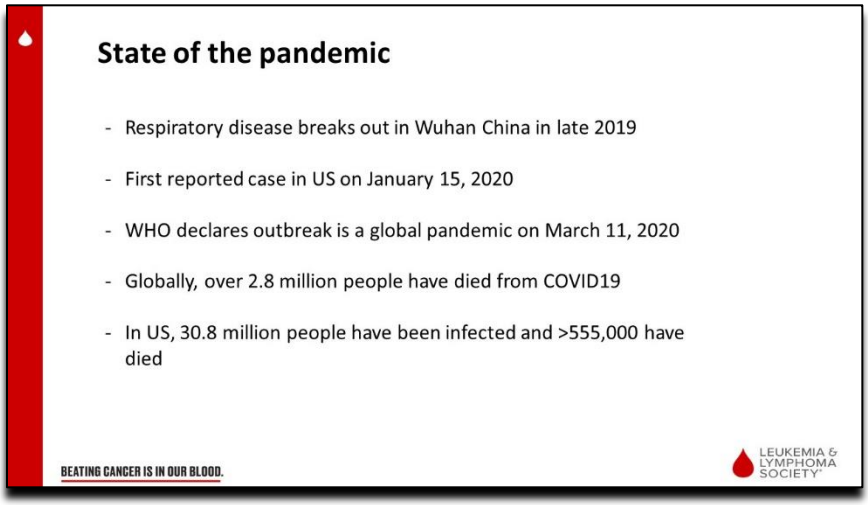
Slide 3- Vaccination in the Time of SARS-CoV-2 and COVID19 Pandemic

Derrick Rossi, PhD
Good evening, everybody. Evening, my time, I'm on the east coast. So, I'm Derrick Rossi. I was the co-founder of Moderna in 2010, kind of a household name now. At the time, I was a Professor at the Harvard Medical School, and I was a Professor all the way through up until about two years ago when I retired from academia. And I'm doing other biotech ventures right now, including running a company in Cleveland called Convelo Therapeutics, focused on remyelination therapies.

I guess I should just start with a disclosure. Obviously, since I founded Moderna, I'm a stockholder in Moderna. And I'm not really here to do anything to pitch the company. Which I, by the way, haven't been involved with, since 2014, but rather to talk to you about vaccination in general and the importance of this. And I'm also happy to talk about mRNA. It's a therapy or this modified mRNA technology is a technology that was developed in my lab, so I know it well.

But I thought I would first start because I do a lot of, ever since the COVID pandemic emerged in early 2020, I've been talking to the public quite a bit through radio and television and webinars. And speaking to a lot of science reporters. And what's become evident to me, and it's perhaps not surprising, is that actually, a vast majority of the public actually doesn't really know what vaccination is or does. And quite frankly, why should they? I mean, we get our first vaccinations when we're infants, and barely sentience and unable to ask questions about why you given me this, these vaccines.

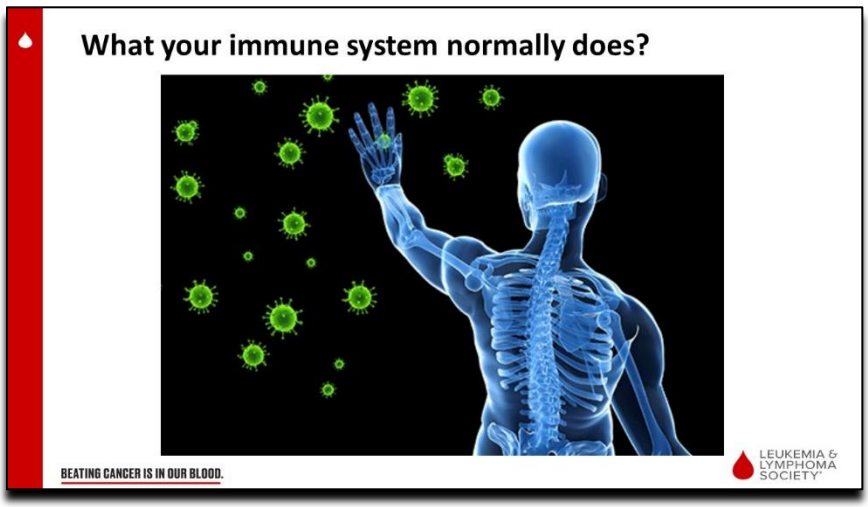
Later, we get them as young people, and we're really only concerned about getting needles then. And by the time you're a young adult, you've gotten so many vaccines that you don't really ask a question about why am I getting this. You just like, well, it doesn't really do any harm. And apparently, it does me some good, so I'll take the vaccine. And that's really the way most people think about vaccines. And that had become apparent to me when I kept getting these questions from science reporters, science reporters that didn't even know what vaccination was about. So, I thought I would tell you a little bit about that today.



Slide 4- State of the pandemic

Okay, good. So, we all know that COVID-19 is now a global pandemic. It started off as respiratory disease that broke out in Wuhan in late 2019. First reported case was in the US in January of 2020. The WHO didn't declare it a pandemic until March 11th, 2020.

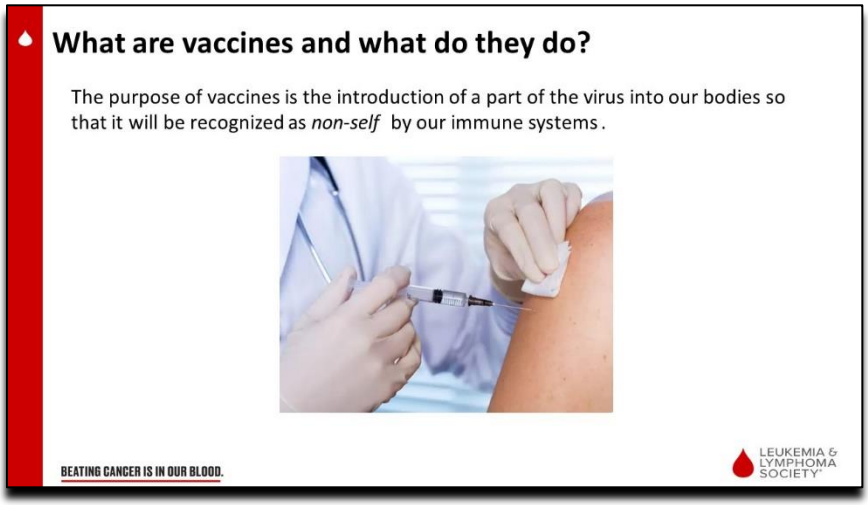
And as of a couple of days ago, when I made this slide, there're currently over 2.8 million people have died from COVID-19. And in the US, over 30 million people have been infected, and over 550,000 people have died. So, that's the numbers. And that's pretty striking, and scary.



Slide 5- What your Immune System Normally Does?

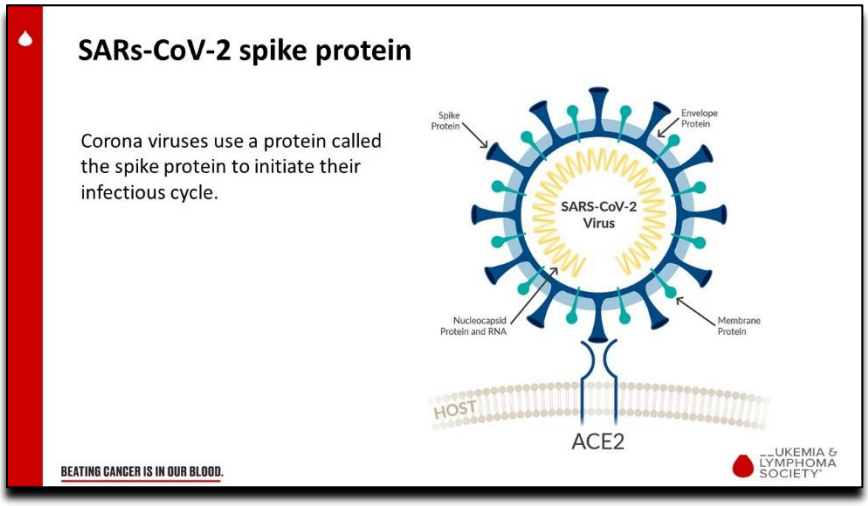
So, let's talk a little bit about why one would want to vaccinate oneself. And I think to do this, you have to start off by thinking about what it is that our immune systems normally do.

Ever since our immune systems encountered pathogens, such as viruses, our bodies have been trying to defend ourselves against these pathogens and coming up with cellular pathways and cell types to prevent this. While at the same time, the pathogens have been coming up with new and clever ways to get into us and replicate, because they have to for their life cycle. So, what our immune systems normally do is constantly surveil ourselves, what's come into our body, looking for what is self-versus non-self. That's essentially, there are many different types of immune cells, there's innate immune cells, adaptive immune cells, but essentially, the immune system is all about recognizing self from non-self.



Slide 6- What are Vaccines and What Do They Do?

So, when we go to vaccines, the whole goal, the whole purpose of getting vaccinated is to harness this intrinsic ability of our immune systems to recognize self from non self. So, really, at its most basic, the vaccination introduces some part of the pathogen, which is of course foreign, because it's coming from a pathogen, so that our body will recognize it and respond to it. And as I said, this is the normal function of our immune system. So, it's a good thing for us to ask the immune system to do, just harnessing a day-to-day activity, as it were.



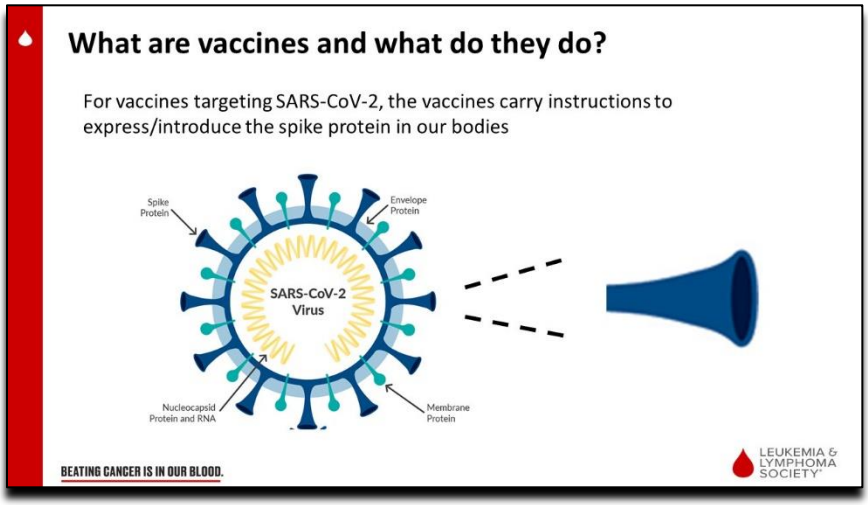
Slide 7- SARs-CoV-2 Spike Protein

So, in the case of SARS-CoV-2, which is the virus that causes COVID-19, and is running rampant around the planet. This is sort of a schematic here, I don't know if you can see my pointer, but I think you can appreciate that the virus on the right side of the slide here as a schematic of what it looks like. And I think by this point, now, everybody's heard of the spike protein. It's these sort of blue bugles, if you will, on the outside surface, the capsid of the virus. And it's actually, the spike protein is what engages with human cells to initiate the infectious cycle.

So, if the human cell is down here, and here, I'm waving my wand here, I don't know if you can see it at all. But the ACE-2 receptor, which is expressed on essentially all of our cells, is what interacts, what the SARS-CoV-2 spike protein interacts with, that is the first contact that it makes with human cells. It latches on to that and that initiates the infection cycle. So, pretty much for almost all of the vaccines that are being made, they're targeting this so-called spike protein.

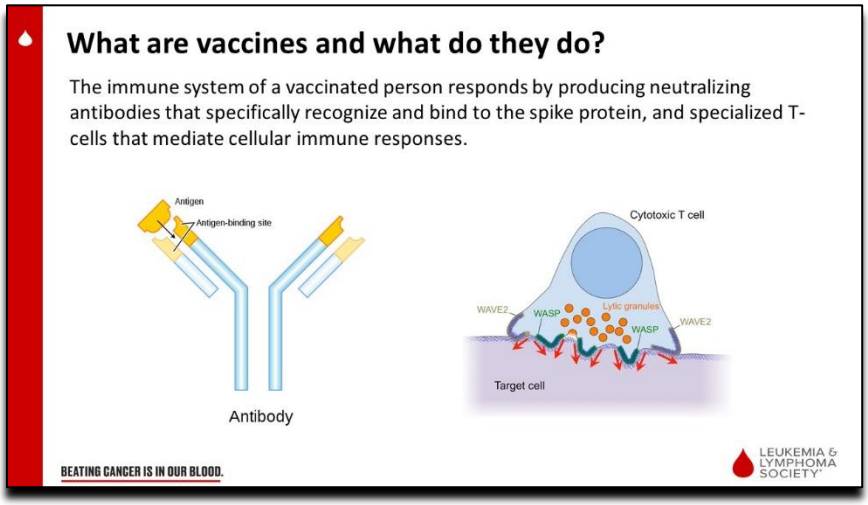
And you can imagine why. If you can block, the initial step in the infectious cycle, block the ability of this spike protein to interact with the ACE-2 receptor, you might have a good chance of warding off infection. So, essentially, all of, not all, but most of the vaccines, we'll talk a little bit more about that in a while, target this spike protein as the thing that's introduced to our immune systems to initiate an immune response. It makes sense.

And by the way, it's years and years of biologists doing fantastic work that gave us the knowledge that coronaviruses, in general, it's a family of viruses, use spike proteins as a way of initiating their infectious cycle, latching on to human cells. And by the way, you've heard that the term Coronavirus comes from, actually, what these viruses look like, due to the spike proteins. It sort of gives it a Corona like appearance, and this is where the name Coronavirus comes from. And it's essentially the spike protein, which sticks out, the hand is a good demonstration of this, my fingers.



Slide 8- What are Vaccines and What Do They Do?

So, I just said this, that basically, what you're getting in most of the vaccines is not the whole Coronavirus, the SARS-CoV-2 virus, you're not getting its genetic material. You're not getting its capsid proteins, it's envelope proteins, you're pretty much getting something that either expresses or encodes this blue bugle, if you will, this spike protein. And that is what your immune system is being asked to mount a response to.

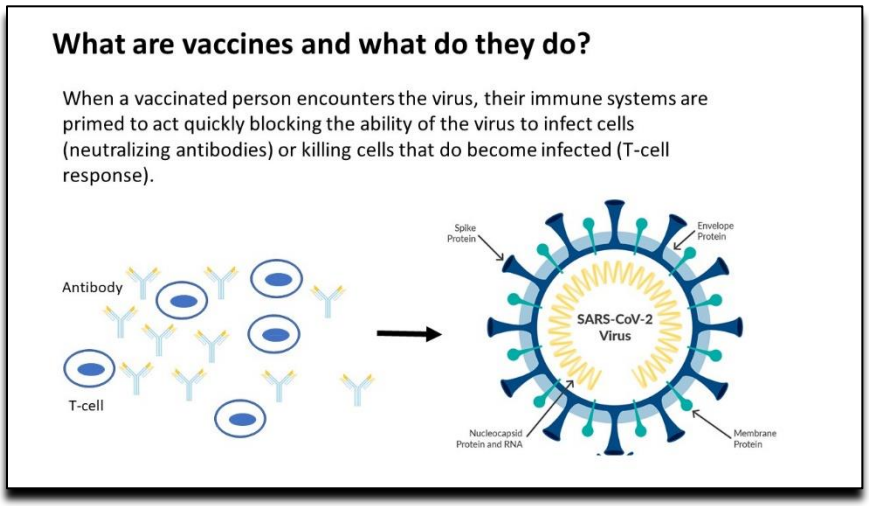


Slide 9- What are Vaccines and What Do They Do?

So, what does your immune system do when it sees this spike protein, because that's basically the purpose of vaccination? Well, if it does a number of things. Our immune systems are sophisticated. As I said, ever since humans and pathogens first met one another, pathogens have been trying to get in and our bodies have been evolving pathways and cell types to try to keep that from happening.

So, you've heard, for example, that antibodies are produced. So, antibodies are produced by a certain type of immune cell called B cells. And they are very specific to antigen. So, I've just introduced a new term. So, an antigen is something that the immune system responds to, so in this case, the antigen is this little bit of the Coronavirus that's put into people, the spike protein in this case. So, the spike protein is the antigen in this case.

And our antibodies developed so that they're very specific and it's very elegant system for how they developed to be very tight binders of antigens. And in this case, the spike protein. So, antibodies will be produced that have very, very high affinity for binding to the antigen, the spike protein in this case. But there are other aspects of the immune system which are activated. For example, you might have heard of T cell response in patients that are vaccinated. And indeed, a host of T cells are activated. It's a different type of immune system, which can, for example, in the case of cytotoxic T cells, recognize cells that are infected with the pathogen and kill those cells. Because it's actually a good thing to kill cells that have been infected prior to the pathogen taking over, making millions of copies of itself, releasing that and having many more cells infected. So, this is the job of the T cell compartment of our immune cells.

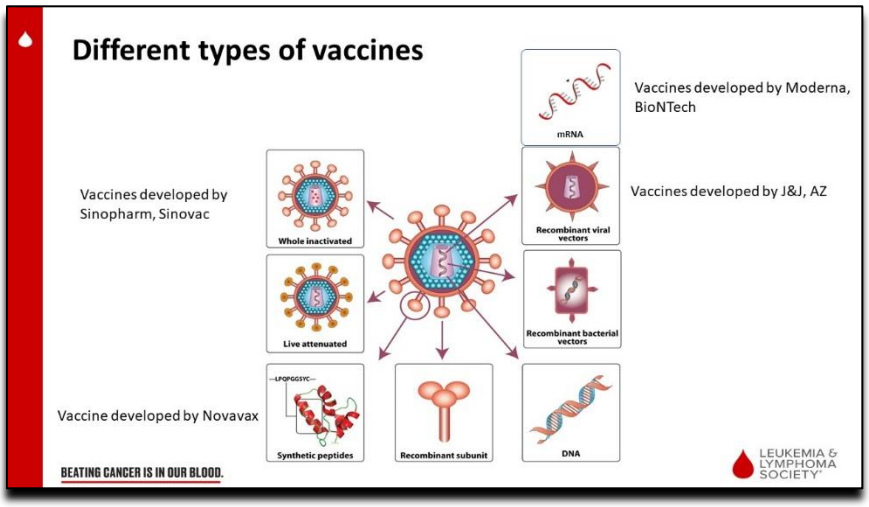


Slide 10- What are Vaccines and What Do They Do?

Just advance here. So, when a person gets vaccinated, they generate an antibody response. And you've probably heard the term neutralizing antibodies. Neutralizing antibodies means that when you expose the antibody to the viral particle, it actually does what you anticipated it would do, which is bind strong to the spike protein and inhibit its ability to latch on to the ACE-2 receptor and thereby neutralize the ability of the virus to infect the cells. So, neutralizing antibodies are generated, the T cell compartment is readied and that's all that happens in the vaccinated person, actually.

And so, the idea is that this immune system has been put at the ready. The antibodies are made, the T cells are at the ready, and now when the person has been vaccinated goes out into the grocery store or the bank or wherever they happen to be. And they encounter the virus in real time, and you go out and get infected. You've got a friend or a colleague or a school mate or whoever it is that's infected, they pass that infection on to you. But now, instead of having an immune system that's never seen the pathogen before, it's already ready with neutralizing antibodies, and a T cell response to really blunt the infection very, very early and mitigate getting COVID-19 and getting really sick and getting put in the hospital and potentially dying.

So, that's the whole objective of getting vaccinated. And indeed, as we've seen borne out by the clinical trials, and the real life studies of these vaccines, they're actually very effective at doing that. So, somebody is advancing my slides. Not sure who, but I'll take control again, if I may.



Slide 11- Different Types of Vaccines

So, I talk about vaccination and there's kind of two stages of vaccination. There's the how do you deliver this antigen to the to the person, to initiate the immune response. And then there's the whole immune response side, which is essentially the same no matter what you get vaccinated for, the objective is always the same, to ready the immune system, should you encounter the pathogen post vaccination.

So, you've heard a lot about different technologies that have been used now to give the front end of that, which is how do you deliver the antigen? How do you present the antigen to the person that's being vaccinated? And there are actually many different ways of doing it, and they're just sort of outlined in these boxes here. So, for example, traditionally vaccines were made, and for many years, they're actually made by actually growing up large amounts of the actual pathogen that one wanted to vaccinate against. And inactivating that pathogen so that it wouldn't be infectious anymore.

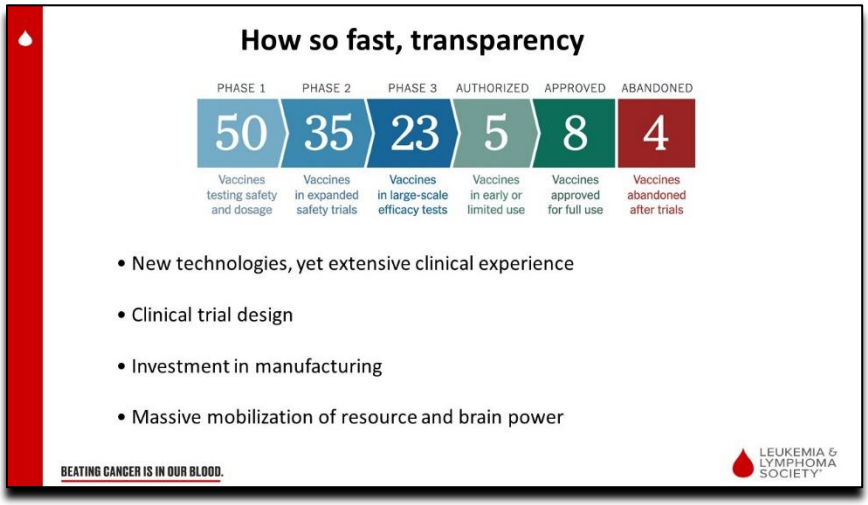
But essentially giving the whole virus minus it's, basically, its replication potential, to person to have the mount and immune response against this sort of inert yet whole virus and initiate their immune response in that way. Attenuated virus, that's a live virus, but it's function has been disabled, to some degree. So, it's still functions, it's still infects, but it's basically, been seriously, had three of its tires blown out, so it's not a very fast-moving vehicle anymore. So, you can mount an immune response to that.

So, vaccines that are made, for example, by Sinopharm or Sinovac in China, use whole inactivated virus technology. It's an old, true technology. You could also just, for example, introduce the protein itself. Do you remember, I said, we just really need to immunize or have our immune systems be readied to respond to the spike protein. So, for example, the vaccine being developed by Novavax does just a recombinant protein, just an artificial protein made, and that's given to people to stimulate their immune system to respond to this.

You've heard a lot, and we'll talk more about it today, of newer technologies. For example, the mRNA, modified mRNA technologies developed by Moderna or BioNTech, Pfizer. And I'll tell you more about that. Although I haven't planned, I don't have it in the slideshow, but I'll happily tell you what those do. And then you've also heard of another technology, which is this adenovirus-based technology. And you might be thinking to yourself, when you hear that for the first time, adenovirus, they're give me a virus to make me, is that because it stimulates my immune system? What's going on there?

No, actually what those are doing. So adenovirus are actually very common viruses for many different species, including humans and apes. And so, what you can do with these viruses in the laboratory, is you can sort of gut out their genetic material, which would express adenovirus proteins in you and replace it with, for example, the Coronavirus spike protein. So, that when you get infected by these recombinant, they're called recombinant viruses, what those viruses are now delivering is information to express the spike protein.

And those are actually really very new technologies as well. And those are being developed by AstraZeneca, which you've heard, and J&J and others. So, we'll talk more about RNA, although I don't have it in the slide deck here, but I'm sure you want to hear more about that, considering that the two fastest to market vaccines were from Moderna, Pfizer, BioNTech. And many of you are probably being offered these because they're being given by the 10s, or hundreds of millions of doses in the US So, I'm sure you know, somebody who's received one of these vaccines.



Slide 12- How So Fast, Transparency

So, a question that I get a lot is, well, how did this happen so quickly? How is it that, because I remember watching on the TV last year in 2020, and it really, I could see it coming. You would see these sort of talking heads on these new shows. And they'd be asked the question, well, when are we going to have a vaccine for this pandemic? And they would say, well, three, two, three, four years, that's the usual time it takes to develop a vaccine.

And so, when the vaccines, well, I should say that these newer technologies, the adenovirus and the mRNA, are actually, by themselves, lend themselves to speed. So, unlike traditional vaccines, where you have to grow up huge amounts of virus and inactivate them to give them to people, these are very easily made quickly. That's number one.

But number two, and I think this is the, oh, so the first bullet that I should spend a little bit more time on there, is that low mRNA vaccines, this is the first time mRNA therapeutics have actually come to market. It's not for lack of clinical experience. So, for example, I founded Moderna in 2010. And prior to the start of this pandemic, they had already run many, many, many clinical trials for different drugs in their pipeline, which are all involve mRNA, many of which were targeting different pathogens, vaccines.

So, there was that clinical experience. And in fact, that was part of the bet that the U.S. government made, because, of course, all those clinical trials had been seen by the U.S. FDA, and the authorities. And they had seen the clinical experience that this was a technology that could be put into people safely. And indeed, do what the objective was, which was to elicit immune response to a particular pathogen, or part of a pathogen that was being expressed.

So, that clinical experience was actually had already. And that's something that isn't really talked about in the media. But that's actually true. I think the other really important thing that people don't realize is that typically what happens with clinical trials, is that you run a phase one trial, that's the first one you run. And that's usually a dose finding trial and a safety trial. And usually, companies don't start, well, sure, it's a mirror image of me, so I got to move my hand this way, I guess.

Usually, what you don't do, is you don't run a phase two before you finish your phase one. And you don't run a phase three before you finish your phase two. And the reason for that is because, well, if it doesn't work in phase one, and you're ready in phase two, or phase three, companies would be spending a lot of money on those clinical trials, and that money would be sort of all at risk or it would be down the drain.

So, typically, what you do is you do your phase one, you wait for the data, you look at all the data. You do your phase two, you wait until that ends, look at all your data. You do your phase three. That was not done in this case, because of the severity of the pandemic, how pathogenic, how deadly the virus was. When it first emerged, it had a lethality rate of about 2% of people. This is before we started to develop other therapies that helped, mitigated that. And ventilators and know how to deal with people that got sick.

So, the decision was made to start the phase two shortly after the beginning of phase one and start the phase three shortly after the beginning of phase two. Now, that could be done, as I said, because already there was extensive clinical experience with other vaccines that had already sort of figured out dose finding, what an appropriate dose would be. And even though, still in the phase one, it was still a dose finding study. And there was the safety data associated with it as well.

And quite frankly, governments around the world, including the US government, stepped in and put their money on the line to really accelerate the progress of these vaccines. So, that was really critical. And kudos to the people in charge for having the foresight to be able to do that. Because it really, we went from, as I said at the beginning, respiratory disease breaks out in Wuhan in late 2019, first cases, January 2020 in the U.S. And we had emergency approved vaccines by December of 2020, kind of 10 months after the fact this whole effort was started.

And that really is unprecedented. But it wasn't because any steps were skipped. In fact, all of the necessary phase one, phase two, phase three were done. They were just done in an overlapping manner, not a sequential manner. The other thing that I've heard a lot and I get asked a lot about, which actually turns out to be not true is, well, you see a lot of these, people writing on the Facebook or whatever it is that everything was done in secret and I should be really worried about this because it was done in secret.

Actually, the committees of the panels of experts, which are independent experts that analyze the clinical trial data, and assess its safety and efficacy, and ultimately, the bodies responsible for governing emergency use authorization, those, and this is unprecedented as well, those meetings were actually all live streamed. And again, it was partly, the idea was, hey, this happened really quick, we want to make sure that people have confidence in this process, so they live streamed these meetings. And I actually watch them for a day long on the web; anybody could watch them.

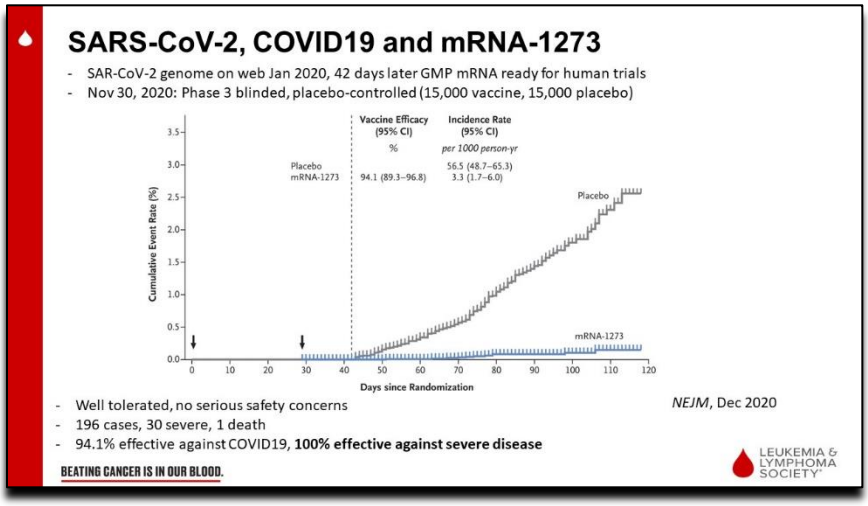
I'm not actually sure if they're recorded or not, I bet they are. So, you can go out and watch them yourselves. But they are, just as they are every time for every drug that passes through a clinical trial, a large team of experts that are asking really important questions about safety and efficacy. And only when they get comfortable with the data that says this is safe and efficacious, do they give the thumbs up to the regulatory agencies to say we think this should go into patients. So, you can, like I said, I'm not sure if it's recorded, but I'll bet you it is.

Another part of the reason that this happens so quickly, was that there was actually an investment in manufacturing done by the companies. And even though there're new technologies, mRNA had never

been an approved drug before. There have been large investment in manufacturing that allowed, for example, once the sequence of the virus was put on the web by the Shanghai consortia In January, the next day, the NIH and Moderna had designed an mRNA for the spike protein. And 42 days later, Moderna had a clinical grade vaccine ready to go into people that they ship to the National Institutes of Health.

So, 42 days is to make a new medicine, to make a new vaccine. Again, that is really amazing. And it normally would not take that long. If you had to grow up vaccine, or I'm sorry, virus and inactivate it or attenuate it, it would take much longer, because it does take much longer. So, that was important. The manufacturing infrastructure was there to do this, not at scale, not at billions of doses. And this is where the bottleneck arises. But certainly, for getting clinical trials run.

And then, I think I've already mentioned this, there was a massive mobilization of resource and brain power. I mean, really, everybody, every scientist on the planet was thinking about this and trying to move this, move the ball forward, and how can we mitigate this. And that's just not just in the vaccine world, but also in the therapeutic domain. And we can probably talk about some of the therapies that emerged as well.



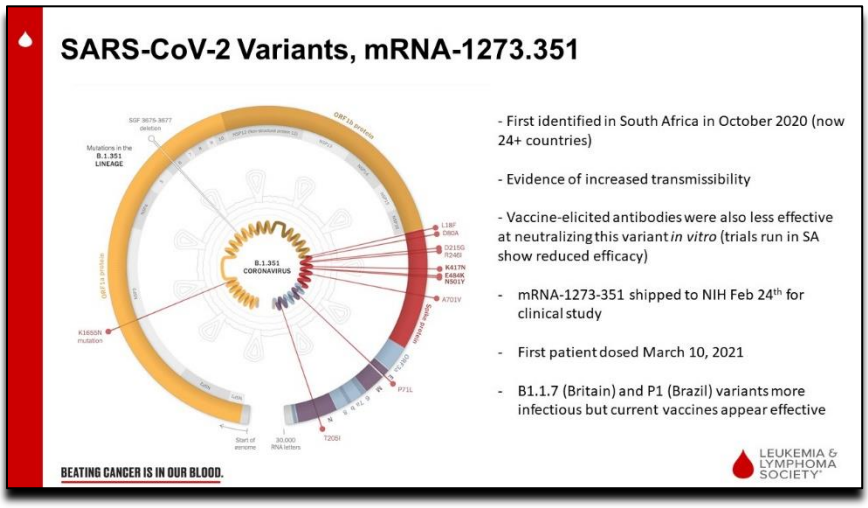
Slide 13- SARS-CoV-2, COVID19 and mRNA-1273

So, this is just a slide. This is science data. And I realize that most watching are probably not scientists, but it's relatively easy to understand. It's actually data that was published on the clinical trial that was run for the Moderna vaccine, which is called mRNA 1273. And I already told you this, that SARS was published, the genome was published. And so, this very specific spike protein mRNA was designed.

Phase Three placebo-controlled trial was run, 15,000 people got the vaccine. 15,000 got the placebo, that was blinded, so one didn't know if you got the placebo or the vaccine, you are expected to go on with your normal life. And then they measured the incidence of people getting COVID. And so, the cumulative event rate is on the y axis here, and time is on the x axis. And there's a gray bar or a gray line here, which is placebo arm and the blue line, which is those that were vaccinated.

So, you can see that dose one was here on day zero, dose two on day 28. And then they started evaluating the data from this dashed line here. And what you can see is, that those that got the mRNA were protected from getting COVID and getting severe disease, that's on the y axis. Whereas those that were unvaccinated continued, and don't forget, it was a raging pandemic, at this point, continued at a very, very fast rate to get COVID-19. And so, this is where the efficacy numbers are deemed from.

When you do large trials like that, 30,000 participants, you have the statistical power. You've powered it to be able to say that this data basically represents a 94.1% efficacy. Those that were vaccinated had that much protection against getting COVID. There were 30 severe cases in this clinical trial of 196 cases, all 30 of those people that got severe COVID, were in the placebo arm, none in the vaccine arm. And unfortunately, there was one death of somebody, and that was also in the placebo arm. So, there was 94% effective at getting COVID-19. But 100% effective against severe disease. And this type of data has been borne out now in the real world, with tens of millions of people now being vaccinated and being protected.



Slide 14- SARS-CoV-2 Variants, mRNA-1273.351

So, people always ask me about variants. And how is the vaccine that they're going to get now, is it going to be protective against the variants that are emerging? First thing I'll say about variants is, that they are absolutely expected. Viruses are, from an evolutionary perspective, wonders of nature. They're very, very impressive. The rate by which they replicate in any one person is hundreds of millions of replications.

And what you need to get for variants who arise is mutations arising during these replications. And then there's a selective pressure that will, if most of mutation that happens during replication is bad, and it doesn't do the virus any good at all. But occasionally, you'll get mutations that, for example, alter the spike protein. This is the spike protein. This is the genome, the proteins made by the Coronavirus. And this is a variant that emerged in South Africa called the B 1351 variant.

And you can see that actually many of the mutations, these are mutations, these little dots here and these, what the amino acid change is, actually occur in the spike protein, but not just the spike protein. But what will happen when there's selective pressure, is that a variant that has a selective advantage over its original strain, will do better. So, for example, strains that emerge that are more infectious will do better, because they'll infect more people and they'll propagate themselves at a more effective rate.

So, I highlight this particular variant, 351, which emerged in South Africa in October of 2020. And scientists, of course, as soon as a new variant emerges, they want to ask, well, are the vaccines that we've already got out in the population, will they protect us against this? And you can do that experiment pretty simply, by taking antibodies from a person that's been vaccinated from the gen one vaccine, let's call it that, and or gen one, get a COVID-19 infection. And then ask whether or not those antibodies, which you can take out and then put in a dish, ask whether or not they can neutralize the variant virus.

And it was actually determined in these experiments that this particular variant, this 351, while the antibodies that are generated by the gen one vaccine are still probably considered sufficient to

neutralize this variant, they did so, certainly less effectively. In contrast to many of the other variants, by the way, which the neutralizing antibodies, for example, in the British variant, which is more infectious, and therefore more deadly, and becoming pervasive because it's more infectious. And the reason it's more infectious is it, again, spike protein binds better to human cells through a mutation that just has a tighter bond to the ACE-2 receptor.

But yet, the antibodies work very, very effectively against those variants. They work a little less effectively against this variant, although probably still sufficient to protect. But that said, these new technologies, which can turn on a dime, after getting the data that suggested that gen one vaccines might not, might not be quite as good against this variant, they very quickly synthesized a variant specific mRNA. They did so in February of 2021.

So, from October '20, when it first emerged to February 24th, it's a very short time period, they ship material to the NIH to begin clinical studies on this variant specific mRNA, which is called 1273/351 for this variant's name. And the first patient was dosed in March of 2021. And as I said, the British frame, which you've heard a lot, which is certainly more infectious and more deadly, this B 117. And even the P1, Brazil strain, which is also raging through New York, current vaccines appear to be quite good at neutralizing those.

So, people ask me, well, what's going to be the strategy going forward? Are variants going to emerge that don't work at all, with these vaccines? And actually, we're a little bit in luck here. So, how the spike protein interacts with the ACE-2 receptor, it's a physical interaction, it's a structural interaction. I try to make a structure here. So, the spike protein fits into this ACE-2 receptor, and it's a nice fit. And that's what initiates the infection cycle.

So, there's a selective pressure on keeping this spike protein looking more or less what it looks like. For example, if it mutated to look like this, that wouldn't fit into the ACE-2 receptor anymore. And it basically would be noninfectious. So, that would not be a very advantageous mutation or set of mutations for the virus to get. So, it's got to be something that still fits in and maybe it fits in and binds a little bit tighter, for example, like, B 117. But there is a selective pressure that it just can't look so completely different.

Point being, that if the vaccines are made, and what shape was I using here, I guess I was using the handshape, here, maybe the other way. Vaccines were made against something that looked like this. And so, even though that thing might change a little bit, I can scrunch my fingers a little bit more, the vaccine still, nonetheless, gen one are working pretty effectively against it. And if it changes so much, the technologies that we have, the adenovirus, the mRNA, other technologies can respond very quickly, and we'll be able to address it.

So, that's what I wanted to talk about. And I know I didn't talk about mRNA too much. And I'm happy to tell you about what mRNA is, but maybe we'll save it for the Q&A section. I think I've gone over time here. And I would like to turn it over to Catriona to talk to you as well.

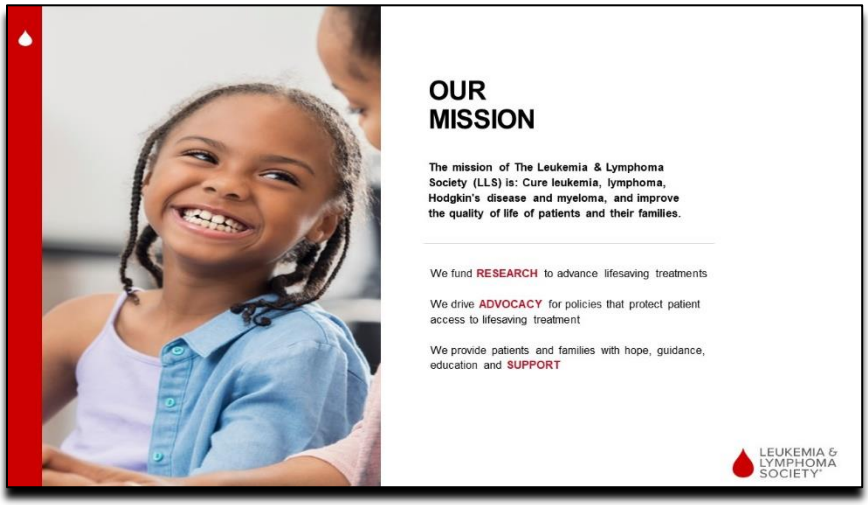
Slide 15- Blood Cancer Research and Treatment in the Time of COVID

Catriona Jamieson, MD, PhD
Thank you so much. Derrick, as usual, you've been extremely self-deprecating about this life saving technology that you were at the forefront of developing, all the way back in 2010. I remember when you were Person of the Year for Time Magazine, and it was very impressive then. And none of us knew how important that technology would be and how that would change the trajectory for people, not just with blood cancer, it's very, very important field, but all of us, so thank you.

I got the Moderna vaccine. I know you got the Pfizer one. But it really changed the paradigm for how quickly new therapies can be introduced, including vaccines. So, I'd like to talk a little bit about what do we do beyond vaccinating patients, and all of us, actually, to try and keep us safe from this deadly pandemic. And I really wanted to think about the book *Blood Cancer*, or the book, *Love in the Time of Cholera* by Gabrielle Garcia Marquez. He got the Nobel Prize. It was basically to remind us that love reigned supreme, love wins out, despite cholera.

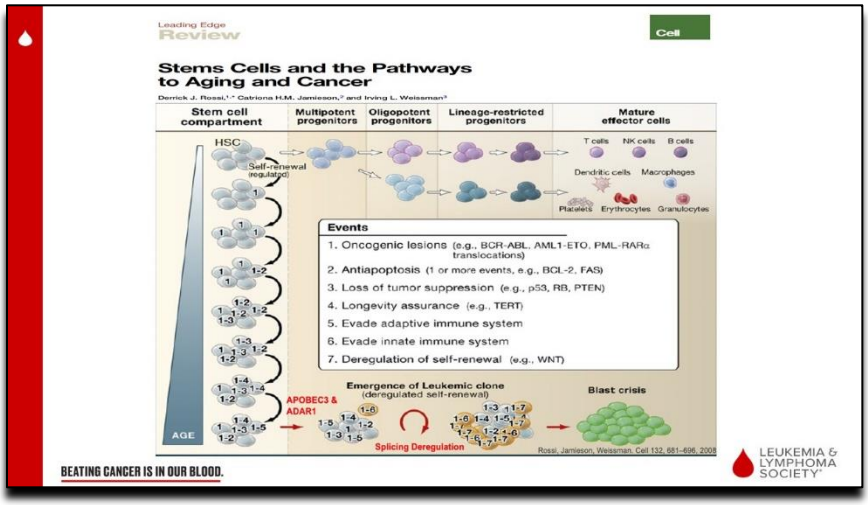
Similarly, blood cancer research and the kind of research that you just summarized so nicely, Derrick, wins out as well. So, it's a very similar bottom line essentially. So, cancer doesn't stop for COVID. Neither does blood cancer research, funded by The Leukemia Lymphoma Society and or other very strong funding partners. So, I wanted to say there is a good news story, weirdly, to this COVID pandemic. You heard about the massive mobilization of resources from Derrick, and these are resources to really help us understand the basic underpinnings of immune responses to this SARS-CoV-2 virus.

But also, it helps us to understand how cancers evolve, how the immune system doesn't see a cancer, and how we can invigorate the immune system to see it better.



Slide 16- Our Mission

So, we know that The Leukemia Lymphoma Society has put a lot of time, effort.



Slide 17- Stems Cells and the Pathways to Aging and Cancer

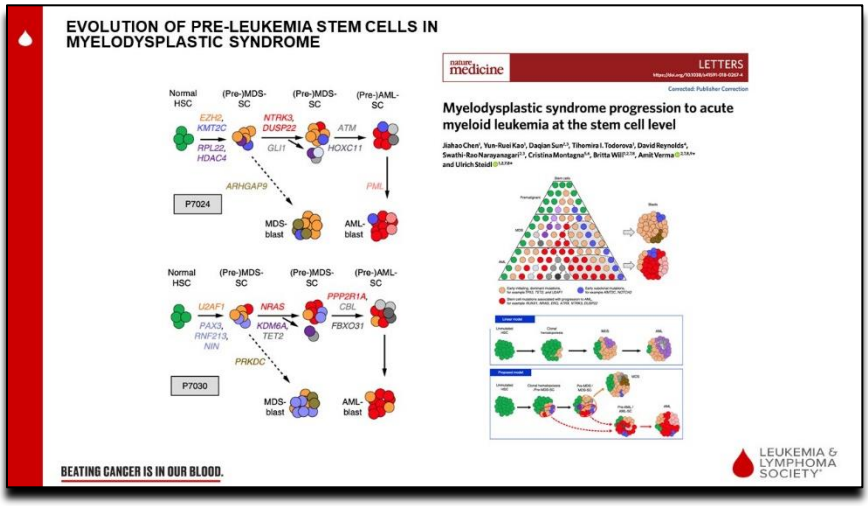
And funding into understanding the basis for blood cancer development, Actually, going all the way back to the blood forming stem cell. So, the hematopoietic stem cells that we have in our bone marrow can give rise to all the different blood types in our body.

And of course, this gives rise to a functioning immune system. As Dr. Rossi mentioned, we have B and T cells that help to fight viruses like SARS-CoV-2, but all those cells actually derive initially from a hematopoietic stem cell. And so, too, can a number of blood cancers. So, Derrick Rossi or Weissman and I published actually way back in 2008, is that our stem cells age in inflammatory microenvironment. And perhaps in response to sustained inflammation from viral infections, we activate this mutagenic pattern. Whereas the mutations arise in the stem cell and that leads to propagation of cells that lack the capacity to undergo what's called apoptosis. So, they can't die, they can't turn the tumor pathways off, and they live for a long time because they activate this enzyme called telomerase.

And then ultimately, they learn to evade, both innate immune responses that are driven by cells called natural killer cells and our cells called neutrophils, as well as adaptive immune responses driven by

cells called T cells, that Derek alluded to. Then, finally, they learned to clone themselves. And that process called self-renewal is a very malignant process.

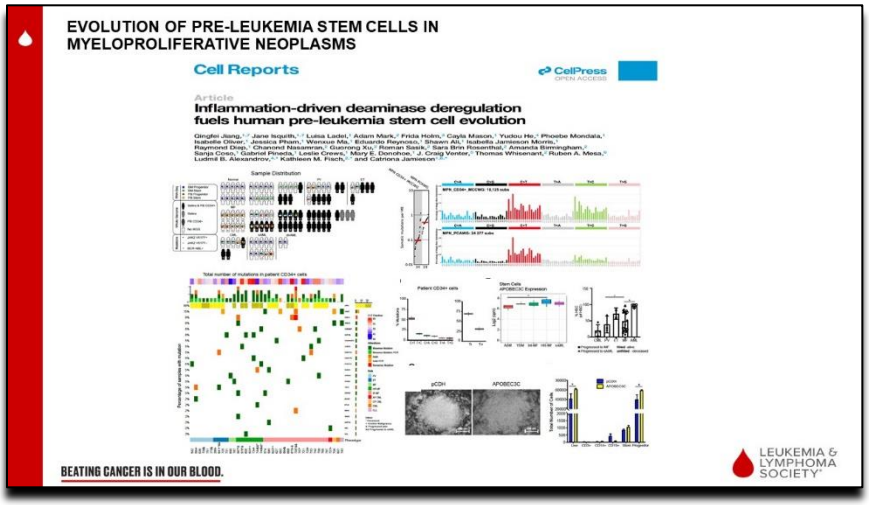
So, why am I talking about all this, it's supposed to be about COVID. Well, it turns out that if we can make people's immune systems healthier, if we can treat blood cancers more effectively, and get more people into sustainable remission, they're less likely to have severe outcomes from COVID, less likely to get the infection in the first place, provided they've had a good vaccine strategy. So, really, what we're interested in is looking at how blood cancers evolve from a normal stem cell state to a pre leukemia stem cells state if talk about myeloid disorders like myelodysplastic syndrome and myeloproliferative neoplasms. And how they evolve ultimately to what are called leukemia stem cells that can clone themselves.



Slide 18- Evolution of Pre-Leukemia Stem Cells in Myelodysplastic Syndrome

So, this is the way the field has really taken off recently. You see how all of the understanding of vaccination technology has really allowed us to move ahead very, very quickly, in terms of understanding the immune system. It's also provided a better infrastructure for understanding how cancers evolve. How is the cancer initiated? How is it born from a stem cell? There's been seminal work done in this area by only Ulrich Steidl and Amit Verma, and Britta Will and others in myelodysplastic syndrome, to show that there are very specific mutations that occur at the level of the hematopoietic stem cell. And they give rise to disordered maturation. So, these cells don't function quite properly.

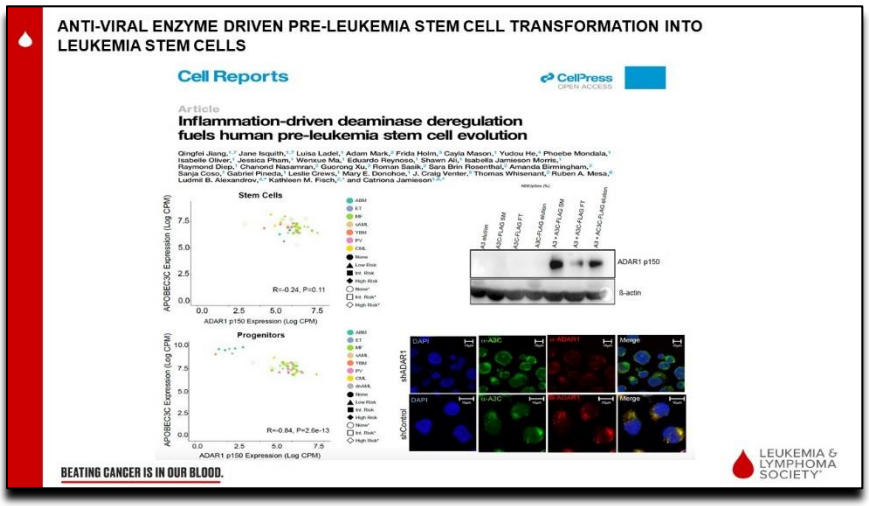
And that's something that we can start to detect very early on. So, we can detect the pre leukemia stem cells before they even become leukemia stem cells. And a lot of the technology that was developed to make the vaccine and to understand how these vaccines, or these strains of COVID-19, evolve, actually can be brought to bear to understand how blood cancers evolve. Can we actually start to detect and treat blood cancers in their infancy and actually prevent progression to full blown cancer? And by making people's immune systems healthier actually reduce their risk of having severe infections with SARS-CoV-2, in addition to having very effective vaccines for everyone.



Slide 19- Evolution of Pre-Leukemia Stem Cells in Myeloproliferative Neoplasms

So, we know that myelodysplastic syndrome can be a pre leukemic disorder that progresses to leukemia, well, so can myeloproliferative neoplasms. These are disorders where you make too many of one type of blood cell in the bone marrow. Major advances have been made in this area. Leukemia Lymphoma Society has invested heavily in understanding why people develop the myeloproliferative neoplasms and why they progress.

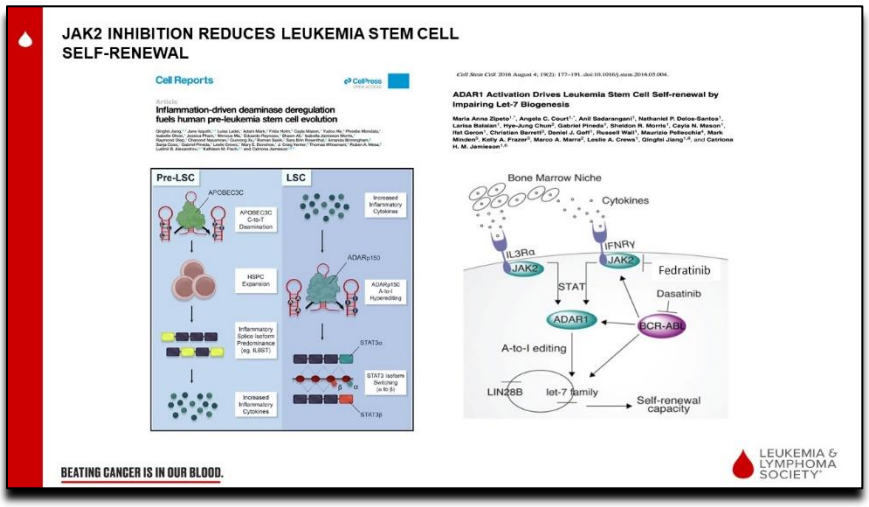
So, recently, we discovered that an antiviral enzyme that protects our stem cells from viruses, prevents them from integrating into our DNA, is actually activated in pre leukemia stem cells, and actually leads to stem cell expansion. So, the reason that's important, is it tells us that if we have our antiviral enzymes turned on for too long, if that capacity of the antiviral enzymes isn't brought into proper control, they can actually lead to pre leukemia and leukemia. So, APOBEC3C is one enzyme.



Slide 20- Anti-Viral Enzyme Driven Pre-Leukemia Stem Cell Transformation into Leukemia Stem Cells

Another enzyme that we see activated at the same time is an enzyme called ADAR1. In the same cells that overexpress APOBEC. So, at this demo progenitor level, we get APOBEC3C, and ADAR1 being activated. This leads to full leukemic transformation. You can see here they bind to each other. And they actually co localize in leukemia cells. So, it's essentially a Bonnie and Clyde story.

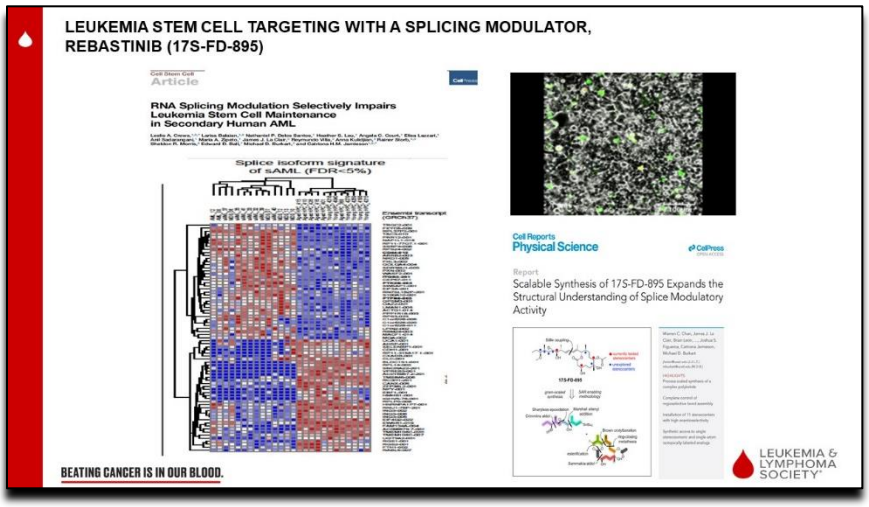
So, the bottom line is, you don't want these antiviral enzymes to be activated to robust there for too long, because they can actually take a pre leukemia and make it a full-blown leukemia.



Slide 21- JAK2 Inhibition Reduces Leukemia Stem Cell Self-Renewal

So, that all sounds rather alarming, except, that we think that there's a way to block that. We can detect the cells as they go from pre leukemia to leukemia stem cells. We know that we can shut down this process using JAK2 inhibitors, fedratinib is one, ruxolitinib is another one that seems to block the ability of this antiviral enzyme called ADAR1, to induce the problems that lead to leukemia stem cell generation.

So, we already have fedratinib and as I mentioned, ruxolitinib that seemed to turn this down. And then this other drug called the dasatinib, that I'm sure some of you on this call know about. It blocks the gene that induces chronic myeloid leukemia called BCR-ABL, but also ADAR1.

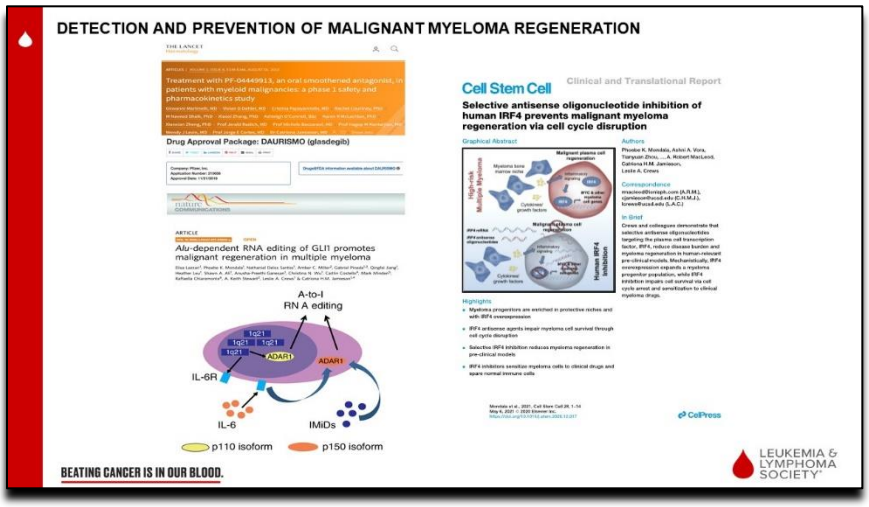


Slide 22- Leukemia Stem Cell Targeting with a Splicing Modulator, Rebastinib (17S-FD-895)

So, what else do we do to prevent pre leukemia stem cell progression to full blown leukemia? What we find is, when people start to transition from normal stem cell aging over into leukemia stem cells, they actually change splicing.

So, splicing is how we make different copies of the same gene. What we found is, that we can block that splicing process. We have a splicing for us at reporter and we scale up production of this splicing

modulator to really say, can we turn back the clock on leukemia stem cells and make them behave like normal aged stem cells.



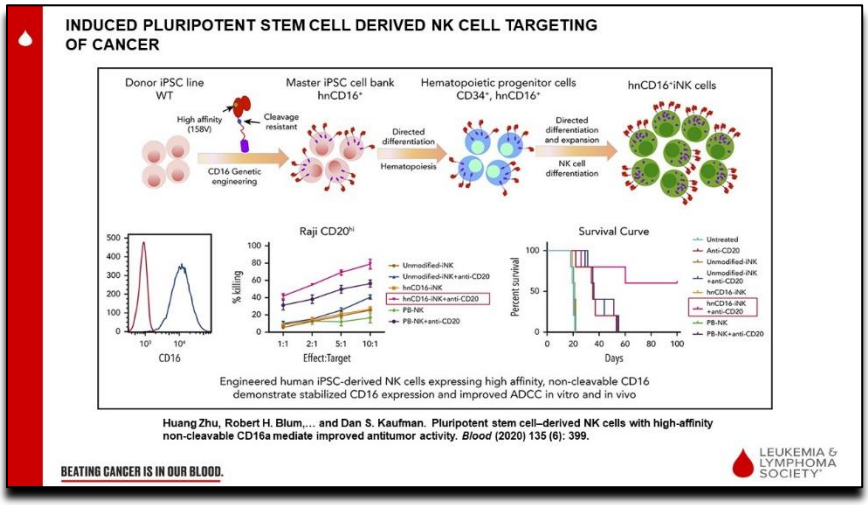
Slide 23- Detection and Prevention of Malignant Myeloma Regeneration

In another attempt to improve the immune system by inducing deeper responses, we've developed other leukemias to cancer stem cell targeting agents. So, in other words, cancer sometimes hijacks stem cell pathways, and specifically the capacity of stem cells to regenerate or calm themselves.

Myeloma does this. We know that we can inhibit or block a stem cell pathway called the hedgehog pathway, and the large array of blood cancers that has been very effective. We did this for myeloid leukemias, and it doubled survival, with a drug called glasdegib, now FDA approved as Daurismo™. But that strategy didn't work as well, in multiple myeloma, where they developed ADAR driven methods or the cells themselves to get around the hedgehog inhibitors.

So, more recently, we use RNA technology to actually target these myeloma stem cells in a preclinical model, together with a local company called Iohannis. And just published the results, showing that if you target this essential driver of myeloma regeneration, called IRF4, you can actually block myeloma from regenerating it. So, the reason I'm bringing this story up is, this is RNA technologies. This is what's coming from the technology that Derrick Rossi and others help to bring to the fore.

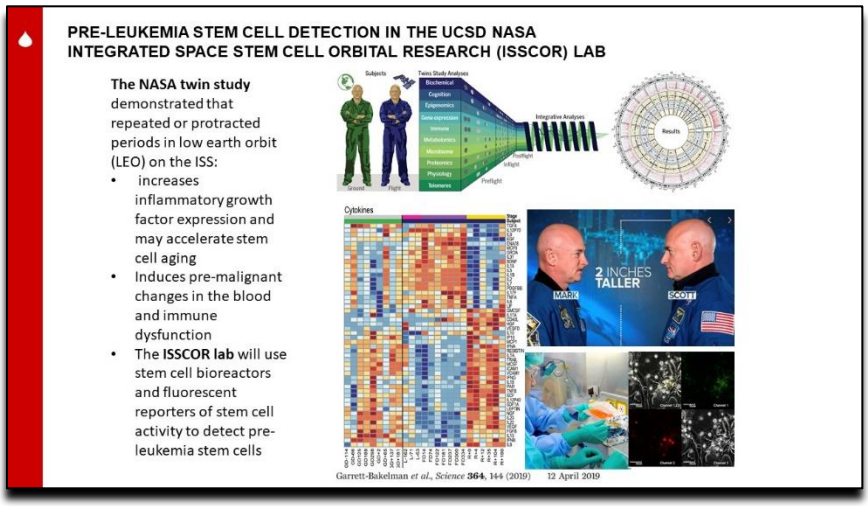
Now, RNA technologies or therapeutics go beyond vaccines, and we can now think about really using them to target cancer and some of the most refractory cancers.



Slide 24- Induced Pluripotent Stem Cell Derived NK Cell Targeting of Cancer

The other thing we've learned is, that we can also use technologies like the technologies that Derrick Rossi developed, for making what are called induced pluripotent stem cells to make them grow up and become parts of the immune system natural killer cells. Sometimes what happens with cancer is, our immune system is distracted looking at other things, perhaps a virus, and it doesn't know to attack the cancer.

Dan Kaufman, working together with a company called Fate Therapeutics, developed an NK natural killer cell, from an induced pluripotent stem cell and showed that these cells were extremely effective at targeting a number of tumors, lymphoma and other solid tumors. That clinical trials started a year and a half ago here at UC San Diego at the Moore's Cancer Center. But it just shows you, we can make new technologies by our expanded understanding of the immune system because of problems like having a pandemic where we need to understand how the immune system works.

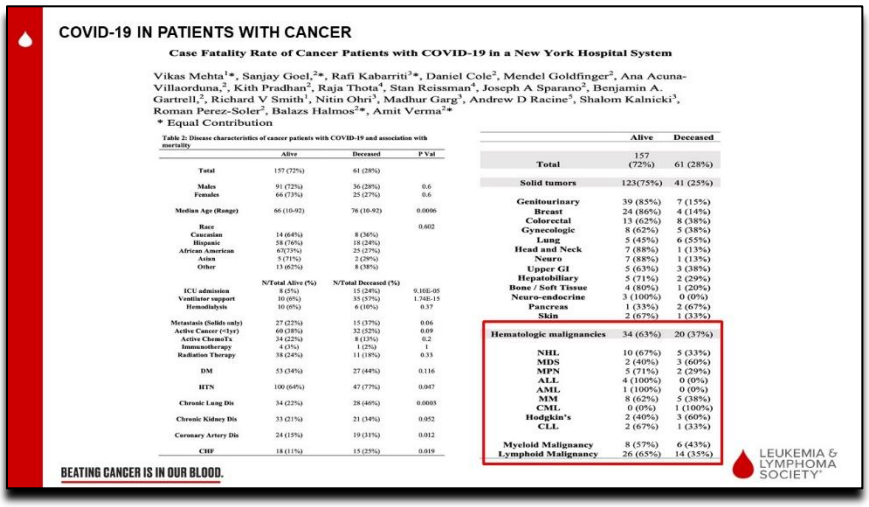


Slide 25- Pre-Leukemia Stem Cell Detection in the UCSD NASA Integrated Space Stem Cell Orbital Research (ISSCOR) Lab

The other group that's very interested in understanding the process of pre cancer stem cell development, particularly in the blood, is actually NASA. So, as you may have seen a NASA twin study demonstrated, that repeated or protracted periods and low Earth orbit on the International Space Station, seem to increase inflammatory growth factor expression. And seem to accelerate themselves aging in Scott Kelly. So, even though Scott Kelly who spent almost a year in space came back two

inches taller than his twin brother, unfortunately, his blood had AIDS and he developed in versions translocations and other aspects of accelerated stem cell aging that make us think that he would be put at risk for pre cancer or pre leukemia.

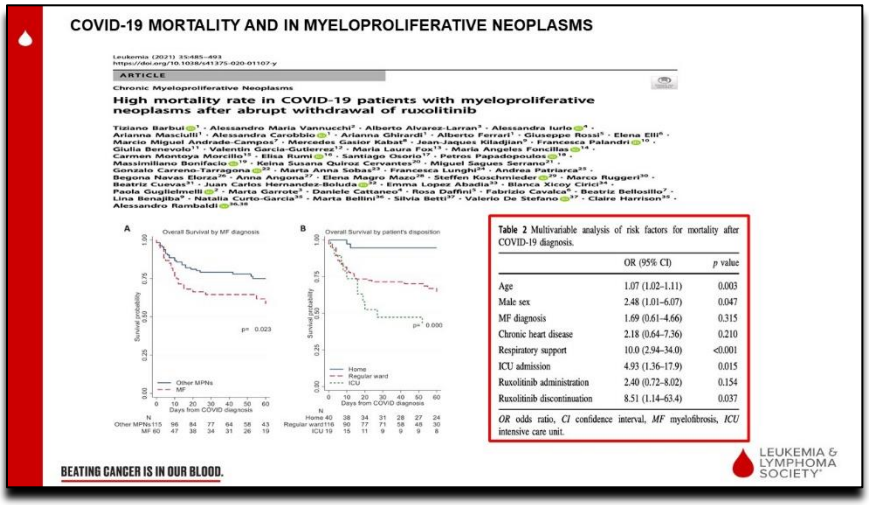
So, we're developing a viral reactor, then we'll go up on to the International Space Station in what's called the integrated space, stem cell orbital research lab. This is a collaboration with NASA, as well as Space Tango, to see, can we understand the process of pre cancer development in an environment where there's a considerable amount of radiation higher than we have on earth and more exposure to inflammatory growth factor, stimulating signals that would activate this pre leukemia stem cell path.



Slide 26- COVID-19 in Patients with Cancer
So, we've had a lot more than we're able to do now in blood cancer research, partly as a result of just having more funding for research, more interest in really trying to normalize the immune system.

So, what about COVID-19 and patients with cancer? There have been a few papers published on the case vitality rate of patients with cancer. This is one. In a New York Hospital System with Amit Verma. I'm really looking at what happens in people with blood cancers or hematologic malignancies, as they're known, compared to solid tumors. And you'll see that the rates of mortality are actually higher in patients with hematologic malignancies. So, whereas with solid tumors, the mortality rate is about 25% with hematologic malignancies or blood cancers, it's about 37%, with the highest being in myelodysplastic syndrome, and in diseases like multiple myeloma, which is why I was showing you the data for that. And then in myeloid malignancies, like the myeloproliferative neoplasms.

So, there does seem to be an emerging difference between the different types of blood cancers. These numbers are very small. This is a single institution study, so we really need to start looking at larger studies, larger data sets.

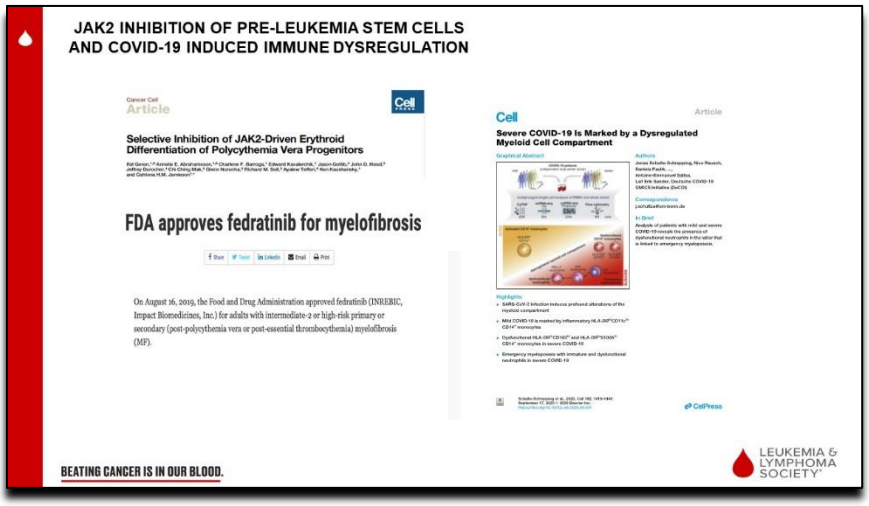


Slide 27- COVID-19 Mortality and in Myeloproliferative Neoplasms

This is one focusing specifically on COVID-19 infection related mortality in patients with mild proliferative neoplasms. This was published by Claire Harrison and Alessandro Rambaldi, a very big cooperative group that works on myeloproliferative neoplasms, where they looked at actually a fairly high mortality rate in patients with COVID-19. Particularly, after withdrawal of a standard of care drug called ruxolitinib.

So, what they found was, in the patients with myelofibrosis, which is an advanced form of a myeloproliferative disorder, their survival was lower than the earlier stage myeloproliferative neoplasms. In patients who were admitted to the ICU, their survival rate was lower than those who were able to stay at home. And when you look at the kinds of reasons for mortality and this group, it looked like advanced age, male sex, the diagnosis of myelofibrosis were associated with an increased risk of deaths from COVID. Really came down to this difference, as well, with ruxolitinib or Jakafi® discontinuation.

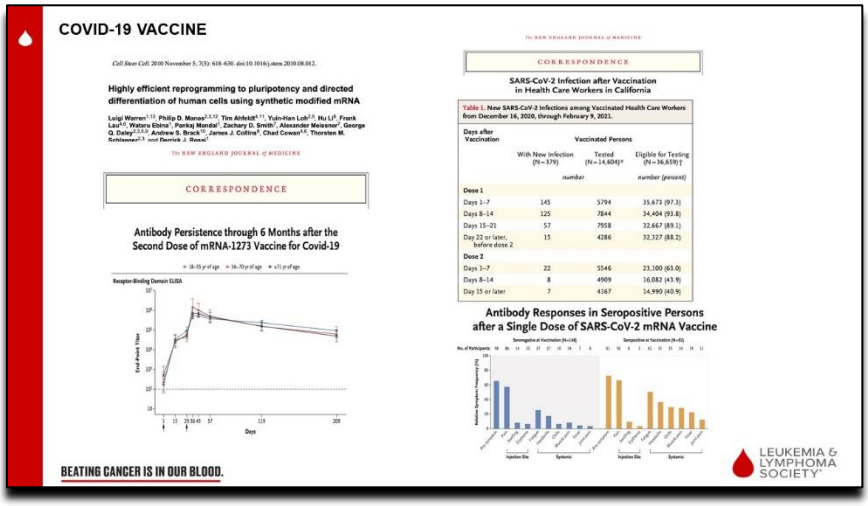
And we know that people can drop their blood pressure if they discontinue ruxolitinib, also known as Jakafi®, but it kind of begs the question, is this JAK2 inhibitor actually inhibiting viral replication? Is that why people did a little bit better if they didn't have the ruxolitinib stopped? And that's still a question for the field that everyone's trying to answer.



Slide 28- JAK2 INHIBITION OF Pre-Leukemia Stem cells and Covid-19 Induced Immune Dysregulation

We know that ruxolitinib is not the only JAK2 inhibitor, the FDA approved another JAK2 inhibitor called fedratinib.

We know with severe COVID, there's a marked expansion and dysregulation of what's called a myeloid cell compartment. So, you've heard of cytokine storm in the setting of severe COVID-19. Part of that is because we massively expand these cells that are called the myeloid compartment in the immune system, to try and fight the virus, but it makes so many inflammatory growth factors that it really overwhelms our system. So, the question is, can that be dialed down a little bit with drugs like fedratinib or ruxolitinib. And basically, those clinical trials are being done now, but we'll see how they go. The main point is, prevent infection as much as possible and really get vaccinated.



Slide 29- Covid-19 Vaccine

In terms of the COVID-19 vaccine, as Derek was alluding to, this highly efficient method for making our vaccines now, it's predicated on a modified mRNA. And if you think about it, so DNA is like the blueprint, the architect's blueprint for your house. The RNA is like the engineers interpretation of that, there may be a support beam that has to go up. And then the protein is what the builder would interpret in terms of what materials to use. Because of this modified mRNA technology that Derrick, and colleagues really initially made to make induced pluripotent stem cells more effectively and then repurposed for making vaccines, we have a completely novel and safe way of making vaccines now.

And of course, this is up to Pfizer and Moderna and other companies. But it looks like this is a very effective strategy. And I think this is just going to change the landscape in general for how vaccines are made. And what you see, was recently published in the New England Journal, is antibody persistence through over six months after the second dose. This is of the Moderna vaccine, but the data are looking very similar for Pfizer, in terms of efficacy.

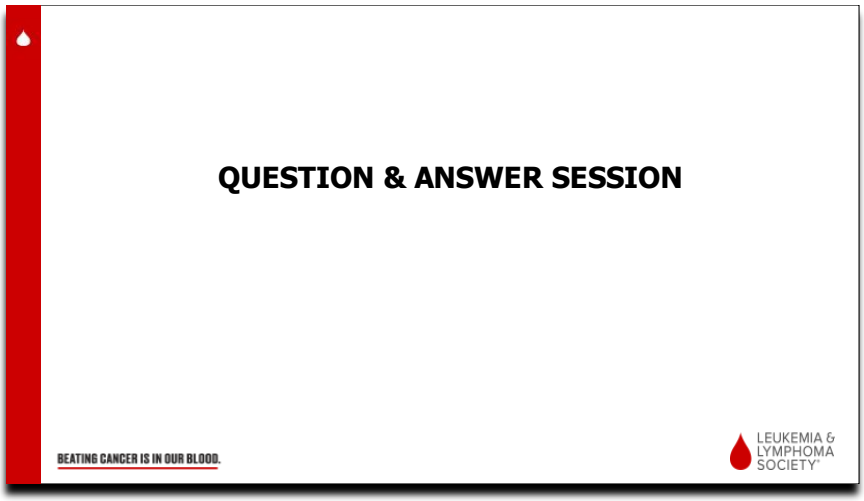
And it looks similar whether you're 18 to 55, 56 to 70, or greater than 71. So, that's a very good news story for these vaccines. SARS-CoV-2 infection after vaccination in health care workers was published by our group here at UC San Diego. And what you see is, you really have to wait 14 days, at least 14 days after you've had your second dose, because we are seeing a slight rate of infection in people that have been vaccinated, but they didn't wait. So, we have to make sure that there's the right timing, so that you've got a proper immune response to the vaccines before you start going out and seeing everyone.

We should all still be wearing masks in public. So, we still have to take a lot of precautions. These masks really work. I know it's not high tech, but it really works.

Slide 30- Thank You

And I've got to say, when I was on call in January for the inpatient hematology service, I was really shocked by the number of people that had COVID, who were in hospital that look quite a bit younger.

We had 177 people in the hospital with COVID, it was a severe infection. Today it's 20, in all our hospitals. That's a dramatic decline. Our positivity rate here is 2% in San Diego. It's gone down dramatically because of vaccination. So, the main point with COVID, is prevent it. I'd like to thank our funding agencies and really move on to the next discussion, because we know you have a lot of questions, and we'd like to be able to answer them. Thanks very much for your time.



Slide 31 Question & Answer Session

Lauren Hall
Wonderful. Thank you so much, Dr. Jamieson and Dr. Rossi for that foundation of learning. So, we are going to move into the question-and-answer session. So that this is a benefit for all in attendance, we are only going to be asking questions that are general in nature. If you have a more specific question that you'd like answered after the program, please contact our Information Specialists at 1-800-955-4572 or reach out to your treating oncologist. I'd now like to introduce you to our moderator for the Q&A session, the Chief Medical Officer at The Leukemia and Lymphoma Society, Dr. Gwen Nichols. Dr. Nichols, I will turn it over to you.

Gwen Nichols, MD
Thank you so much, Lauren. And I just want to say thank you to Dr. Rossi and Dr. Jamieson, for being so kind to donate your time and giving such really clear and interesting information. And I want to also thank the participants, because we got just a really wide array of incredibly interesting and important questions, and I'll do my best to give some flavor and we'll have answers as best as we can.

So, the first area that a lot of people asked about, had to do with the risk of death and severe disease from COVID-19. And I think Dr. Jamieson spoke to that very eloquently. But I wondered if you might talk a little bit more about any specifics for people who are survivors or who are further out or who are not currently taking treatment, about their risk for COVID-19?

Catriona Jamieson, MD, PhD
Yeah. And I imagine this has a lot to do with people's concern about their individual blood cancer. And there are certainly certain types of blood cancers, as I showed there, were there seems to be a higher risk of mortality or having severe COVID-19, if you can track that. One of those types of cancer is called myeloproliferative neoplasm, where the mortality rate seemed higher in people that contracted COVID-19.

The other one we're seeing slightly higher rates of severe COVID-19 infection, are people with chronic lymphocytic leukemia, even if they're in the watch and wait period where they're not having active treatment. And part of the reason for that is, the B cell part of the immune response doesn't work very well, because the cancer arises in that B cell population, so the B cells don't work. People still have active T cells, though.

And so, I think that there are ways to mitigate the risk of having severe COVID-19 infection. First of all, get vaccinated. Even if you had the infection before, as Derrick mentioned so eloquently, there are four variants, at least, that we know of, that really may not have seen your immune system before, where you may need a vaccination to really ensure that you have proper immunity. So, the rate of severity of COVID-19 has a lot to do with age, it has a lot to do with male sex, partly because there's a co receptor for ACE-2, called TMPRSS2 and that is the male hormone responsive receptor.

But not all is lost. What we've found over the last more than year, since we've been dealing with COVID as a pandemic in the U.S. and around the world is, early detection of infection, early intervention, preferably, a vaccination to prevent infection, as Derrick was alluding to. But early intervention with passive immune sera, meeting antibodies from people that have had COVID before, that's very effective. Early intervention with Regeneron really works. Remdesivir works to some extent, in established and more severe infection, as does steroid dosing. And potentially, as I alluded to, JAK2 inhibition, partly because the virus seems to bind to the AC2 receptors Derrick was mentioning, but then go in, un-coat and be activated to replicate in part to JAK2 stats signaling.

So, there are different ways to block viral replication. That's the next step. So, you remember with the flu, we had the flu vaccine. Nowhere near as effective as this, Moderna or Pfizer mRNA vaccine strategy or other vaccines strategies, but nonetheless, we had the vaccine. And then what took a little bit longer is to make the targeted agent that prevented flu virus from replicating, and that was Tamiflu®. And that it's really effective.

So, really talk to your doctor, find out what your risk is. We have National Comprehensive Cancer Centers in the US. In California, we have eight NCI designated Comprehensive Cancer Centers, and we all have very specific strategies for prevention of COVID. And early detection and intervention when people have the COVID-19 infection.

Gwen Nichols, MD
Thank you. Thank you. That's great. And I got some mRNA questions that I'd like to direct to Dr. Rossi. Which, I think, it's terrific that the level of questions that we've gotten. And one of them has to do with

how many cells in the body are these mRNA therapeutics likely to enter? Doe it enter every cell in the body? And what is the likelihood of interaction of these

Derrick Rossi, PhD
Well, okay. So, I'm gonna step back a little bit. I'll answer it, and I may ask you to remind me. But Catriona sort of told us a little bit about what mRNA is. And you used an analogy that I've never used before, but I liked it, the architect and the builder.

I mean, so I'll give you my version of that. Because I think it's important that people know what mRNA is, because the question was about that. If people understand what mRNA is, they start to get a little bit more comfortable with what it is. So, Catriona was right to start with DNA. I think everybody knows, everybody on Earth has heard of the word DNA. And everybody gets that it has something to do with heredity.

But what people don't actually realize, that DNA is actually a rather passive molecule. It doesn't actually do the busy work of the cell. It encodes the book, the instructions are all there, but the busy work is actually done by effector molecules called proteins. And those are really the worker bees of the hive, they do all the work. But in order for DNA to encode proteins, to have that actually made, there's a sort of a neglected middle child, which is mRNA. And it's a necessary intermediate.

The gene, which is encoded on the DNA, is basically, mRNA is synthesized. It's basically a faithful replication of the code. It carries the code out of a cellular compartment called the nucleus to the cytoplasm, takes that code to the site of, protein synthesis factory called the ribosome. It's read by the ribosome, and a protein is made, a specific protein is made. So, every one of our cells has hundreds of millions of copies of mRNA in it. So, it is not an alien molecule, it's in all cells of our body. And it's it's one of the fundamental molecules of life.

I call it the trifecta of life. DNA makes RNA, makes protein, makes life. That's the first thing that everybody should realize. The question is a good one, though. When you're getting the mRNA vaccine, where's it going? How many cells in the body? Well, turns out, as many of us know, with that sore upper arm, it's an intramuscular injection. And it's actually a pretty localized delivery. The cells are in proximity to the needle track, the mRNA, and some professional antigen. Again, another type of immune cells see it, but it's a very, very localized infection, not infection, delivery of the of the cargo.

The other important thing in which people ask about is, well, do you just get the mRNA? Or like, what, I've heard about these lipid nanoparticles, what are those exactly? So, that's actually, sort of a delivery vehicle, if you will. It's a little, fat droplet. If anything, it's a little fatty droplet, and the mRNA is put inside of this. The reason for that is two-fold, actually. mRNA is actually a very unstable molecule. And it's readily degraded by enzymes proteins in our body called RNAsis

So, by putting it in this fatty capsule, when you deliver that into the person, you protect the RNA from being eaten and degraded by these RNASIS. The other thing the lipid nanoparticle does, this is my daughter here. The other thing the lipid nanoparticle does, is it facilitates uptake into cells, localized cells. And you need uptake of the RNA, it has to get into the cell, in order for it to be effective, because it must, that mRNA must go to this protein factory called the ribosome. It's code must be read to express the spike protein to initiate this immune response.

But really, it is, it's a super localized environment. So, if you're getting injected in your left arm, and you'll know from those that get a sore arm, particularly after the second dose, it's pretty localized to the spot of injection. That's because all the immune action is happening there, it's actually a good sign that your arm hurts. Whenever my friends or family tell me, oh, I got my vaccine, it really hurt my arm, I'm like good your immune system is working. That's a good thing.

It's very localized. So, it's not systemic at all. And it's picked up by muscle cells, dendritic cells, macrophages, other cells in the localized environment. So, that's the first issue. Now, could we

envision a time that there is delivery vehicles. And to be honest, for mRNA therapeutics, you might want them in more cells in the body, or other cells in the body. You might use a different delivery strategy at that point. But right now, that delivery strategy is a localized strategy, because that's all you need to initiate a localized, which then becomes a systemic immune response.

So, that's, I think, answer to the first part of the question. And the second part was, oh, interact with any drugs. There's no reason, a priority to believe that that would be occurring, although I don't believe it's been studied. But there's really no reason to think that that should interfere with any enzymes in your body. As I said, its job and what mRNA does, is it goes into the ribosome. It's relatively inert until it does that. It's basically a code carrier. It goes into your ribosome, it's code is read, the protein is made. And that's what elicits the immune response.

And although, never say never with biology. And I always say that, never say never with biology. We don't understand all the all the machinations of everything, but I'll remind everybody, I told you at the beginning, each and every one of the cells in your body has hundreds of millions of copies of mRNA in it right now.

Gwen Nichols, MD
I think that was a great explanation. Dr. Jamieson, I have a question for you. It's a compilation of a bunch of questions. People are wondering, are there blood cancer patients who should not get vaccinated? And people are asking about particular therapies, bone marrow transplant, CAR T therapy, Rituxan® or BTK inhibitors? Are there any caveats?

Obviously, everyone's cases individual, and they should speak with their own healthcare provider. I don't want to make Dr. Jamieson, everybody's doctor. But I think if you can give us some general ideas about this, it will answer a lot of the questions that we received.

Catriona Jamieson, MD, PhD
Yeah. I think the main point is that vaccines are lifesaving. Regardless of the type of blood cancer you have, they're lifesaving. They have been an absolute game changer. I think initially, we had trepidation thinking, oh, maybe they'll have a lot of side effects that will make it difficult to treat people with blood cancers at any state. And what we're finding is quite the opposite. That by having people not have to deal with COVID-19 infections, because, as Derrick pointed out at 94% effectiveness is amazing.

I mean, we don't have to deal with this sequela, those short and long term sequela,of getting COVID-19. So, we haven't restricted access to the vaccination. We do want people to be able to mount a proper immune response. And essentially what it takes, you have your first vaccination, whether we're talking about Pfizer or Moderna, and then you need a couple of weeks to be able to get your B cells to realize, hey, I have to do something, I have to make an antibody.

And then you get the second vaccination and then that reminds them, oh, yeah, I'm supposed to make what are called antibodies, that are able to neutralize or turn off the virus prevented from getting into cells and replicating, if you actually see real COVID-19 infection. I think the big question comes up when people are on therapies that suppress B cells, like rituximab, or BTK inhibitors like ibrutinib, they still have a T cell response. So, even though they don't have as good a B cell response, their T cell response is still there and can come to the rescue.

The other thing is, we have other cells in our system called natural killer cells. And as I mentioned, other cells that form part of what's called the myeloid compartment that can also come to the rescue. And our stem cells, as I was alluding to, are somewhat protected because they have their own internal antiviral strategies. These anti-viral enzymes, called APOBEC and the other enzyme is called ADAR. So, they may provide some protection to our stem cells as well.

So, there are certain types of blood cancers where components of the immune system don't work as well as in B cell malignancies. But the data so far, suggests that having vaccination is more protective

than not having it. And if we have to time the dosing of our therapies to try and ensure that people have an appropriate immune response where we can, we'll do that. But ultimately, preventing COVID is the most important charge that we have as physicians, right now. Primum non nocere, above all, do no harm, so make sure people get the vaccine.

Gwen Nichols, MD
Thank you. And couldn't agree more. I am actually going to take the next question area, because there were a huge number of questions related to both the safety of the vaccine for blood cancer patients, and efficacy in the case where patients know or they're concerned that they may not be making the antibody that is now, in some cases, being measured after vaccination to see the effectiveness of antibody production. And right now, there are only reports of some patients with blood cancer not making adequate antibody.

But as Dr. Jamieson has said, that's not the full immune response. And so, just because you don't have an evident antibody in your system, we still don't know that that does could mean you're protected. And in fact, there are patients who have no detectable antibody and still seem to be able to fight off COVID. So, we have a lot left to learn. I want to have a little time to pitch what LLS is doing, because we realized early on that physicians and patients needed this information, that there may not be an adequate antibody response for blood cancer patients under certain conditions.

So, how do we learn about this as quickly as possible? Well, we are supporting a lot of scientists who are looking at this in the research setting. But we also have the LLS Michael Garil Patient Registry. And this is a registry where you, as patients, can be citizen scientists. You agree to take surveys and provide de-identified medical information that we can compile and work with researchers to answer questions.

And this way we crowd, basically, crowd-source some of the answers that it takes a long time to test in a very rigorous scientific fashion. But we can get some ideas from real world data. And I have to tell you, that while we don't have all the answers, we're going to be able to publish some of this data that will help understand how people do with making antibody and whether their T cells can compensate. And the thing that I can tell you right now, is that since the end of February, when we started asking questions and having patients sign consent for COVID specific questions, we have 3,200 blood cancer patients who have answered this survey and have been fully vaccinated with either Moderna, Pfizer, or J&J vaccine.

And I can tell you that the safety profile in this group of patients is not different than that that Dr. Rossi showed you, in the 1000s of healthy volunteers that participated in the trial. And so, I can echo what

Dr. Jamieson says. Talk to your doctor, if there is not a medical reason why you shouldn't get the vaccine, you and everyone around you should be vaccinated. And please, go to LLS.org/registry, if you're interested in joining us, and in answering these questions as a citizen scientist.

So, now, I want to go to a couple of questions that I think both of you answered. There are a lot of questions about the variants, the need for booster vaccines against the variants. And how long, if you get vaccinated now, is it likely to last? So, I'll leave this, because I think both of you can speak about these questions.

Derrick Rossi, PhD
Well, I'll just start and Catriona, you can jump in. So, for how long, Dr. Jamieson showed a study that's been published recently, that at least six months post, and this is true of both Moderna and Pfizer, antibody levels are very high in patients. But the answer is, we don't know how long because it's time dependent and we just don't know yet. So, it could be that after a year or a year and a half that that immune response starts to wane.

Well, guess what? That will definitely be studied. This is one of the most studied populations on the planet right now, as you can well imagine. So, we'll see that, that'll be well reported. In which case, if the virus has become endemic, and this is something we haven't talked about, which I think is worth talking about is, is this virus going to be around forever? Are we going to be able to eradicate this? Or when I say become endemic, the flu virus is endemic, it comes every year, and it comes in variants every year, by the way. So, we continually have to get our flu vaccine every year to try to mitigate symptoms of flu infection.

So, that's an endemic virus and it's possible. And I would say, based on what I was sort of alluding to earlier about the massive opportunity for this virus to, for mutant variant strains to emerge, the massive opportunity given the 10s of millions of people, hundreds of millions of people infected on the planet, I think there's likely to be variants that emerge and persist. And by the way, this has to do with vaccine hesitancy. And if there's a certain amount of vaccine hesitancy on the planet, or a certain percentage of people, maybe approximating herd immunity gets vaccinated, but the others don't, well, then we're more likely to see endemic virus emerge.

So, though, and again, I talked about it, might we get variant specific boosters, if you will, I think that's likely. They're already in clinical testing right now. So, I think that's likely. So, it may be that the booster you get in a year's time, if your immunity wanes, or a variant emerges that is more effective and still infecting you, despite the fact that you've been vaccinated. I think, likely, you'll see a variant specific booster strategy being applied by the companies. And indeed, that's already in testing right now, i.e. it's foreseeable.

Catriona Jamieson, MD, PhD
Yeah, my take on it is, the follow on to that, is if we have a healthier community, if we have a healthier country, so we have fewer people who have viral persistence, or in other words become human reservoirs for the virus, they just can't get rid of it very quickly. So, the virus is more likely to mutate in that person or a person can get reinfected with these different strains, and then the virus mutates, then we'll all be better off. So, I'm doing a big plug for blood cancer research because of the increased rates of infection and people with blood cancers, both pre blood cancers, and full-blown blood cancers. So, I think the more effectively we eradicate blood cancers, and we get back to normal functioning immune systems, the better off we'll be.

The other thing is, if we vaccinate, and we learn what The Leukemia & Lymphoma Society is putting into place in terms of how well the people mount an antibody response, and how well do they mount a T cell response, we'll be better able to gauge how frequently we should be applying a booster strategy. The other thing is, how random is it that people get these strains, these mutated strains? Is this something that our own bodies are doing, and I alluded to these two antiviral enzymes, they can actually mutate different viruses. We learned in the case of HIV, that our bodies can actually prevent

HIV propagation if we get the immune system working properly. But if we stress out the immune system too much, it can hyper mutate HIV, in part, because of our antiviral enzymes just going awry, and not getting turned off.

So, there's a lot we've learned from previous infectious scourges in this country and in the world. And we've learned a lot about how the immune system works. Because of COVID being a pandemic, we're gonna learn more than ever, about immune responses and how we get them to be healthy again. And the key is what Derrick mentioned, is getting back to a greater proportion of patients who are people in the country and in the world, who have not only had the vaccine, but showing that they have an effective response to the vaccine. And ultimately, we want anti replicative strategies, strategies that prevent the virus from propagating itself.

When I was in medical school, and doing my PhD in microbiology and immunology, we were very concerned about HIV. Thinking we'll never get rid of it, it's the worst possible diagnosis in the world, it's worse than cancer. Well, look at HIV now, we have multi agent therapy, we don't eradicate it, but

people live long, normal lives with HIV. So, I agree with you, Derrick, that we're likely to see this virus in different forms. But we'll have many strategies to prevent people from getting it, just like we do with HIV.

There's actually a prep program, which is preemptive treatment to prevent people from HIV. But we may have something similar for COVID. I think that silly, simple thing, like a mask, I'm not advertising for Lacoste here, there's a little crocodile there, fight the virus. These things work. It worked in 1920 and 1918, and 1920. It still works.

Gwen Nichols, MD
It still works.

Catriona Jamieson, MD, PhD
Washing your hands. This is my PhD in microbiology, I can't help it. It was beaten into my head. It really works.

Gwen Nichols, MD
I think that brings me up, maybe, a final question for us to end with. And that has to do with how all of us have COVID fatigue. And many of the people that put in questions have been vaccinated, and they want to know, can blood cancer patients start returning to normal life? Can they go back to an open workplace? Can they go to restaurants? Can they travel to see their family on an airplane? Can you give us some advice for those types of questions?

I will also put in another pitch that we have lots of information about that on the LLS website, specifically for blood cancer patients. So, it's a good source of reputable information, because it comes from experts like Dr. Jamieson and Dr. Rossi, and many of the other researchers that work so tirelessly for our patients. But I'd like to hear your thoughts about what blood cancer patients ought to do, in terms of going back to normal life if they've been vaccinated.

Catriona Jamieson, MD, PhD
Well, I'll say something, and then I'll pass it over to Derrick to have the last word, because he invented this technology that I'm benefiting from, and so many of our friends and family members and the whole country is benefiting from. But basically what I would say is, still take precaution. No vaccine is 100% effective, this is 94% percent effective in people that have a healthy functioning immune system.

Really, we don't know how effective or how durable the responses will be to the vaccine of people that have different types of blood cancers. It's great that the LLS is doing that, we can do that in our own institutions as well, by looking at antibody immunoglobulin responses, as well as T cell responses. But I don't think we quite know yet how safe it is to travel. I would still take precautions, wear a mask when you're in public spaces. Now, restaurants are 50% occupancy here.

You can go out, wash your hands a lot, just be careful. If you're going to go on a plane, just be really, really careful. I would still think that's fairly high risk. And it depends on the type of blood cancer, the type of treatment you're getting. But take all the precautions as if you hadn't been vaccinated, essentially, because it may be that it's not 100% effective in you, and you could still be at risk for getting the infection.

So, the most important thing with COVID is prevent it, don't get it. We still need to take precautions. We're not out of the woods yet, but it's looking so much better. Until a larger proportion of the population is negative, it just won't be that safe. So, now, I think we're at 25% of the population in the US being vaccinated, we still have quite a way to go. We think we need to be in at least 70% or 75% to make it safer for everyone. So, just please take precautions, protect yourself, protect others, get vaccinated as soon as you can. And we're hoping for a better fall and better holidays this year than last.

Derrick Rossi, PhD
Well said and I echo all that. I'll just say one other thing. And I would have liked to have pulled up the daily reported infection rate today. So, vaccination are providing the light at the end of the tunnel, there's no question about that. But we're still at a daily infection rate in the U.S. of in the many tens of thousands. And that's reportable and that's reported and all of us can see it every single day on a day-by-day basis.

So, I would actually say that keep monitoring that. And if everybody or as many people continue to get back vaccinated, those numbers, those daily infection rates will go down, they will. And, though, if everybody continues to practice good hygiene and responsible social distancing and mask wearing, so I would say that when you see those numbers really hitting the floor, by the way, it'll be big news. So, you won't even have to look for it, it'll be all over your, but then of course, you realize that okay, the viruses not infecting five people on my street right now. There might be five people in my state today that have been reported to be infected, or five people in the northeast.

When you start to see really low numbers like that, then you can start to feel confident about going out and having a really, getting back to like true normalcy. But until that point, I couldn't agree with Dr. Jamieson more, than, certain things are risky. Particularly if you're a cancer patient, you should consider yourself at higher risk for sure. And practice good, all the things that we've been doing for the past year, all of us, hopefully, and to keep yourself safe.

Slide 32- LLS Education & Support Resources

Gwen Nichols, MD
Well, I thank you both. And I will eliminate my final question, which is, which vaccines should you get? Because we already know that each of you got a different vaccine. And by the way, Dr. Rossi did not get the Moderna vaccine, he got the Pfizer vaccine. Get whatever vaccine you can get your hands on. Thank you both for being so giving of your time and your intelligence to LLS and to our patients. We really thank you.

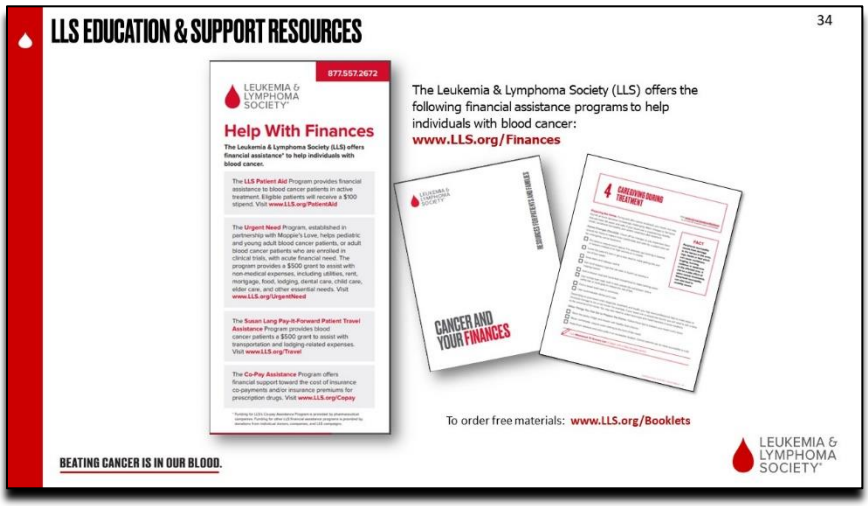
Catriona Jamieson, MD, PhD
Thanks so much to you and the audience. And thanks, Derrick, yet again, for your wisdom here. And Gwen, for guiding the conversation and providing LLS resources for patients, thank you to your whole team.

Derrick Rossi, PhD
Yes, thank you all, I really enjoyed it. It was fun. And hopefully, it helped answer some of your questions. I noticed I was scrolling through the question, the new question coming in section, there are

many, many hundreds of questions that were coming in. So, I guarantee we didn't get to respond to all of those. But hopefully, what we talked about today, provides some light on the subject that you can feel comfort in. And by the way, I would say, encourage your family members that might not be watching, to think about maybe some of the things that were talked about this evening as well.

Lauren Hall
Wonderful. So, I'll reiterate my gratitude for all of our speakers. Thank you so much. And thank you to each of you for being here with us today and for submitting your questions. As Dr. Rossi mentioned, if we were not able to get to your questions today, please contact an Information Specialist at 1-800-955-4572. Or you can reach us by email at infocenter@lls.org. Our Information Specialists are available to answer your questions about COVID-19 and any other blood cancer related questions you may have.

Slide 33- LLS Education & Support Resources



Slide 34- LLS Education & Support Resources

And lastly, participants, please complete the program evaluation, which supports us in developing programs that meet your needs. The link will appear at the conclusion of this presentation. We really appreciate you all taking time out of your evening to participate in this program. And in these unusual times, please rest assured that we're all in this together. Stay well.

Slide 35- Thank You

Catriona Jamieson, MD, PhD
Thanks very much. Have a good night. Bye.

Operator
This concludes our web education program. Thank you for your participation. Please take a moment to complete the evaluation by clicking on the link.