

WEBVTT

NOTE duration:"01:02:30.082000"

NOTE language:en-us

NOTE Confidence: 0.899671792984009

00:00:00.040 --> 00:00:30.110 A few and few of you will have remember Joe he passed away about. I guess 3 years ago, or so now. Joe is originally a product of University of Maryland in Dartmouth and Boston University and then was recruited to Yale here in 1959 by the first chair of the Department of laboratory medicine. Here really to create the entire transfusion. Medison program and the run the blood bank at the Yellow Haven Hospital, which in those days, was just the Elmer Haven Hospital as opposed to the extensive young New Haven health system.

NOTE Confidence: 0.891805052757263

00:00:30.110 --> 00:01:00.680 Joe really did pioneer at this institution as a very forward looking manner, the therapeutic a pheresis program, which these days is of course, also involved in the collection processing and engineering of stem cells for a variety of patients predominantly cancer patients himself and I won't go through the list of things to Seminole work in the transfusion transmitted diseases area as well as alloimmunization and really was.

NOTE Confidence: 0.890196025371552

00:01:00.680 --> 00:01:30.470 A linchpin and main stay here, at the Apple with the hospital and the University for for many, many years, so we all Miss Joe immensely. I think Bob Alper and actually a couple years ago when JoJo passed away it kind of summarize this very nicely, said Doctor Beauvais was known for his love of Science and served as an example and a great mentor to many generations of clinicians and researchers so this is an honor a joke. Today I'll turn things over to Charlie. No thank you.

NOTE Confidence: 0.916258335113525

00:01:31.070 --> 00:02:02.480 And you know, I just want to reiterate what a privilege it is. This is yet another example. I think of the terrific collaboration between Laboratory Medison and Cancer Center. An obviously a wonderful tribute to the legacy of Doctor Beauvais. It's a real privilege to introduce our lecturer who I've known for quite some time for those of you who are unaware of doctor Peter Marks is the director of the Center for biological evaluation research.

NOTE Confidence: 0.928799033164978

00:02:02.480 --> 00:02:33.810 At the US Food and Drug Administration Ann has uh the awesome responsibility to oversee Essentia. Lee effectiveness and safety of biological products, which include abroad away array of vaccines blood product cellular therapies. Gene therapies among others. Include this is an area

of drug development that is forever, expanding and I've talked into Peter last night at dinner. It sounds like his center and his staff are forever, expanding to deal.

NOTE Confidence: 0.93220978975296

00:02:33.810 --> 00:03:05.700 With the demands now of the various biological products that are now entering in all forms of medical therapy. I think Peter exemplifies somebody who throughout his career has been committed to the care of patients, as a provider as a researcher as an educator and now as a leader of a very elaborate and complex organization. Peter received his medical degree and PhD from New York University.

NOTE Confidence: 0.910139441490173

00:03:05.700 --> 00:03:35.770 And then where I met Peter is he joined the residency class at Brigham's Hospital where very auspicious class where member of his class included Doctor Herps, and I had the privilege when they were junior residents to be there. Chief resident and it really was an impressive group. After that, he received his medical training at the Brigham and joined the faculty there where he served as the clinical director for hematology ultimately as many of you know, he was recruited here.

NOTE Confidence: 0.847020506858826

00:03:35.770 --> 00:03:39.520 TL to lead both the adult leukemia service.

NOTE Confidence: 0.916356921195984

00:03:40.080 --> 00:04:04.190 And uh and also to be the chief clinical officer for Smilow Cancer Hospital and as I think that introduction demonstrates Peter has had numerous leadership jobs. And I think has been really an asset for all of us in cancer. Medical and experimental. Therapeutics and science. So it really is a privilege in welcoming doctor Peter Marks back to the.

NOTE Confidence: 0.867669403553009

00:04:10.170 --> 00:04:16.410 Wow, now, I have a lot of people here. Let me try to get the slides up.

NOTE Confidence: 0.899725794792175

00:04:20.160 --> 00:04:50.230 Thanks so much for that kind introduction, So what I'm going to do today is try to tell you about what I would consider are kind of next wave in amino oncology, which will be genetically modified cell therapies particular going to talk about Chimeric Antigen Receptor T cells and the reason why I call it the next wave and not just the wave is because you know oncology has been around for a while. Some people always like to say that the latest thing is the.

NOTE Confidence: 0.882328748703003

00:04:50.230 --> 00:04:55.250 Newest thing, but I'll try to put it in perspective for you.

NOTE Confidence: 0.914391040802002

00:04:55.800 --> 00:05:05.230 So what I'd like to do is put a cellular immunotherapy in context. Review some of the science underlying recent advances on this area.

NOTE Confidence: 0.919478058815002

00:05:05.740 --> 00:05:37.710 Give you a little bit of an idea of some of the approved products. The two that we have approved in the United States talk about some of what's coming up in development and talk a little bit about some challenges in the field and what we do at FDA to try to help move along product development. I'm going to apologize in advance to people who are very familiar with this field because I'm not going to tell you Brown ground breaking. New information, but I'm going to hopefully put it in perspective. So those of you who might not be so familiar.

NOTE Confidence: 0.921389162540436

00:05:37.710 --> 00:05:41.930 We'll see what's really capable and what we're capable love in this area.

NOTE Confidence: 0.89129251241684

00:05:42.570 --> 00:06:13.440 So we think about therapeutic modalities to treat cancer and I do this with a little bit of trepidation with Doctor Devita in the audience. I mean, there was originally you had surgery radiation therapy and whether you consider cytotoxic chemotherapy and targeted therapy 2 different tellers or the same pillar doesn't matter. We've had these modalities and we've had the immunotherapy modality and although some people say wow. You know therapy new new 21st century.

NOTE Confidence: 0.948951601982117

00:06:13.440 --> 00:06:28.360 It's been around for actually since the 19th century and in fact, the essentially the groundbreaking work that led to Coley's toxin at the beginning of the 20th century was done in the late 19th century.

NOTE Confidence: 0.897730827331543

00:06:28.940 --> 00:07:00.410 And types of immunotherapy. They include bacterial product such as BCG the activity of BCG was actually discovered by Lloyd Old in 1959. So it's been around for awhile and it's still in use their issues with BCG manufactured. We could be a whole discussion for another days grand rounds. There's cytokinin such as Interleukin 2 interferons. There's cancer vaccines and although we could spend the rest of the day talking about whether simple loose Lt is.

NOTE Confidence: 0.834482133388519

00:07:00.410 --> 00:07:11.580 An effective cancer vaccine or not will just skip that for now, there uncle lytic viruses telina gene which is from Melanoma.

NOTE Confidence: 0.873592495918274

00:07:12.110 --> 00:07:42.680 Immune checkpoint inhibitors and this is should be no no secret to this audience because with doctor snow. Pflueger others have used these and have pioneered some of their uses and Melanoma and others. Here, who use these and other diseases. You obviously very aware of these antibodies and the power. They have and they are expanding use in oncology, so kind of a shout out to everyone who's using those here.

NOTE Confidence: 0.911002814769745

00:07:42.680 --> 00:08:14.610 And then there are the cellular immunotherapy's and I'm going to talk about sell you know therapy day we could have talked about lots of different cellular immunotherapy's there are tumor, infiltrating lymphocytes. Those have been investigated for several decades. Now, doctor Steven Rosenberg at National Institute of Health has been looking at these and there are some pretty interesting nifty responses with them. People have been expanding T cell clones or expanding natural killer cells and getting results again. We could talk about results in those areas, but

NOTE Confidence: 0.923429787158966

00:08:14.610 --> 00:08:42.260 Where I thought it would be really most useful to talk about her in genetically modified T cells because that's where there's been tremendous innovation and it's a great example of how molecular biology manufacturing innovation can all come together ultimately to benefit people, and so we'll talk about mainly about autologous a car T cells. The beginning of this and then we'll talk about some of where things might head with alginate car T cells.

NOTE Confidence: 0.908381283283234

00:08:43.100 --> 00:09:18.110 So again indulge me those of you who understand what America Antigen Receptor T cells are like hymera Here is the fact that you have in this case in the example here on the right you see an antibody head. That's been linked to AT cell receptor on the inside will talk about a little bit more in a moment about what one can do to that internal domain to make the thing work, but you have this chimeric receptor, which is made possible by advances in molecular biology.

NOTE Confidence: 0.892194867134094

00:09:18.110 --> 00:09:48.430 Insert it into a T cell in this case in the autologous case coming that comes from the patient then allowed to proliferate and that technology has been enabled as I said by base invents is basic immunology cell molecular biology. An importantly manufacturing technology because none of these products is useful unless you can make them at sufficient scale and we sufficient quality to treat patients repeatedly.

NOTE Confidence: 0.916851878166199

00:09:49.050 --> 00:10:17.320 And that construct allows one to have targeting an activation of T cells to eliminate cancerous cells and there is a lot packed in there to unpack because one wants to have a cell that persists, but doesn't persist too long one that kill cells, but doesn't kill them, too vigorously because one might remember that when T cells are activated they cause. Other immune cells to become activated inside a kind release and will talk about what can happen there.

NOTE Confidence: 0.889521181583405

00:10:17.860 --> 00:10:48.530 Let's talk a little bit more about the construct for a moment think I went ahead one, too many. The potential advantages of using genetically modified so other therapies and some of this is the fact that this work can be done ex vivo when you're doing your genetic modification, which is a nice thing because you don't have to let a virus loose in the body, particularly if you're using lentivirus or other integrating vectors that can be an issue.

NOTE Confidence: 0.919528841972351

00:10:48.530 --> 00:10:55.640 One can figure out before you put the cell back into a person where the genetic modification has occurred if you want.

NOTE Confidence: 0.912179291248322

00:10:56.300 --> 00:11:23.630 You can do things like use crisper more with impunity. Then you could otherwise CRISPR. CAS 9 gene editing is something that we're a little hesitant still to let loose in a viral vector it directly into the bloodstream because well God knows what it will do it off target whereas if you do that. In a cell ex vivo outside of the body and then put it back in and we're a little more comfortable with it.

NOTE Confidence: 0.924401521682739

00:11:24.300 --> 00:11:56.520 And the other nice thing about this technology is one could potentially if need be controlled. The effector function because you don't want. These cells as I told you to potentially get out of control and nice thing is, you can introduce things like suicide genes. If you need to that could be activated by a small molecule if you need to modulate function so those are some nice advantages there. Plus, you have this ability to provide therapeutic benefit with extended duration of effect in some cases, we already know that these are.

NOTE Confidence: 0.889375269412994

00:11:56.520 --> 00:12:05.880 She says they can they have memory and if cancer comes back in a year or 2 they may proliferate and then put it back down again.

NOTE Confidence: 0.92089706659317

00:12:06.810 --> 00:12:36.980 There are some potential disadvantages and one of them is that one has to have a process to consistently manufacturing characterized cells. That sounds so like this in this boring? Why is that we boring us with this manufacturing stuff it's because at the end of the day being able to consistently manufacturer product is really important here because if one has products that are not consistently manufactured and people have adverse events.

NOTE Confidence: 0.902959942817688

00:12:36.980 --> 00:12:42.270 That can shut down a whole field an I could give you examples of that, but trust me for now.

NOTE Confidence: 0.912721216678619

00:12:42.800 --> 00:13:08.100 Another issue that's challenging with these cellular therapies is that there are logistical issues. When you show in a moment the process of making these cells is not simple when there are autologous. It's a relatively complex process, which involves at this point. I'm shipping sells off and getting back to the right person and there are also some developmental challenges in these.

NOTE Confidence: 0.912098288536072

00:13:08.710 --> 00:13:33.470 But and ultimately So what you might ultimately like is an allogeneic cell line. But we're still not quite there and that's because you have to deal with the issues of wanting to get rid of major compatibility complex specificity. Class 1 while also not leading to the cells getting killed off by natural killer cells. There are ways that you can get around that will talk about those.

NOTE Confidence: 0.896896958351135

00:13:34.150 --> 00:13:50.040 And then the other problem with some of these cells is that these actually really are therapies that work. There can be short and long term side effects, So what? What is the engine here that is led to a lot of this well.

NOTE Confidence: 0.880168497562408

00:13:50.610 --> 00:14:20.890 I this is taken from a recent review by Walshe Yang color, but I put this up here because I think it's a nice view on the left, you see kind of a normal set up in T cell signaling the T cell signaling involves a complex of different receptors coming together, leading to a relatively organized and powerful signal when the T cell. Receptor is lie gated to a target and with the car T cell does.

NOTE Confidence: 0.920614302158356

00:14:20.890 --> 00:14:51.400 Is it mimics that it's not quite as organized but one has the external immunoglobulin head grafted on to various domains pulled from T cell receptors to lead to both activation and potentially to persistence and as

we've come to succeeding generations of Carty construct second generation 3rd generation and now, even force generation constructs what goes on that inside Linker for activation is really crucial.

NOTE Confidence: 0.932976067066193

00:14:51.400 --> 00:15:20.780 And how crucial we can say that we know this and this is something that's nice to be able to say from I can say from the FDA perspective because we have an end to end view point over an entire class of products, even single nucleotide or a few nucleotides difference in here can make a difference in terms of adverse effect profile. So it's really a lot of room for creativity, but also a lot of variables to have to be dealt with.

NOTE Confidence: 0.902941465377808

00:15:22.370 --> 00:15:55.080 Here's the business end of this that's that's challenging there is a lot to overcome in pudding autologous car. T cell therapy into place. It starts actually very fittingly for Bovey lecture with the fact that you start with in a pheresis product and equality. A pheresis product is quite critical. It turns out that's a challenge in itself because you have to get the right number of cells. Unfortunately, as a former leukemia treat or I'll tell you we beat people up so sometimes it's hard.

NOTE Confidence: 0.905764639377594

00:15:55.080 --> 00:16:26.310 To get enough of the initial cells out of people that you need that are of good quality. Those cells, then have to go be sent to a manufacturing facility or they are taken to a manufacturing area within an institution. They have to be transduced with the vector construct. Currently, the most common vector being used. There lentiviral vectors, although some are exploring other non viral and viral vectors, but the one that's been used most.

NOTE Confidence: 0.904417395591736

00:16:26.310 --> 00:16:56.620 Commonly recently has been lentivirus, which is in itself a large undertaking because just getting the lentiviral vectors is a manufacturing challenge. It turns out making lentiviruses not the simplest thing to do at scale. It's relatively expensive and that's because the yields of production or low. Once you do that. You've got to expand the cells and culture. All of them. All you have to formulate it and something you can give back to the patient you have to make sure the patient.

NOTE Confidence: 0.898755550384521

00:16:56.620 --> 00:17:02.510 Is has some oftentimes will have some preparation for getting that and then will receive the cells?

NOTE Confidence: 0.922994613647461

00:17:03.390 --> 00:17:37.900 Other things, I should mention probably good idea that the same patient. You took the cells from gets the cells back chain of

custody is actually important and then you have to deal afterwards with the fact that you've given this relatively powerful therapy to patients and there could be adverse effects and will talk about some of them. What are the kinds of results that we've been seen with this so the results are pretty remarkable and there? What ultimately led to the approvals. I'm just going to show you a selection from 2 different products.

NOTE Confidence: 0.870356202125549

00:17:37.900 --> 00:18:07.970 Taissa Jenna Laclu sell it only took me like 5000 times trying to say that to be able to say it quickly batissa Jenn look blue cell is a CD19 targeted Carty construct for that was developed for initially developed for human logic malignancies in particular. It was move forward towards approval for pediatric and young adult, acute lymphoid leukemia, it showed.

NOTE Confidence: 0.898955941200256

00:18:07.970 --> 00:18:36.460 It's a mission rate 3 months of 81% in a very heavily pretreated patient population of these were generally kids who had 5 to 6, recommends before summer. We've had transplants before so one did not expect necessary to see responses. That's impressive and then you can see here on the right part of this and overall survival meeting overall survival of 19.1 months and then.

NOTE Confidence: 0.910605370998383

00:18:37.120 --> 00:18:50.510 There are kids now that are out years after this apparently cured, so an impressive impressive result in an area where just one was not going to expect to see much of result.

NOTE Confidence: 0.882507979869843

00:18:52.450 --> 00:19:22.820 It also other same target CD 19 present on non Hodgkin's lymphoma cells and axle cap. The gene was developed by a different company for treatment. Initially and non. Hodgkin's lymphoma's here, you see it's been used in diffuse large B cell lymphoma's primary in this time will be selling. Formazan transform Flickr lymphomas with an overall complete response rate of about 54%.

NOTE Confidence: 0.909009039402008

00:19:22.820 --> 00:19:28.470 Again, pretty nice results in a heavily pretreated population.

NOTE Confidence: 0.938985049724579

00:19:28.990 --> 00:20:00.800 And with about 18 months about a 50% overall survival again, something that just wouldn't be expected. These products ultimately gained approval without needing to have a randomized, controlled trial why? Because it was so clear that these were not the Natural History of these diseases, so, although at FDA we have statutory language that says, we're supposed to approve things based on adequate and well controlled trials generally

to one or 2, randomized control trials. There is a provision that allows us when we have.

NOTE Confidence: 0.91954106092453

00:20:00.800 --> 00:20:05.470 Good evidence to not have to have randomized control trials and this is that type of case.

NOTE Confidence: 0.8999884724617

00:20:07.000 --> 00:20:16.380 Now is it a free lunch. No, it's not a free lunch. Today was maybe you're free lunch. Although you're being burdened by having to listen to me right now, so it's not entirely free.

NOTE Confidence: 0.922040641307831

00:20:17.540 --> 00:20:48.170 But these are actually just shows your great example of something that actually really works. But in part of it really doing its job also comes the fact that it can have some pretty pretty severe side effects. And probably the most notable is this issue of cytokine release syndrome, which nearly killed this therapy off at the beginning because when it was given to patients who had large leukemia burdens this side of kind release syndrome.

NOTE Confidence: 0.902738273143768

00:20:48.190 --> 00:21:19.360 Landed them in the intensive care unit on pressers and until some people at University of Pennsylvania, including people who heralded actually from slightly older in my internship residency fellowship training classes at the Brigham. Steve grew up and Dave Porter until they figured out ways to deal with this nearly was really limiting of these therapies because what happens in this side of kind release syndrome is what you would see.

NOTE Confidence: 0.917933940887451

00:21:19.360 --> 00:21:27.120 When you have a really, really big immune response, which essentially you get fever hypotension.

NOTE Confidence: 0.906705319881439

00:21:27.690 --> 00:21:57.700 Typical essentially capillary leak syndrome, where if you're not careful. It's very easy to fluid overload. Someone patients ended up on ventilators on multiple pressers. After some this is just one of these lucky things that people were at the right place at the right time. People realize that one of the side of kinds. That was quite elevated was P'll 6. Sure enough, there was something on the shelf that's something that could be used for that.

NOTE Confidence: 0.91740620136261

00:21:57.700 --> 00:22:29.350 And that helped move this forward cytokine release syndrome is pretty impressive in that it has its onset of the meeting of 2 to 3 days with a range of one to 22 days. It resolves in about a week's time. This is one of the problems, though that creates real challenges and treating patients because one would like to treat patients in an outpatient setting but

when cytokine release syndrome comes on it can come on very quickly and you don't want people too far from a treatment center, so that's been an issue to deal with.

NOTE Confidence: 0.931076467037201

00:22:30.680 --> 00:22:50.130 The percentage of patients who get this depends on which CAR T cell construct is being given how much residual disease. They have so rather than put up percentages of how many people get this. I'll just tell you it ranges from 15% to 75%, depending on the amount of underlying disease burden in the Kartik construct.

NOTE Confidence: 0.90234386920929

00:22:50.820 --> 00:23:22.110 There's a grading system even for this there are actually several grading systems that have been put together. This is a great example of where it's important to actually try to come to a consistent grading system because without that, we don't know what we're talking about in general low grade is just get fever. The higher grades. You have fever and mild to moderate hypertension or requirements for oxygen as you need more oxygen or more pressers. Then you get to these higher grades and by the time you get to grade for your in ICU on multiple pressers.

NOTE Confidence: 0.905393362045288

00:23:22.110 --> 00:23:23.470 That's not good.

NOTE Confidence: 0.888071715831757

00:23:24.090 --> 00:23:54.700 But as I've mentioned one of the lucky things here is that with careful management. This toxicity can be addressed and managed through one can use monitoring. Obviously careful monitoring post infusion. We've learned that you don't want to flood people with fluids that kind of productive. They leak into their lungs and then you have to put him on a ventilator probably gentle fluid resuscitation and then start to use pressers. If you need to, and use Tulsa Lusa map that was.

NOTE Confidence: 0.882632493972778

00:23:54.700 --> 00:24:16.180 Great example of something off the shelf that was able to be used interesting example of something that FDA gave an approval for use in this treatment, setting even though we invited the sponsor to ask for this indication so it's labeled for sciatica treatment of side of con release syndrome.

NOTE Confidence: 0.863447368144989

00:24:16.910 --> 00:24:47.860 There's some other issues. This one and we don't have it easy in a solution for its this issue of of encephalopathies that can occur. There's this cell mediated encephalopathies syndrome also called immune effector cell associated N toxicity syndrome, which is a range from mild to severe and occasionally is a fatal encephalomyopathy. Manifesta seizures visual field defects a feja tremors facial droop.

NOTE Confidence: 0.92410284280777

00:24:47.860 --> 00:24:59.790 Right now, the management is essentially supportive care although there is possibly some evidence that some of the things that block inflammatory mediators may also be effective here more to come on that is that study.

NOTE Confidence: 0.823682725429535

00:25:01.030 --> 00:25:10.230 And there are some other ID since I'm from the FBI have to be a little exhaust more exhaustive about side effects of things.

NOTE Confidence: 0.898323714733124

00:25:10.880 --> 00:25:41.110 There can be cytopenias I won't say much more about that. But there can be cardiac dysrhythmias associated with cytokine release syndrome's transient. Systolic dysfunction one of the issues with the car 19 T cells is that you get a hypo gamma globulin EMEA that can be pretty pronounced an pretty deep for a long time, so sometimes these patients will need Sup lumentacion with immune globulin and then we don't know the long term side effects here and that's the good news is we're starting to gather those data.

NOTE Confidence: 0.916737854480743

00:25:41.110 --> 00:25:46.890 Through registries, but it is something just to keep in the back of our of our minds.

NOTE Confidence: 0.903609097003937

00:25:48.050 --> 00:26:18.860 So I mentioned there are 2 products approved what you see up here are the product labels decision like looks Ellen Acsec, averaging it. So happens that you might say Well, can't. You just use these for any CD 19 positive malignancy well. You could if someone would pay for them, but they're going to probably pay for what's on the FDA label. An I'm not going to go into this much more. I was thinking of not saying this at all but I should at least mention to you that. These are relatively expensive therapies at FDA we don't approve things on the basis.

NOTE Confidence: 0.868853271007538

00:26:18.860 --> 00:26:48.890 We are cost blind, but it's hard not to know to remember because people from Congress keep writing me or calling me to say to remind me of the price that these are in the range of 400,000 to \$500,000 therapies. This agenda like Lou cell now has 2 indications both for LL an for non. Hodgkin's lymphoma naxa captain Jean has the non Hodgkin's lymphoma indication.

NOTE Confidence: 0.927213370800018

00:26:48.890 --> 00:26:52.810 It's likely that we'll see these more of these proliferate in the future.

NOTE Confidence: 0.0425024330615997

00:26:53.440 --> 00:26:54.150 Um.

NOTE Confidence: 0.897983312606812

00:26:54.660 --> 00:27:26.610 But these are the 2 approved ones right now, So what I tried to tell you in this part of the talk is that these are a set of therapies. These chimeric Antigen Receptor T cells that have been very powerful CD. 19 is just the 1st of a wave of these they've been most useful to date in human logic malignancies. I've talked about CD 19, there are other human logic malignancy targets that I'll tell you a little bit more about.

NOTE Confidence: 0.907290637493134

00:27:26.610 --> 00:27:57.020 Some of them are very the reason why CD 19, has been the 1st is because it has the largest potential applicability in terms of market size and you can imagine if you're a company that's what you might be targeting first I just put this up there just because it's kind of a cool pseudo. Colored picture of what's going on here in the beautiful thing about about this type of cell targeting is that little pink. Pseudo colored cell can keep on killing and killing and.

NOTE Confidence: 0.872948586940765

00:27:57.020 --> 00:28:00.550 Proliferating if need be so quite a cool therapy.

NOTE Confidence: 0.903733432292938

00:28:01.690 --> 00:28:31.700 So what's the next wave that will come after these well people have worked on anti CD 22 car T cells why? Because CD 22 is a potential antigen that you might be able to knock off in people with a LL because you actually do get breakthrough growth of LL after treatment with anti CD 19 T cells and this is another way of potentially controlling leukemia.

NOTE Confidence: 0.903124511241913

00:28:31.700 --> 00:29:02.990 That's a very small population very interesting development plan and it shows how one sometimes has to think very creatively about developing things for small populations and I'll mention more about that in a minute and other though probably the next large indication in potentially in human logic malignancy is in myeloma where people have developed car. T cells against B cell maturation, Antigen and these are earlier in development, but they're showing reasonable promise here.

NOTE Confidence: 0.915929973125458

00:29:02.990 --> 00:29:35.300 Their variety of different BC, MA constructs. I'm just showing you one example published from the New England Journal by nipple. Ragueh Roger and colleagues earlier this year, but you can see that in this particular case. If you look towards the right with that graph graph is trying to show you is that they found really it depended on how many cells you

actually gave to see whether you were going to get a good response or not, and you can see that they were actually getting a reasonable response rate here.

NOTE Confidence: 0.906874179840088

00:29:35.300 --> 00:30:08.100 With a reasonable duration of response getting up towards a year in very heavily pretreated patients with multiple myeloma and we're talking about people with very heavy pretreatment. People who had gotten the whole 9 yards of the various images, etc. Monoclonal so another area of promise. Lots of clinical trials going on here will see as this winds its way towards potential approval. Then there's the area of car T cells for solid tumors. This has been an area, which Unfortunately.

NOTE Confidence: 0.904412508010864

00:30:08.500 --> 00:30:39.450 Citing as it seems has been a little bit disappointing, and that's because of the challenges talent challenges associated with solid tumors. I mean, it sounds like this should be just what the doctor ordered right something that you can go after here. These T cells should be able to go after and eliminate a solid tumor. Just the way they do it for a human logic malignancy. And Unfortunately, it just doesn't work. That way, first of it all. It's hard to get the car T cells to the tumor.

NOTE Confidence: 0.957018852233887

00:30:39.450 --> 00:30:40.990 Location in the 1st place.

NOTE Confidence: 0.923518061637878

00:30:41.800 --> 00:31:06.100 Tumors tend to have this essentially immunosuppressive micro environment, so you have to do something to overcome that there are ways to do that. But that's something one has to think about one has to make sure that the car T cell you get in. There is able to maintain its function. Overtime and it doesn't get shut down by things in the tumor microenvironment. Another thing to deal with, and then there's another big question.

NOTE Confidence: 0.92432826757431

00:31:06.640 --> 00:31:14.850 Unfortunately, unlike human logic malignancies, where we're lucky enough to have cell surface molecules that are relatively unique their present on B cells?

NOTE Confidence: 0.902020454406738

00:31:15.350 --> 00:31:37.520 Non other cells, not a lot of other cells and it turns out that we can do without CD 19 positive cells without ending four paws up on the floor. Unfortunately, there are not a ton of antigens that are absolutely specific just as a single antigen for cancer cells so one has to think someone creatively here.

NOTE Confidence: 0.907351493835449

00:31:38.170 --> 00:32:01.550 This is just to remind me to tell you that people have been trying through a whole host of different antigens. This is a recent review from bio drugs. It just goes over the fact that people have been trying a variety of different logins to go after including NYS 01 CEACD 70 things things around here.

NOTE Confidence: 0.90480500459671

00:32:02.830 --> 00:32:34.820 Generally, the non optimized cars have not shown tremendous promise in this area, but people now started to combine them with PD one inhibitors with novel targeting strategies that I'll tell you about in a minute. We'll see where this goes. This is clearly an area where people would like to be able to go. But whether it will be truly successful. I can't say for sure. Part of it is. There's this whole question of can cells overcome bulk disease or?

NOTE Confidence: 0.932908713817596

00:32:34.820 --> 00:32:58.440 Is this better a better strategy in solid tumors for minimal disease problem that is that's one that's going to be hard to figure out because it's going to be hard to get people to fund trials for minimal residual disease for therapies that are 300 to \$500,000, which is why a message here. Maybe that getting the cost of these down may help the clinical development.

NOTE Confidence: 0.85968691110611

00:32:59.000 --> 00:33:29.120 So what are some novel car T cell it constructs well I was I was excited was actually fun to come here today because you have people working in your Cancer Center on cool novel car T cell constructs so people are working both to broaden antigen targeting and to tailor it back. The idea here being that if you could basically say maybe maybe if you saw two things on the surface of a cancer cell that would activate the car T cell that might be better for.

NOTE Confidence: 0.889889478683472

00:33:29.120 --> 00:33:30.040 Knocking off.

NOTE Confidence: 0.896416306495667

00:33:30.630 --> 00:33:46.690 A a cancer cell that's from a solid tumor. And so in contrast to a monovalent car. That's for a human logic, Millidge and see if you had a bivalent car. You'd have to see 2 things at the same time, and that would lead to activation that might be good.

NOTE Confidence: 0.908868968486786

00:33:47.210 --> 00:34:05.290 You could also have this idea of maybe you want. One car T cell and I could see either something that's an or car and either way, it would try to kill the cell, but then there's this idea of things that would lead you like the and car that I mentioned where you have 2 separate.

NOTE Confidence: 0.902877032756805

00:34:05.820 --> 00:34:36.530 Car T cells instead of a grafted second car, head where the signaling molecules are distributed among the two receptors. So when you have both car constructs lie gated you get activation. There's uh not car where the idea. There is well. You see a positive signal and if you saw something on his cell that could be a normal cell. You would not activate. But if you didn't see that you would activate and then there are other constructs with the idea that.

NOTE Confidence: 0.919151246547699

00:34:36.530 --> 00:35:02.500 You have one receptor on the car T cell surface, which, if it's lie gated then activates transcription of a second or even 3rd that can come up and potentially bind with the target so a lot of creativity here and I'm not even going to take you through some of the creativity that people are doing now with genome editing because people are now working to make 567 edits into car T cells to make these affective.

NOTE Confidence: 0.913478255271912

00:35:04.110 --> 00:35:19.560 Ultimately, a lot of people would like to see the development of allogeneic car T cells. Why well first of all. It's now possible. One can potentially use genome editing to knock off cell surface molecules like the MHC.

NOTE Confidence: 0.90965861082077

00:35:20.070 --> 00:35:51.560 And one can put something on the surface that will keep the natural killer cells happy for those of you who are unaware. MHC one on all of ourselves. You take it off. Unfortunately, your natural killer cells get a little upset and they tend to try to kill the cells. So you have to put something on the surface of the cell sorry. I'm simplifying this a bit so that you keep the NK cells happy that can be done and in fact, it can actually be done in one fell swoop so you with genome editing you can actually.

NOTE Confidence: 0.894436240196228

00:35:51.560 --> 00:36:00.810 Put something in where you're knocking out the MHC either by using the beta 2, Microglobulin Locus or other low side.

NOTE Confidence: 0.914390861988068

00:36:01.470 --> 00:36:29.110 So what's the idea here is you'd like to have an off the shelf product? Why off the shelf products are invariably going to be less expensive in the long run why? Because you can make large batches. You can make them consistently probably from 3 sources of T cells from normal donors healthy donors. There are plenty of college students out there that are looking to make money by donating their T cells for posterity kind of like they will do for plasma.

NOTE Confidence: 0.921450912952423

00:36:29.710 --> 00:36:57.480 And so that would potentially to an off the shelf product. It could be very useful because one of the problems with car. T cells is that oftentimes people need them in a hurry and the manufacturing process. Even Essentia Lee at the most rapid pace. You can make them generally takes 1 to 2 weeks and that's really probably speeding it as much as you can in some cases, it's a 3 to 6 week process.

NOTE Confidence: 0.930082142353058

00:36:58.170 --> 00:37:30.350 And reducing the cost of this therapy is probably something that's really important here again, although our job. Sometimes you take on things in government that aren't exactly your job. I actually take it on as one of the things that our job to do scientifically is to help ultimately reduce the cost of this therapy not by pressuring the manufacturers by helping to improve the technology because if the cost of the technology goes down people will start to investigate. These products in settings that they may be more effective such as in earlier stages of disease and for other diseases.

NOTE Confidence: 0.918015778064728

00:37:31.060 --> 00:38:01.230 I put this up here as the minimum ecology landscape to show why I think we need to be judicious. In what we're doing. For those of you who know the PD one inhibitor story. You'll know that every company has their own PD. One inhibitor that they're developing because well, we need to have a PD one inhibitor in our pipeline. But the economist will tell you that once you have 7 to 10 of a given type of product in the same space on the market. You're not going to bring down cost anymore, so these are things that are just essentially taking up.

NOTE Confidence: 0.916821241378784

00:38:02.030 --> 00:38:34.080 Taking up space in some ways that's a personal opinion, not one of the FDA or these United States, you can see in the car T cell space. We have something similar happening because you can see that over the past year in the car T cell space there has been about 1/3 increase in activity between 2018 and 2019, which is really pretty nice growth. You'll see that for the other cellular therapies. There hasn't been quite the same growth. Perhaps some in some novelty cell technologies Ann.

NOTE Confidence: 0.895179688930511

00:38:34.080 --> 00:39:04.530 In some of the T cell receptor on manipulation. But the next slide is what I think is very telling most of this growth or a lot of it is in the CD 19 car T cell space, which again is that the best this is just people go where their success. But I'm not sure how many more CD 19 based therapies. We need you can see the other area of growth, which makes sense in the BCMA and the rest are kind of stable there, you can see other targets.

NOTE Confidence: 0.840573728084564

00:39:04.530 --> 00:39:10.360 In development, there CD 20 NYS so for solid tumors.

NOTE Confidence: 0.916717350482941

00:39:10.940 --> 00:39:14.070 And people, obviously are doing other novel designs.

NOTE Confidence: 0.900072872638702

00:39:15.110 --> 00:39:25.090 So what I want to finish up with his talk about some of the challenges and development of these therapies and what FDA can do an does to try to help move them forward.

NOTE Confidence: 0.93157434463501

00:39:26.110 --> 00:39:57.080 So one of the issues for some of these therapies is that particularly if one gets very creative about targeting to specific mutations. One is going to get to a place where one is going to have if not, individualized car T cell therapies car T cell therapies for relatively small populations and because of that when one wants to do clinical trials. One is going to have to be very creative about the clinical trial designs that one uses so we're very much aware of that and we actually just actually just went live earlier.

NOTE Confidence: 0.909037709236145

00:39:57.080 --> 00:40:28.950 This week, a complex and innovative clinical trial design guidance, which basically talks about how one can use Bayesian designs and adaptive designs to try to reduce the number of patients to get to an answer. So we know about that. The other issue with these therapies that people aren't used to sometimes is that when you have a highly effective therapy. You need to be prepared very early on that you're actually could have a marketed therapy and this is something that people forget.

NOTE Confidence: 0.931987106800079

00:40:28.950 --> 00:40:36.860 They and I think it's important for academic investigation remember if you have a therapy that could could be very effective.

NOTE Confidence: 0.919922351837158

00:40:37.700 --> 00:41:07.750 Understanding a little more about how to manufacture well early on may be important because it could actually be a real product sooner than you think and that means thinking about manufacturing. Issues is something to deal with, we don't hold academic investigators to the same manufacturing standard, that we do industrial sponsors good manufacturing practices in its full scale. But we do think it's something that's good to think about.

NOTE Confidence: 0.920039892196655

00:41:07.770 --> 00:41:23.180 And we think about it, particularly because it's really important with these products to understand how you're going to go from

pilot scale to larger commercial scale scale up in part because even though these are individually made products now for autologous car T cells.

NOTE Confidence: 0.93497222661972

00:41:23.890 --> 00:41:35.420 It turns out that sometimes scaling up the operation leads to problems. You change media. You change operators and believe it or not these are cellular therapies?

NOTE Confidence: 0.867890417575836

00:41:35.950 --> 00:41:50.310 And there is there's a hate to say it at Yale, but it is actually a Harvard rule. the Harvard Rule of cell biology is that cells when put under very constrained conditions.

NOTE Confidence: 0.906474173069

00:41:50.810 --> 00:42:21.140 Will do whatever the heck they want to do and that's the problem here is that cells can be very tricky to work with so that's something that people have to deal with, and one of the issues that come up to that. I'll bring to you is that there is this current tension and I don't know which one I don't have a favorite of the horses that on both horses. There are equally good horses whether they'll be centralized or distributed manufacturing that will take the day. The idea of centralized manufacturing is you collect the T cells in one place.

NOTE Confidence: 0.892632603645325

00:42:21.140 --> 00:42:34.340 Right now with the autologous cells, you send them to some manufacturing site, they make the product. They send it back to you. The distributed manufacturing? Is there's a machine here at Yale. You do it everything here at Yale.

NOTE Confidence: 0.915633857250214

00:42:34.840 --> 00:43:04.990 The potential advantages to each of these related both to some to quality control on the centralized and to the ability to move quickly and potentially at lower cost on the distributed end so I just put this up here to show you that people are trying to address these on the left side you see one of the ideas for scale. Up, which is you can actually buy these essentially GMP compliant manufacturing facilities, they come like little Lego bricks.

NOTE Confidence: 0.913184821605682

00:43:04.990 --> 00:43:33.170 You stack them up as you want and as your manufacturing capacity grows. If you have a central manufacturing facility. It grows with it and on the right here and this is not meant to advertise any particular manufacture. It just so happens. This is 1 device that is basically a closed system for the manufacture. It's largely largely automated for the manufacture of car of car T cells so.

NOTE Confidence: 0.90515547990799

00:43:33.680 --> 00:43:40.860 We'll see which of these these models pans out it's probably going to be some combination of the 2?

NOTE Confidence: 0.897078037261963

00:43:41.550 --> 00:44:12.250 Actually, obviously also genetic approach that suits itself more towards a central model. But the autologous are relatively personalized approach, which may for solid tumors be the way it will have to go favors potentially the this kind of distributed model and I will tell you that again in the United States right now. The trend has been more Tours. The centralized model. I can tell you that there are leading competitor in the car T cell space does anyone know what's the next the next most number?

NOTE Confidence: 0.906932234764099

00:44:12.250 --> 00:44:14.330 Car T cells being investigated in the world.

NOTE Confidence: 0.910498559474945

00:44:15.320 --> 00:44:46.890 China actually heard it, I heard it right so China has just we're just ahead of China in terms of the number of trials on going. I think it's something like in the US if I recall correctly don't quote me and because these figures are a little out of date. We have about 350 clinical trials. They have about 250. Three hundred and the rest of the world has about 150 combined so but again China is a little different because they have more of a distributed.

NOTE Confidence: 0.898694932460785

00:44:46.890 --> 00:44:55.220 I distributed technology model anyway because they regulate car T cells as at health technology rather than as a drug a biologic.

NOTE Confidence: 0.898344099521637

00:44:55.960 --> 00:45:23.370 So the last couple minutes here. I'll tell you what we do at FDA. This is the usual talk. I give so everything I just told you if you challenge me on it. I'll say you're probably right because I don't know what I'm talking about this is the stuff. I actually do know what I'm talking about this is what I do at the FDA everyday we try to promote product development. I'm not a good doctor. Snyder is a much better comedian than I am I've never been able to learn his excellent comedic skills.

NOTE Confidence: 0.935512542724609

00:45:24.080 --> 00:45:54.370 In terms of promoting product development. We really have an increasingly important role in this regard. The Biologics Control Act of 1902, which established the precursor to the organization that I lead was actually before the FDA was formed. It was actually part of the Department of Treasury and it happened because of a terrible accident where somebody released a lot of Horse Serum. That was contaminated with tetanus and killed a bunch of children in St Louis Mo.

NOTE Confidence: 0.92237389087677

00:45:54.370 --> 00:46:25.880 And then another lot was released of smallpox vaccine that killed people in Camden. NJ so bad things happen. So initially for the first number of decades of the existence of our organization, we were really mainly concerned about safety, then thalidomide came along in 1919 fifties and with John F Kennedy signed the key for Harris amendments to the food drug and Cosmetic Act in 1960s and 70s, we became concerned about Efficacy.

NOTE Confidence: 0.922337234020233

00:46:26.680 --> 00:46:49.140 And then later on as more innovation came along over the past 2 decades. We've been increasingly tasked with trying to promote innovation and that's happened through user fee. Axe FDA charges user fees for products that are submitted and that covers about half the cost of the agencies review processes for new drugs and biologics.

NOTE Confidence: 0.825161933898926

00:46:50.020 --> 00:46:57.980 Play blood blood accepted blood and tissues or not user fee products but the rest are.

NOTE Confidence: 0.910010695457459

00:46:59.010 --> 00:47:32.100 And we have other things like orphan designation, which gives companies advantages and development if they have products that are targeting less than 200,000 individuals in the United States. We have vouchers which are essentially priority review vouchers or essentially an inducement to people developing things in certain spaces like the rare disease space for Pediatrics Medical Countermeasures. That is things that essentially protect against anthrax a bowl those kind of things.

NOTE Confidence: 0.798395812511444

00:47:32.100 --> 00:47:33.080 And.

NOTE Confidence: 0.924351394176483

00:47:33.760 --> 00:48:04.440 A rare tropical diseases and those are basically ways of speeding up the review from a 10 month review Clock to a 6 month review Clock. You might say why do I care if the FDA review something for months faster well if you have a blockbuster drug that translates into hundreds of millions of dollars so that's why those are useful and we have our expedited development programs, which include programs that have been around for awhile like fast track designation priority view, which I just explained to you.

NOTE Confidence: 0.892709851264954

00:48:04.440 --> 00:48:25.820 Get things reviewed at the agency couple months faster accelerated approval, which allows us to approve a product. Not on a clinical endpoint that is how someone feels functions are survives, but rather on

an end point. That's reasonably likely to predict whether that's clinical or a bio marker and then.

NOTE Confidence: 0.925838947296143

00:48:26.420 --> 00:48:57.690 And then we have other things that have come more recently out like breakthrough therapy designation in 2012, which is an amalgam of the other programs that also leads to additional agency attention for products that get this designation. It breakthrough therapy designated product does not mean the product is breakthrough. It's not like some incredible breakthrough. What it means is that it's not a bar that it appears to be superior to in early data to existing therapies.

NOTE Confidence: 0.926596701145172

00:48:57.690 --> 00:49:18.900 And that's not definitive evidence and then most recently with the 21st century cures act of 2016. There was this regenerative. Madison advanced therapy designation that was developed and that's applicable to car T cells. Another gene therapies, which is very much like breakthrough therapy designation in what it accomplishes.

NOTE Confidence: 0.897026240825653

00:49:19.490 --> 00:49:38.760 And we have this is a designation program that specifically run by our center where people have been using this there are a lot of products that have come in asking for the designation. We've given 44 of these what this gives them is additional interaction with the agency.

NOTE Confidence: 0.896846234798431

00:49:39.390 --> 00:49:50.750 Interaction with the agency is helpful an it's something I encourage you to do because that actually helps you move product stored the clinic faster we encourage that because.

NOTE Confidence: 0.90479451417923

00:49:51.670 --> 00:50:21.720 Sometimes people, bringing things to the clinic try to follow here say they try to follow what their surgical mentor did they try to follow? What somebody did 10 years ago. An I wasn't at FDA 10 years ago, so don't for my Centaur don't follow what someone did 10 years ago because it might not be what we require now so good to come in and talk to us. We don't buy generally an since everyone since we actually do.

NOTE Confidence: 0.891742169857025

00:50:21.720 --> 00:50:27.960 Regulate rabies vaccine, we can have everyone vaccinated, so that you won't catch anything bad.

NOTE Confidence: 0.021772837266326

00:50:28.540 --> 00:50:29.510 I.

NOTE Confidence: 0.922634840011597

00:50:30.750 --> 00:51:00.960 This interact program is one that we established a few years ago with the idea being that we want to encourage particularly academics and small companies to come in early and talk to us in an opportunity to have a non binding informal conversation about a product that you might want to develop so you have to have a product concept in mind. You have to know what questions you want to ask but the idea here is you don't have to write big regulatory submission. You write us a couple of pages and say Hey.

NOTE Confidence: 0.900831401348114

00:51:00.960 --> 00:51:31.070 I have a car T cell that I want to eliminate colon cancer. It's going to have 2 receptors on it, and I would like to know what toxicology I need to do, if any water. My manufacturing requirements. That's the kind of thing that people can come in and we give you non binding answers. So if you decide you want to ignore us we won't hold it against you. People find these generally pretty useful.

NOTE Confidence: 0.901613771915436

00:51:31.090 --> 00:52:01.420 Sometimes we do these meetings in person, sometimes we do them by phone and sometimes we just give answers in writing people like answers in writing because then they can take it to venture capitalists and they can say all the FDA sent us something but this is something we encourage you. It's easy to find this and I actually found a trick. It turns out that so few people want to interact with the FDA that if you search up interact and Sieber or interact in FDA this will come up and it's good because you're taxpaying dollars.

NOTE Confidence: 0.915766477584839

00:52:01.420 --> 00:52:19.640 Did not have to pay for product placement? We didn't have to get Google to like put this at the Top of the list. It just comes up there. So you can find that if you want to use and there is all kidding aside. There's pretty specific instructions about how to go about submitting one of these requests and you see it's not very it's not very onerous.

NOTE Confidence: 0.91369092464447

00:52:20.270 --> 00:52:50.740 We also have another type of meeting that we more recently started because some people say, well. I don't have a product. But I have this idea that I want to make car T cells that are going to have 8 Genomic edits that are going to modify all these different cell surface antigens and then I'm going to put in different different cars. Actual antibodies on the surface well. That's not a specific product. But it is a platform other people want to talk about how they're going to make blood in culture.

NOTE Confidence: 0.918797791004181

00:52:50.740 --> 00:53:21.990 And so we've had another type of meeting where we have our manufacturing experts and we have quite a number of people who specialize in manufacturing. Some of them came from industry. Some of them?

Do lab work and are very familiar with manufacturing technologies and we have an opportunity to come in for a meeting about that. The need for the regulatory submission. Here is very similar to the interact meeting it's not a big formal submission is give us 2 or 3 pages. So we know when you come in and we're going to be talking about.

NOTE Confidence: 0.922750115394592

00:53:22.410 --> 00:53:47.070 And we're really trying to encourage interaction because at the end of the day. You know at the end of the day. FDA is here, although we have to have statutory standards. There were here to make sure that stuff is safe. We don't do our jobs either. If we don't get products that help people to the market. And so there's this balance that we have to deal with which is we want things to be safe and effective.

NOTE Confidence: 0.897724390029907

00:53:47.600 --> 00:54:18.650 And get to people who need them, and so we it's an interesting juggling act so I'll just summarize hear that autologous cartis are the 1st wave and what will probably be a wave of more effective therapies. My guess is there going to be combined in every which way with other protein molecules their small molecules and potentially even with multiple cell types ultimately.

NOTE Confidence: 0.911448061466217

00:54:18.650 --> 00:54:49.360 But more to come on that and I think what we will hopefully see in the coming years. Our car T cell product with reduce toxicities. Ultimately, hopefully to allogeneic car T cells, which will reduce the cost of these and a car T cell products that are effective against solid tumors. My final just contemplation again not the opinion of the United States or the FDA is that the reason to see the cost of these come down is that at least from what I can see from the breath of the literature.

NOTE Confidence: 0.925732851028442

00:54:49.360 --> 00:55:21.170 Some of the most intriguing uses of car T cells in the solid tumor world might be to eliminate minimal residual disease or small amounts of cancer cells. That's what immune surveillance does well. We're never going to get to do those studies and less the cost of these therapies comes way down. In addition, in the United States were not going to maintain our leadership in this area. If we don't figure out a way to bring down the cost because one of the things I can see from my level is the fact that there are people around the globe that are already figuring out how to do this for an order of magnitude less.

NOTE Confidence: 0.904902756214142

00:55:21.170 --> 00:55:31.570 Cost and we are so it's kind of an exciting time to be in this area. I think hopefully will see advances for patients and I thank you for your attention.

NOTE Confidence: 0.786091923713684

00:55:32.110 --> 00:55:38.370 Peter thank you questions.

NOTE Confidence: 0.91483473777771

00:55:40.600 --> 00:56:12.590 You talk about the China having a series of projects, which are any cooperation between China or is it politically not a good idea or is it actually we were actually trying to work with China in this area. It's actually the Chinese regulators are struggling in their own right. With this because there's actually a reason for regulation believe it or not. It's so that people don't go off and do whatever they want and the way they realize that the way they've been regulating it as a health technology.

NOTE Confidence: 0.915516912937164

00:56:12.590 --> 00:56:45.120 Has led touch some untoward events on so we actually we are meeting with them. We've met with them or meeting with them again to discuss this because ultimately you'd like to have global harmonization in these products because it's hard. These are niche products to begin with, and if you have to like go to different regulators and they have different requirements. That's not that's not optimal for patient care globally so we do want to try to achieve regulatory harmonisation to the extent that we can actually that's something that I'm excited about because I think we can find.

NOTE Confidence: 0.928192019462585

00:56:45.120 --> 00:57:16.040 This was something we were trying to get to 2 or 3 years ago. It got put on hold a little bit because our major regulatory partner. the European Medicines Agency was a little busy moving they had to move from the fact their headquarters happened to be located in London and there was this little problem called the brexit so there now located in Amsterdam and that really Unfortunately distracted them. But we're working with them, too, so the idea here is to try to get not just not just China but S Korea other Asian regulators.

NOTE Confidence: 0.926329791545868

00:57:16.040 --> 00:57:24.440 European regulators together, so that we essentially come to some general agreement about this that will be good for patients would be good for product developers as well.

NOTE Confidence: 0.291747093200684

00:57:25.060 --> 00:57:31.070 Bent.

NOTE Confidence: 0.875537395477295

00:57:31.590 --> 00:58:02.600 And indeed we, we are, we monitor the eye and one of the funny things I can tell you they're very interesting. I can tell you the details because some of these things we know it. Turns out if you submit one of the really interesting things if you submit an investigational new drug

applications to the FDA. I can't tell anyone that it even exists. You can tell someone that exists. I can tell it. I can't tell anyone that exists unless you.

NOTE Confidence: 0.881959319114685

00:58:02.600 --> 00:58:09.130 Happened to note it in the public domain and even then I'll just say that you happen to note in the public domain.

NOTE Confidence: 0.929089307785034

00:58:09.640 --> 00:58:16.350 So, but it's a very exciting. I think this is a very exciting area and people are trying to again trying to take advantage of these.

NOTE Confidence: 0.805703938007355

00:58:20.240 --> 00:58:50.890 How do you think about the balance between the manufacturing of so many different target so that's a great question so the question is how do you balance this concept that you can now make a bunch of genome edits 5 Seven pick pick some number you can make a bunch of edits.

NOTE Confidence: 0.949459135532379

00:58:50.890 --> 00:58:55.930 To try to make something that will hopefully have the most chance of actually.

NOTE Confidence: 0.897593557834625

00:58:56.430 --> 00:59:27.240 Having an effect and how do you balance that with a chance that oops each time you do genome editing there is that chance that you could well P 53. There are various other molecules their regulatory. I think what will do is will continue to look at data. People provide an off target effects and the nice thing is with single cell seek etc. You can try to get some of that. We also will balance it against what disease it's being used for?

NOTE Confidence: 0.910453617572784

00:59:27.240 --> 00:59:50.630 I think that's part of the strategy here. That's a little bit being strategic in what you use something for that if you're developing a construct like that and you're using it for I don't know pancreatic refractory pancreatic cancer. It's probably going to have a different bar in some ways at least for the initial studies than if you were developing it for first line breast cancer.

NOTE Confidence: 0.913688600063324

00:59:51.590 --> 01:00:01.300 So we definitely way this kind of benefit risk as we think about products that are in development in terms of medical need.

NOTE Confidence: 0.891199350357056

01:00:02.480 --> 01:00:04.180 Have time for one more question?

NOTE Confidence: 0.739829540252686

01:00:04.780 --> 01:00:05.330 Yes.

NOTE Confidence: 0.803667962551117

01:00:06.060 --> 01:00:36.490 I don't know if you can answer this with your own personal opinion. But like no one so I actually think what we do is appropriate. I think it's very easy for companies to hurl at the FDA just like I don't want to hurl at companies.

NOTE Confidence: 0.91584849357605

01:00:36.490 --> 01:01:07.530 It's tough developing drugs, the problem that leads to the largest increase in cost of drug development is all the failures. It's it's not going to help us to lower the bar so that stuff gets on the market that doesn't really help people, a whole lot. And in fact, if you look some would criticize us at FDA recently. I'm not just just reporting not my opinion that we've approved too many cancer therapies that have very small, incremental benefits that aren't game changers.

NOTE Confidence: 0.922789096832275

01:01:07.530 --> 01:01:40.400 I don't I'm not saying that I'm not going to pass judgment on that. But the issue. Is there is some there is some need to have some standard that there is some improvement. But the large, the large cost is not the cost of making it through I mean, people love look our regulatory process takes for review of DLA biologics license application. The maximum amount of time. It takes even if you don't have a priority review is 10 months. That's not where the cost of this is coming, the regulatory submission preparation, yeah, it cost some money.

NOTE Confidence: 0.913737773895264

01:01:40.420 --> 01:02:12.410 The cost is the fact that to get there a bunch of things failed and development and that's because in general is something in Phase 1 if it makes it to Phase 1, there's only about a one in 10 chance. It's going to make it further now that is a little different. Perhaps for targeted gene therapies and things. But overall that's so you pay at the end of the day for all of those failures. So I think I have empathy for industry because there it's tough. It's biology is hard to deal with, but I also think I have a little.

NOTE Confidence: 0.908283650875092

01:02:12.410 --> 01:02:19.530 Defense of FDA because I don't think were the Big Bad Wolf. That's creating the price problems for drugs.

NOTE Confidence: 0.768570303916931

01:02:20.720 --> 01:02:30.080 Thanks so much for your attention today for educating us and to mark this.