We’re going to start with a few introductory remarks from the head of our Cancer Center, Dr. Fuchs, and then we’ll go into a few short presentations by really outstanding panelists from our center and also Doctor IRA Melman from Jeanetta. And after that will be opening up the program to questions and answers and hopefully a freeform discussion to cover some of these topics. We really know that in order to treat effectively develop cures for cancer,
there has to be a collaboration between industry, academics, government. It’s really very, very important, and we designed this session specifically to build connections between your medicine, Yale science and industry leaders. We’ve collected your questions in advance and we invite you to submit your questions at during the time of discussion in the chat room. We also encourage you to share your questions with everyone. Heading into engaging in the discussion, we know that we have a wealth of expertise in the audience today.
Not only do we have outstanding panelists, we have an amazing list of participants from industry.

Will review the chat room throughout and will pull a number of the questions for discussion in the question and answer portion of the session will also have a staff member monitoring the chat room and if we’re unable to answer your question today, will try and follow up as soon as as possible.

And please also know that the webinar is being recorded.

Let me now just welcome doctor Charlie Fuchs.
He’s the head of our Cancer Center.

He’s a Richard Sackler and Jonathan Sackler Professor of Medicine.

And professor of chronic disease Epidemiology.

As I said, he’s a director of the Yale Cancer Center and also the physician in chief of Smilow Hospital.

Charlie has brought an amazing vision of building science at this Institute.

is be immeasurably successful.

Charlie please.

Error, thank you and thank you

for your leadership and I want to
Welcome or many attendees today to.

What is the 1st of a new series, namely Yale engage cancer which is really intended to be to stimulate discussion and collaboration in what is our mutual interest in combatting cancer?

And this first one, I think, really highlights the great depth at our center has. Enemy know biology and Immuno Oncology. Mario certainly are our leader for the session. Has has really had an incredibly accomplished career in science and drug development in Iowa recently. The president of the Society.
 NOTE Confidence: 0.8715226
00:02:51.800 --> 00:02:53.376 of immunotherapy and cancer.
 NOTE Confidence: 0.8715226
00:02:53.380 --> 00:02:55.350 But obviously, as you'll hear,
 NOTE Confidence: 0.8715226
00:02:55.365 --> 00:02:57.365 we have assembled Marios assembled
 NOTE Confidence: 0.8715226
00:02:57.365 --> 00:02:59.815 an extraordinary talent to team to
 NOTE Confidence: 0.8715226
00:02:59.815 --> 00:03:01.650 really engage in this discussion.
 NOTE Confidence: 0.8715226
00:03:01.650 --> 00:03:04.359 You know, we I joined the Kansas
 NOTE Confidence: 0.8715226
00:03:04.359 --> 00:03:06.379 center about four years ago,
 NOTE Confidence: 0.8715226
00:03:06.380 --> 00:03:09.989 and you know what attracted me here was the.
 NOTE Confidence: 0.8715226
00:03:09.990 --> 00:03:12.768 Great depth of talent and accomplishment.
 NOTE Confidence: 0.8715226
00:03:12.770 --> 00:03:15.548 The science here is really unparalleled
 NOTE Confidence: 0.8715226
00:03:15.548 --> 00:03:18.324 in terms of genetics, cell biology,
 NOTE Confidence: 0.8715226
00:03:18.324 --> 00:03:19.710 pharmacology among others,
 NOTE Confidence: 0.8715226
00:03:19.710 --> 00:03:21.006 and most notably,
 NOTE Confidence: 0.8715226
00:03:21.006 --> 00:03:23.166 today Immunobiology and beyond that
 NOTE Confidence: 0.8715226
00:03:23.166 --> 00:03:25.730 I think the clinical operation.
 NOTE Confidence: 0.8715226
6
Frankly,

the 10th anniversary of swallow cancer hospital has enabled an incredible growth of a clinical operation it now sees.

48% of all cancer patients in the state of Connecticut and is enabled a fourfold increase in trials, clinical trial enrollment,

Moreover, actually this year. Yale had studies that have that have enabled 4 new drug approvals in the cancer space.

You know,

obviously,

we’re in the midst of a pandemic,

and we’re focused on kovid.

But we all recognize that
in the 21st century, cancer is really the great landscape for what we want to accomplish in medicine. And I think I owe. Is an important leg that’s going to get us to where we need to be. We really value the partnerships that we develop at Yale with our colleagues and so many of you. Perhaps all of you with backgrounds and industry, an biotech and related areas are obviously sharing a mutual interest in this fight. You know, we welcome your participation in this forum.
But Moreover,

either during or even after the webinar,

we would like to.

Engage with you in terms of

conversations and collaborations.

'cause first and foremost,

we know it takes a village to

combat cancer and we hope with

this does beyond other things.

Is actually enable new collaboration.

So please reach out to me.

Mario or the other panelists because

we want this to be the beginning of

conversations and new engagements

as we work together to leverage

the great work in Immuno Oncology.
So Mario, thank you for allowing me to share a few thoughts and I look forward to this symposium.

Thank you Charlie.

I just again want to repeat that our format today will be a combination of brief introductory comments by our panelists and then a moderated discussion including your questions. We’ve invited our faculty to briefly address several questions, including what their core expertise says, what questions are driving their research, how can we work with the corporate sector in order to address this disease,
and finally, what types of resources, capabilities, and partnerships align with those brought to bear by the corporate sector to advance. This work remind all the speakers that you have 5 minutes to speak and then I will cut you off. Very nicely because we want to get on to the discussion afterwards. After the Yale speakers, I'll then introduce Doctor IRA Melman from genetic. So with that, let me just go ahead and proceed. Our first speaker will be doctor Marcus Bosenberg.
He's the Professor of dermatology, pathology and Immunobiology at the El School of Medicine. He's currently the interim director of the Yale Center framing oncology and he's also the director for the Center for position cans. He's also the Co leader of the genetics, genomics and epigenetics. So I've now taken up almost all of the five minutes with Retitles and I'll turn it over to Mario.
next slide that be great thanks.
I had the great pleasure of working
with Mario on a regular basis
as part of the Melanoma team.
As a practicing dramatic
pathologist and I think you know,
the Yale Center for immuno
oncology in this session is
really focused on Immuno Oncology.
Is kind of at the center of a hub of a
number of very important pieces at Yale.
So doctor Fuchs really nicely
summarized some of the really
impact that the Cancer Center has.
I think many of you are aware
of the sort of world.
Leading world renowned capability of the Immunobiology Department at Yale, traditionally with real strengths in basic immunology but now branching out toward human translation. Really one of my jobs is to try to bring folks into the realm of IO from that Department which has really been, I think, a great success so far. A couple of the talks here from doctor and Doctor Wisocky sort of are related to some of those efforts. Also kind of giving you a feel for.
the landscape and this is really just an introductory session with myself. There’s also the advanced cell therapy lab that Diane Kraus directs and had established an it’s a full GNP facility that can harvest to multithreading. Lymphocytes expand and then allow that product to be reinfused into patients runs clinical trials. This is a real opportunity for Yale to move forward on the scientific front with regard to cell therapies and we’re really positioned well. To do that, doctor Herbst will be talking right after me about some of the
00:08:19.972 --> 00:08:21.917 translation TLE efforts at Yale,

00:08:21.920 --> 00:08:24.278 and I’ll let him do so.

00:08:24.280 --> 00:08:26.863 As doctor snow mentioned in my role

00:08:26.863 --> 00:08:29.695 in as directing the Yale Sport and

00:08:29.695 --> 00:08:31.750 skin cancer with Harriet Cougar,

00:08:31.750 --> 00:08:33.318 there’s really excellent access

00:08:33.318 --> 00:08:34.494 to patient samples,

00:08:34.500 --> 00:08:36.064 patient materials through now.

00:08:36.064 --> 00:08:38.029 Doctor Hertz will explain 3

00:08:38.030 --> 00:08:40.000 now spore grants at Yale,

00:08:40.000 --> 00:08:44.165 especially with regard to Iota

00:08:44.165 --> 00:08:45.929 getting access to specimens.

00:08:45.930 --> 00:08:48.751 Which I think will be important for

00:08:48.751 --> 00:08:49.960 industrial academic collaborations

NOTE Confidence: 0.82695603
in my role now too. I also tend to be at a lot of the discussions related to industrial academic collaborations between other entities, aniele with respect. And, you know, oncology Ann, I really enjoy that interaction, and obviously try to move those things forward in the way that’s most productive for both parties in each of those interactions. So if we can go on to the next slide, I’ll talk about the remaining thing on the. We’ll hear so, and that’s the Center for precision cut cancer modeling,
which I also direct with vision

with Sammy and what this is, a state of the art preclinical testing facility. It’s really focused on Immuno Oncology.

And we will do testing of agents with respect to syngenetic models and other things that have been developed at Yale that are unique to Yale.

We have sponsored research agreements with some members who are on this call related to things like class one deficient models that were uniquely developed at Yale that don’t have to be.
licensed out as a result of that, and we have a lot of experience which some of which will hear about in later talks just after me looking at responses to IO agents in these models, what were particularly.

Cited about right now is the idea of doing patient derived explant studies to evaluate human immuno oncology agents. So the idea here is you take fragments of tumors, embed them in a proprietary 3D matrix and then use agents that might be biologics that are using humans to test responses in those samples and on the right you can see this is
an example of a mouse based tumor, but one in which when we gave a checkpoint inhibitor we see a compute complete curatives response. And so we’re looking at readouts for these systems. But the idea is to have personalized immunotherapy where you can actually look at different combinations in a patient in real time and decide what might work best for that patient. And we’re not fully there yet, but we think we’re pretty close and hope to have this available for others within the next six months to a year.
So I'll stop there and allow the next speakers to go on. The next speaker is doctor Roy Herbst. He's the head of medical oncology, Yale Cancer Center and smile cancer hospital and The Associated Cancer Center director for Translational Research and a professor of Medicine and professor of pharmacology, Roy. Thanks Mary, and thanks to everyone for being here today. So in my role as the associate director of Translational Research, I just want to describe, you know, a little bit about your disease.
00:11:27.838 --> 00:11:30.060 programs or so-called darts and what
NOTE Confidence: 0.84727836
00:11:30.060 --> 00:11:32.870 you can see is UCR disease programs,
NOTE Confidence: 0.84727836
00:11:32.870 --> 00:11:34.010 immunology, population Sciences,
NOTE Confidence: 0.84727836
00:11:34.010 --> 00:11:34.770 Developmental Therapeutics,
NOTE Confidence: 0.84727836
00:11:34.770 --> 00:11:35.904 microbiology, cell signaling,
NOTE Confidence: 0.84727836
00:11:35.904 --> 00:11:36.660 radiation genetics,
NOTE Confidence: 0.84727836
00:11:36.660 --> 00:11:38.560 and all of these disease
NOTE Confidence: 0.84727836
00:11:38.560 --> 00:11:39.700 programs are amazing,
NOTE Confidence: 0.84727836
00:11:39.700 --> 00:11:42.548 but we want to interact them with the
NOTE Confidence: 0.84727836
00:11:42.548 --> 00:11:45.090 clinic with the clinical teams have.
NOTE Confidence: 0.84727836
00:11:45.090 --> 00:11:47.208 Access to patient specimens move move
NOTE Confidence: 0.84727836
00:11:47.208 --> 00:11:50.068 new drugs from the the lab to the clinic,
NOTE Confidence: 0.84727836
00:11:50.070 --> 00:11:52.240 and I think we’re doing that quite
NOTE Confidence: 0.84727836
00:11:52.240 --> 00:11:54.388 well and we form these darts.
NOTE Confidence: 0.84727836
00:11:54.390 --> 00:11:55.730 Diseased aligned research teams
NOTE Confidence: 0.84727836
and that’s where we build our industry alliances in our spores and we have a number of industry alliances right now with Genentech, Astra Zeneca, Eli Lilly to name a few and these darts promote translational research through the scientific discovery. We test new discoveries in our clinics as I mentioned and really take ideas back and forth. We’ve worked very hard this last year too and to improve integration to increase the number of investigator trials that we have at Yale. Now in this day and age,
investigator initiated trials can be where we hold the Ind or it can be a small trial with industry. But at least we are closely involved in the correlative studies or it’s built on Yale Science and we want to build clinical basic teams to move forward. So in the next slide I’ll just show you. We’ve been very successful in this, and you know, there was already an existing Melanoma spore here 10 years ago. But now with the support of the darts and some monies that we were able to supply, we’ve been very successful in this, and you know, there was already an existing Melanoma spore here 10 years ago. But now with the support of the darts and some monies that we were able to supply,
Marcus and Harry have renewed the skins for, so it’s a third renewal now. A third span.

For that we formed a new lung cancer spore myself, We did this now six years ago. We just renewed it building a large part on the immunology from his lab. I think propelled this forward was a signal 15 for which it was developed in the lab paper nature medicine, and then of course, clinical trials ongoing. Really proud that Barbara Burtness,
NOTE Confidence: 0.84727836
00:13:26.800 --> 00:13:28.060 who actually was recruited
NOTE Confidence: 0.84727836
00:13:28.060 --> 00:13:29.635 in the last 10 years,
NOTE Confidence: 0.84727836
00:13:29.640 --> 00:13:31.747 built a head and neck program and
NOTE Confidence: 0.84727836
00:13:31.747 --> 00:13:33.429 with support working with surgery,
NOTE Confidence: 0.84727836
00:13:33.430 --> 00:13:35.010 working with some of the
NOTE Confidence: 0.84727836
00:13:35.010 --> 00:13:35.958 great scientific leaders,
NOTE Confidence: 0.84727836
00:13:35.960 --> 00:13:38.192 now hasn’t had an export and we actually
NOTE Confidence: 0.84727836
00:13:38.192 --> 00:13:41.019 have a group that’s working in brain cancer.
NOTE Confidence: 0.84727836
00:13:41.020 --> 00:13:41.650 They’ve submitted.
NOTE Confidence: 0.84727836
00:13:41.650 --> 00:13:42.910 They’re working on it.
NOTE Confidence: 0.84727836
00:13:42.910 --> 00:13:43.652 Pat Larusso,
NOTE Confidence: 0.84727836
00:13:43.652 --> 00:13:45.878 who I think you all know.
NOTE Confidence: 0.84727836
00:13:45.880 --> 00:13:48.202 Or many of you will know has been working
NOTE Confidence: 0.84727836
00:13:48.202 --> 00:13:50.879 on something in phase One South DNA repair,
NOTE Confidence: 0.84727836
00:13:50.880 --> 00:13:52.446 so we have many many translations
NOTE Confidence: 0.84727836

26
from lab to clinic programs and these are great opportunities for specimens to work with industry for new drugs. We these things will only survive if we have alliances with the outside next slide. So I just want to give one example today and I know iris on the phone and he’s going to speak. Actually took a course at Rockefeller University as a student when he was a guest lecture. Of course, IRA has a history with Yale, so I was approached nine years ago.
NOTE Confidence: 0.82979816
00:14:22.938 --> 00:14:25.078 ago with a drug called MPL 3280.
NOTE Confidence: 0.82979816
00:14:25.080 --> 00:14:27.468 It was a PDL one inhibitor.
NOTE Confidence: 0.82979816
00:14:27.470 --> 00:14:28.825 We already knew that these
NOTE Confidence: 0.82979816
00:14:28.825 --> 00:14:29.909 drugs sort of work.
NOTE Confidence: 0.82979816
00:14:29.910 --> 00:14:31.566 The PD one inhibitors cause Mario
NOTE Confidence: 0.82979816
00:14:31.566 --> 00:14:33.159 his office right across the Hall,
NOTE Confidence: 0.82979816
00:14:33.160 --> 00:14:35.128 but we studied this drug and you can
NOTE Confidence: 0.82979816
00:14:35.128 --> 00:14:37.227 see on the left you know activity.
NOTE Confidence: 0.82979816
00:14:37.230 --> 00:14:38.540 You know your complete response
NOTE Confidence: 0.82979816
00:14:38.540 --> 00:14:40.434 in a patient but will yell was
NOTE Confidence: 0.82979816
00:14:40.434 --> 00:14:42.036 able to offer along with many
NOTE Confidence: 0.82979816
00:14:42.036 --> 00:14:43.459 colleagues from around the world.
NOTE Confidence: 0.82979816
00:14:43.460 --> 00:14:44.924 It was a multi national study
NOTE Confidence: 0.82979816
00:14:44.924 --> 00:14:46.689 but we were able to get biopsies
NOTE Confidence: 0.82979816
00:14:46.689 --> 00:14:48.397 and this was the work of Katie
NOTE Confidence: 0.82979816
Poletti and Scott Gettinger and others so we could actually define the adaptive immune response. So I think if we hit one more time so we actually could see what happened in a patient that. Responded but we also could see what happens in patients that didn’t. And you know, this was an important observation. Working closely with Iran, the team danshen this was actually published in nature and it really defined some of the parameters of immune resistance and now of course the challenge is to use this
knowledge in the future prospectively with combinations of agents, and that’s something we’re doing right now on the next slide. And we had the opportunity to take it further. So then, you know, as a lung cancer investigator and having a very robust long group, you know doing phase three all the way from phase one with a spore. As I mentioned, we were the lead site for this trial. The empower 110 trial which actually look at this drug and PDL 3280
became a Tesla Zimride compared with chemotherapy and this trial if we hit again this trial just recently reported in the New England Journal of Medicine two weeks ago was a positive result and actually resulted in the drug being approved in the frontline setting. The reason I showed this, if we go to the next hit is we will look at some of the different PDL one markers in this. So we were able to move one metal up. It wasn’t the first drug approved in this space the 2nd but were able to look at SP142 and 22C3 which are
different biomarkers but even more critical not known to many on this call.
Kurt shoppers now working with these specimens with some amino quantitative studies that he’s developed here at Yale.
So now we have randomized data that we can look at even more exploratory biomarkers and then on the very final slide we’re anxious to work with all of you. No, here this is very interesting story. I forgot to put this in. This is looking at tumor mutational burden. This is blood based tumor mutational burden as done by Foundation.
Medicine and you can see when you have TM be greater than 16. You can see that in this trial. That's a predictive marker with significance for activity. For intensive over chemotherapy. So new markers being developed. So then on the next slide. This is what I, my final slide. We have a whole office of Translational research and this actually expands now throughout the Cancer Center 'cause we work with other teams but with Ed we've really built this office where
00:17:05.182 --> 00:17:07.152 we have the ability to bring these proposals in and then to execute you.
00:17:08.990 --> 00:17:10.908 It’s very easy to make the deal, but to actually execute on the deal is important so I’ll stop there.
00:17:14.490 --> 00:17:15.860 Happy to answer questions later.
00:17:15.860 --> 00:17:17.510 Anxious to work with as many collaborators as makes sense.
00:17:18.610 --> 00:17:19.160 Thank you.
00:17:20.370 --> 00:17:22.146 Right, thank you. I’d like to introduce the next speaker ehrenring.
00:17:22.146 --> 00:17:23.920 He’s an assistant professor of email biology, one of the most creative minds I’ve met.
00:17:31.031 --> 00:17:33.292 we have here, Aaron, you have some
very interesting things to describe.

Please please proceed.

Yeah, thanks so much Mario.

So the focus of my research is to use structure based protein engineering to develop pharmacological tools that we can use to dissecting probe complicated immuno regulatory pathways.

That’s a mouthful.

I should say what we’re really primarily focused on are these proteins called cytokines, which are small hormone like molecules of the immune system have exerted very powerful effects on nearly all aspects of immune
Physiology and biology is really cool, but what’s really important in the context of cancer? Is the study kind for the very first agents that prove the principle that the immune system could be a target of cancer? And that’s evident from this very seminal report on the activity of high dose interleukin two and Melanoma, and you can see that a small fraction of patients actually had very durable responses. In fact, you could call them cures and you see that first tail in the survival curve, and I’ll just note that you know a major leader in this work was.
of course, our colleague, my good friend Mario snow. You know who’s been leading the way so we can advance the next slide, please. So in the past four years, my lab has gotten really interested in one particular cytokine, called Interleukin 18. What makes this study kind compelling is it has really strong activities in vitro in a dish on two key cell types. Tumor infiltrating T cells, which recognize specific tumor antigens in are proven to be some of the most important, if not most important targets.
NOTE Confidence: 0.8315963
00:19:07.105 --> 00:19:08.218 in cancer immunotherapy.
NOTE Confidence: 0.8315963
00:19:08.220 --> 00:19:09.261 I liked it.
NOTE Confidence: 0.8315963
00:19:09.261 --> 00:19:10.996 Also stimulates another class of
NOTE Confidence: 0.8315963
00:19:10.996 --> 00:19:13.040 cells called natural killer cells,
NOTE Confidence: 0.8315963
00:19:13.040 --> 00:19:14.084 which are emerging.
NOTE Confidence: 0.8315963
00:19:14.084 --> 00:19:15.476 As key immune effectors,
NOTE Confidence: 0.8315963
00:19:15.480 --> 00:19:17.045 particularly in the setting of
NOTE Confidence: 0.8315963
00:19:17.045 --> 00:19:17.984 immune checkpoint resistance,
NOTE Confidence: 0.8315963
00:19:17.990 --> 00:19:20.430 as Roy was just alluding to in the
NOTE Confidence: 0.8315963
00:19:20.430 --> 00:19:22.677 setting of image C Class one loss,
NOTE Confidence: 0.8315963
00:19:22.680 --> 00:19:24.558 if you can advance one click
NOTE Confidence: 0.8315963
00:19:24.558 --> 00:19:25.810 that was really shocking,
NOTE Confidence: 0.8315963
00:19:25.810 --> 00:19:26.102 though,
NOTE Confidence: 0.8315963
00:19:26.102 --> 00:19:28.146 as we dug into the biology violate
NOTE Confidence: 0.8315963
00:19:28.146 --> 00:19:30.643 teams that have been tried in clinical
NOTE Confidence: 0.8315963
trials before GlaxoSmithKline had taken it through a phase two trial of over 60 Melanoma patients. What they found was that it was very well tolerated for cytokine, but it completely bombed due to lack of Efficacy. Only one out of 60 patients had a partial response. So what we discovered in my lab is that the activity of Alateen is highly restricted by a molecule produced by tumors within tumors called Interleukin 18 binding protein.
This is an ultra high affinity inhibitor. Violating that binds. I’ll inhibit its ability to interact with its receptor on, till and NK cells. And so what we did is we use directed evolution to create a version of violating that was completely impervious to the decoy receptor, but was still able to engage with highlighting receptor on until and what we found in mouse models with cancer. This is a very close collaboration with Marcus Bosenberg in the Center for precision cancer modeling.
Is that just like in patients?

Natural wild type Interleukin 18?

That’s the blue survival curve here was entirely ineffective.

It had no ability to slow tumor growth or cure mice.

Where’s the decoy resistant variant?

Had single agent activity that could clear two well established tumors from the door to these mice with activity that was commensurate in fact a bit better than checkpoint immunotherapy.

We describe these findings in that recent publication in nature.
Earlier this summer.

Next slide, please.

Now, obviously we’re tremendously excited about the potential impact of the decor Resistant Valley Team D R18 in the clinic, and we particularly want to test it out here at Yale. We have such a leading phase one unit and an experience with set of kind of new therapies instead of that.

And I recently started a company called Simcha Therapeutics. We’ve raised over $25,000,000 to advance this molecule that was developed...
here at Yale into clinical trials, and I’m excited to say that there will be dosing the first patient in the first half of next year.

Next slide, please.

So finally I want to tell you about some emerging research in my lab.

We’re missing a slide, so I’ll just briefly mention it.

Here we go, which is that one more forward, which is that we’re not just interested in making pharmacologic tools drugs against the immune system, but we’re also really interested in developing technologies in profiling
the drugs that are naturally produced by the immune system. That is to say, antibodies in one thing that’s becoming increasingly clear is that immunotherapy doesn’t just affect T cells, but it also seems to be able to affect. Other branch of the immune system. B cells, and he moral immunity, and we hypothesize that that many cancer patients, particularly those true with immunotherapy, may be making protective anti cancer antibodies or antibodies.
that activate the immune system

and we want to learn from these clinical trials of nature.

Seeing what drugs patients made and potentially get ideas for new drug targets and potentially even new therapies from these patients and so that end we’ve developed this technology called Reprap index approach to management profiling that we’ve used to discover new auto antibody targets.

We’ve profiled extensively in autoimmune diseases like this one here shown called ape said, but we’re also now applying it.
00:22:41.432 --> 00:22:43.398 together with samples from the
00:22:43.398 --> 00:22:45.336 various spores that we have here
00:22:45.336 --> 00:22:48.269 at Yale of patients treated with
00:22:48.269 --> 00:22:50.785 immunotherapy in monitored longitudinally.
00:22:50.790 --> 00:22:51.190 So yeah,
00:22:51.190 --> 00:22:52.190 thank you for your attention.
00:22:54.930 --> 00:22:57.625 And thank you, that’s it’s amazing science.
00:23:00.330 --> 00:23:02.260 She’s a relatively recent recruited.
00:23:02.260 --> 00:23:04.395 Yeah, who’s using really fascinating
00:23:04.395 --> 00:23:08.236 work on circular RNAs and could lead to a
00:23:08.236 --> 00:23:10.678 potential new target for immune modulation.
00:23:14.970 --> 00:23:17.330 Hi everybody, I’m excited to great.
00:23:17.330 --> 00:23:19.836 Excited to tell you about my research
00:23:24.970 --> 00:23:27.330 Hi everybody, I’m excited to great.
program so we know that cells need to be able to recognize pathogenic RNA’s to prevent infection but also recognize their own self our days to prevent autoimmunity. And so my research program has two main questions. One we’re trying to understand where the molecular mechanisms for maintaining this vital balance and recognition of self, nonself and then also how can we capitalize on this distinction to develop new? Cancer therapies. And so we had. Discovered that you carry out excels, have a way to distinguish between foreign circular RNAs and self.
circular maze or circular RNAs. Are this newly discovered class of endogenous RNAs that are abundant and ubiquitous in eukaryotes? And so, with this distinction between foreign and sell circular RNAs, we hypothesize that we could engineer foreign circular RNA’s to be a potent vaccine event. And if you go to the next slide, please. We found that if we deliver born circular RNAs into mice and then challenged with cancer b16 Melanoma cells, we were able to protect the mice against those subsequent sort of initiation of
the tumor as well as growth of the tumor, and we’re excited to work with the Center for precision cancer modeling to continue to investigate one of the scope and effects of the circular RNAs as a cancer vaccine. Another area of my program is to understand what are the features of the circular RNA that allows a cell to distinguish between self and foreign, and we identify the specific RNA modification called N 6, methyl adenosine or M6 say. So we saw that self circular RNAs associated with these enzymes that
00:25:19.201 --> 00:25:21.769 recognize M6A or interact with M6A,
00:25:21.770 --> 00:25:23.414 whereas these foreign circular
00:25:23.414 --> 00:25:24.647 armies did not,
00:25:24.650 --> 00:25:28.026 and so we thought we could target the.
00:25:28.030 --> 00:25:31.735 An enzyme that installs this
00:25:31.735 --> 00:25:33.958 modifications next please.
00:25:33.960 --> 00:25:36.032 Next slide,
00:25:36.032 --> 00:25:37.068 please.
00:25:37.070 --> 00:25:39.950 And we saw that and breast cancer
00:25:39.950 --> 00:25:42.245 epithelial cells type 3 interferons
00:25:42.245 --> 00:25:44.797 were specifically upregulated when
00:25:44.797 --> 00:25:47.349 M6A modification is decreased,
00:25:47.350 --> 00:25:50.365 whereas type one interference are
00:25:50.365 --> 00:25:54.230 not changed and so next please.
00:25:54.230 --> 00:25:57.422 My program has been interested in both
00:25:57.422 --> 00:25:59.140
uncovering the molecular mechanism for how RNA modification controls an immune response as well as to understand if there are targets along that pathway that we can identify two to specifically target cancer cells. Thank you.

Great, thank you. I don’t think the next speaker needs any introduction. Doctor Who Saki has become world famous was before but now really very well known for all her work in COVID-19. She’s an outstanding immunologist and also has a research interest in cancer also Kiko, please, please go ahead.
Thank you Mario.

I’m delighted to be here.

So today I’m just going to start with this principle guiding effective cancer immunotherapy.

And I’m borrowing a page from Doctor IRA Mehlman’s cancer immunity cycle book as any one on this call probably has seen this but essentially just wanted to highlight that there are steps in immune surveillance and clearance of cancer that is not working very well and that’s Why.

People develop cancer and some of them are treatable with checkpoint
00:27:20.556 --> 00:27:23.146 inhibitors while others are not.

00:27:23.150 --> 00:27:25.904 So my laboratory has started to

00:27:25.904 --> 00:27:27.740 really examine these fundamental

00:27:27.821 --> 00:27:31.034 issues relating to all those stages of


00:27:33.210 --> 00:27:36.234 So the immune surveillance begins by

00:27:36.234 --> 00:27:38.890 dendritic cells within the cancer.

00:27:38.890 --> 00:27:41.404 Carrying the Antigen to the

00:27:41.404 --> 00:27:44.072 draining lymph node and that stimulates

00:27:44.072 --> 00:27:47.271 T cells that are specific to cancer

00:27:47.271 --> 00:27:49.903 antigens and those T cells can

00:27:49.903 --> 00:27:51.998 divide and become effector cells.

00:27:52.000 --> 00:27:54.534 They will migrate back to the site

00:27:54.534 --> 00:27:56.950 of cancer to infiltrate into that

00:27:56.950 --> 00:28:00.459 issue and that allows for T cells to

00:28:00.459 --> 00:28:03.039 recognize cancer cells through specific
antigen and clearance of the cancer.
Using cytotoxic mechanisms and of course, checkpoint inhibitors can.
Really engage in this whole cycle by allowing the effector function of T cells to occur more robustly.
Next slide, please.
So we began to sort of try to understand why this immunity cycle doesn’t work in most cases, and one of the issues that we tackled recently, which was this paper that published earlier this year, we discovered that the.
Lymphatics that are draining the brain, which is the monagea lymphatics. Do not drain that issue as well as other lymphatics found in the skin. For example by increasing the drainage through the meningeal lymphatics by introducing into the CSF or veg we can actually increase the immune surveillance and better priming for glioblastoma and also other brain meds and so this is so it’s driven us to in new technology we call in faxes where. Doctor Alan Ring and I are collaborating to make a better sort of more specific agent that can
stimulate the meningeal lymphatics to increase immune surveillance in clearance of cancer.

The other key issue is the antigen, so in addition to the mutation load that accumulates in cancer, there's also this other type of antigen that we're focusing on, which is the endogenous retrovirus which Anderson at Nosiness. Retroviruses are occupy 8% of our genome, and many of them have coding capacity, and many are mostly silenced.
after developmental stage.

Early developmental stage, but can be reactivated during oncogenesis and so we're targeting and what first identifying what kinds of endogenous retroviruses or reactivated in some cancers and targeting this using a new tool that we created called Earth map. And this is also an ongoing collaboration with Marcus Bosenberg’s group as well.

Once these energies are recognized by T cells, once these thank you, once these energies are recognized by T cells,
diesel still have to migrate back into the tumor tissue to perform its cytolytic function.

And what we’re trying to do is to encourage this process by stimulating the local micro environment using short RNA that stimulates free guy, which we call Stem Blue Barney SLR.

This is a collaboration with an appliance group here, and we’ve just formed a new company called Rig Immune.

Which is really inoculation of this LR into the tumor to stimulate not only T cell migration,
but also priming of tumor specific T cell and possibly Rick Kumanan clearance of this these tumors, and finally, in order for the checkpoint inhibitors to work in, you know privileged organs like the brain we are allowing those antibodies such as anti PD L1 to come into that issue using a BBB access technology we developed. We call synaxis an. It allows the baby to transient Lee open to enable any kind of macromolecules to come into the brain for transition time period
00:31:44.831 --> 00:31:46.570 for a better access.

00:31:46.570 --> 00:31:48.720 A better clearance of glioblastoma

00:31:48.720 --> 00:31:51.300 so I’ll end there. Thank you.

00:31:54.480 --> 00:31:55.880 OK, cool, thank you.

00:31:55.880 --> 00:31:57.993 It’s really outstanding science so it’s

00:31:57.993 --> 00:32:00.099 my pleasure to introduce our moment.

00:32:00.100 --> 00:32:02.550 He’s as you know, the vice president.

00:32:02.550 --> 00:32:03.978 Cancer immunology for Genentech.

00:32:05.049 --> 00:32:06.410 and biophysics at UCSF,

00:32:06.410 --> 00:32:08.867 but formerly before all of those was

00:32:08.867 --> 00:32:11.678 actually ahead of cell biology here at Yale.

00:32:11.680 --> 00:32:14.264 Higher first of all, let me thank you

00:32:14.264 --> 00:32:16.587 for agreeing to provide some comments.

00:32:16.590 --> 00:32:20.100 We just like to ask you to to give you.
Give us briefly your thoughts about challenges and opportunities in Immuno Oncology. Highlight those that you think might be might benefit from collaborations with. With academics for example.

Thanks Mario Dan Hyder. All my friends who there is been alluded to. I do have multiple connections to deal. In fact, we’ve spent probably well more than half of my adult life there, so I left back in 2007. Really for the purpose of trying to accelerate this field, feeling that what was really needed in the first instance was the
production of experimental agents that we could get into patients and sample what is actually happening. As a consequence of therapy, in order to understand it. As I think I often find myself saying the only model for human cancer is human cancer in the end, and it’s not to say that you can’t learn many critical things from mice, but if you actually want to reduce to practice what it is you’re trying to do in the laboratory, you need access not only to patients,
but to experimental drugs that you can actually perform. These types of critical studies in patients. And it turns out that that's a very difficult thing to do in academia. And moving to a biotech company. Large one is genetic really provided that opportunity. So that's something that the companies do well and I think one reason I chose or took the opportunity to move to Genetec as opposed to other places was because it is a very highly researched based place. In other words, we are as serious I think as you are.
or I was well also faculty member in pushing the field of basic research. Particularly in this area, as as anyone. Part of that was to try and breakdown. With biomarker studies understanding what the various steps in cancer had to be overcome in order to generate a productive immune response, and so called cancer immunity cycle. Now, OK, we've done that. We have a variety of agents in the clinic.
and they’re starting to study them. These range from the checkpoint inhibitors such as the PD one, blockers that Roy Herbst is already brought to your attention and everybody already knows. Second generation checkpoint inhibitors. The one that we have advanced in something called Tigit. We seem to be performing quite well in the clinic thus far in a variety of indications, but I think more importantly, the next major goal is going to be to address those patients. As Akiko was saying,
that do not exhibit much in the way of response to checkpoint inhibitors. In order to do this, you need to have a holistic view of various steps and potential rate limiting steps that impede the progress of an immune response in a cancer patient. The one that I think we find. Most daunting at the moment. Certainly the most common is found here between steps 5 and step 6, which is the egress of tumor reactive T cells. Or other cells from the blood got into the tumor because most
tumors are not just sitting there
NOTE Confidence: 0.834624588
waiting to receive these cells,
NOTE Confidence: 0.834624588
but rather are invested by a highly
NOTE Confidence: 0.834624588
immunosuppressive and physical blockade
NOTE Confidence: 0.834624588
in the form of the Peri Tumoral Strama,
NOTE Confidence: 0.834624588
which basically Christy
cells and inactivates them.
NOTE Confidence: 0.834624588
So I think one of the major scientific
NOTE Confidence: 0.834624588
challenges we have is to how to
NOTE Confidence: 0.834624588
overcome that stromal barrier,
NOTE Confidence: 0.834624588
and by doing so,
NOTE Confidence: 0.834624588
we feel we can probably unlock.
NOTE Confidence: 0.834624588
The benefits of even just first
NOTE Confidence: 0.834624588
generation checkpoint inhibitors to
NOTE Confidence: 0.834624588
as many as 50% more cancer patients
NOTE Confidence: 0.834624588
than are currently being addressed
with just checkpoint inhibitors alone
or in combination with chemotherapy or other types of targeted therapy.
Now this is where the partnership comes in because.
To add a company, we don’t have a medical school or a hospital and less.
Happened to be in a John Le Carre novel which didn’t workout too well for them.
But traditional relationship between companies and academic institutions is to fill that gap.
In other words,
when trials are run of new
investigational agents, they run at hospitals. To a first approximation, those hospitals are in academic centers, but that’s again a really one way relationship that allows you to generate some important clinical data on the Efficacy and safety of a new agent, but doesn’t really allow anybody to learn very much. That can only be done by having a joint enterprise that is still as committed to pushing forward and understanding the science that underlies all of these events. And do that in partnership.
Where where on the company size early on the genetic side we can bring to bear many assays and resources and insights that we’ve gotten from our experience by treating thousands and thousands of cancer patients with these agents, together with the rare and insightful scientific insight that one can find at a top academic institution, and they all certainly for us. Is it’s always at the top of the list and not only because of my own filial loyalty, but simply be cause the focus on
immunology and how that interfaces with human biology at Yale has really emerged over the last 10 years or so is really being quite. Quite inspiring and I also find it much more easy to deal with the culture and the commitment of the faculty and the administration to actually advancing these types of studies. Then I find in many of our other partner institutions where often unfortunately one finds a variety of roadblocks. So I think you know, Yale provides a really good substrate to actually get these kinds of studies done.
What’s needed is to get together on the types of samples that are needed, what types of analytics are required, and then in the matter of any good collaboration each party brings to the table what that party is best at doing. And in our Case No. We believe we have a lot of science to offer, not just support and funding, and in your case certainly got more than just patients to offer. There is a enormous amount of as I said, scientific expertise and insight that. Will turn out to be critical. I think to solving these various problems.
So with that I think I probably end my remarks and continue on to the next element.

Alright, thank you very much and thank you for the kind words.

Let me please invite all the panelists to turn on their microphones in their videos and I want to remind all the attendees to please submit your questions through the chat feature.

I might just start.

I see a couple of questions, but I might just start with just a challenging question to the panelists and any Body can take this.

What do you think we've,
you know, as you know, the problem in the clinic is that a subset respond to anti PD one and PDL one few combinations. The majority of patients don’t respond obviously although we’ve made enormous progress. What do you think we’ve learned from mechanisms of response to anti PD one or video one that would drive? Future targets future development. Maybe I’ll start with that one if that’s OK, Miro and I’ll let others jump in. So I think you know it’s been a bit frustrating on those fronts in that.
Mechanisms of resistance have been determined, one of which is loss of MH C Class one or reduction of MH C Class one through a variety of mechanisms. You know there are some. You know reasons why that you’d think that might not result in an resistance, because natural killer cells might be able to kill those tumors without that inhibitory signal. I’d like to highlight for those of you haven’t followed Aaron rings, I’ll 18 story that this is one of the few therapies that’s actually effective on both class one proficient in class,
one deficient tumors,
but that’s still a pretty small minority of cases.
I think there are also issues with.
Low mutation burden.
Lack of antigenicity.
I think I referred to T cell trafficking
as well and the reasons why T cells
traffic and actually I would say
that as a pathologist we don’t know
if T cells were there and then left.
We typically get one snapshot
and we you know,
we know that they’re not there when we look,
but I think there’s a number of things
that we just simply don’t understand about how anti cancer immunity happens even to the level of our the till are the cells that are in the tumor. Actually what’s responding to PD one blockade? Or is it? Something outside of that, and those are pretty basic questions. I think that’s where yell could help others workout how these things work. So I think the mechanisms of resistance are still need quite a bit of work. If you do any of you think that there’s a, how would we approach those low mutation tumors that the tumors that have load
the mutation burdens may be endogenous?

Retrovirus would be a target, but are there other targets? Or will we eventually need to isolate out rare specific T cells and clone out the T cell receptors?

What do you think are the approaches to address those?

Those types of tumors? Akiko, maybe I can ask you to address that, since you are the world expert on an 8 immunology. First there has to be some sort of
antigen that T cells can recognize

unless we go into the NK type of therapy

that Aaron might want to comment later.

But but you know what?

We are kind of not looking at is

really the endogenous retrovirus.

Sodium in the cancer,

and whether those are many,

are coding capable sequences

that are dysregulated and up

regulated and expressed in cancer,

and so right now what we're

trying to do is to elude the

peptides from the MHC of cancers.

Different cancer cells.
You and I are actually collaborating on this project so we can actually identify if there are peptides that are derived from herbs that can become target of T cell recognition. And can we? Take advantage of that. And methods to upregulate those antigens? I guess you’re also working on it. Yes, Marcus. I’m going to take a question from the audience intermittently, as we’re addressing these questions. One was are there treatments coming along for glioblastomas? Now? I’m not a glioblastoma expert, but akiko.
I'll just turn that over to you because I think your research address is perhaps one of the bigger problems in glioblastoma.

Right, so glioblastoma, unlike other non brain tumors, have an extra layer of challenge, which is the very little immunosurveillance that's occurring in the brain due to a limited drainage by the meningeal lymphatics. And the fact that you know, you know priming T cells and T cells are not migrating into the tissue either. So one of the ways in which we're trying to overcome this is to increase immune
surveillance by injecting veg FCI. Referred to that in my slide and we’re calling it lymph axis and essentially to increase the drainage. An stimulation of T cells against you manage and in the draining lymph node. And once that happens, these diesels can migrate back into the brain. And tackle the CIMA. It obviously works well with checkpoint inhibitors as well, so and we’re also collaborating with Aaron’s lab to make a better reagent that can more specifically stimulate
visit for three to be able to do this efficiently without any side effects. So that’s one possible way that we’re trying to tackle this issue. That’s excellent, Roy maybe. Yeah, I was wondering if you could address the brain tumors for also that maybe that could be a project in this war actually, but but other other approaches not only within immunology but also to mention that there other Yale engage. sessions with other approaches. to glioblastoma is also right. Well, there is this more group and they are studying.
that and I think he goes.

Approach would be a good one,

but I did want to mention Mario was

the need to personalize immunotherapy

and I think we’re right on the

precipice of doing that in a place like

yellow should be able to do that so.

We already heard that you know,

if you don’t have MHT one or you don’t

have the adaptive immune response,

and that’s being shown for 456 years now.

But what do you do if you have a cold tumor?

If you have a tumor that doesn’t have HD one,

no capability had a paper on that.

It’s about 5% of lung cancers,
so I'd like to propose that you
know what we need to do is we need
do dissect tumors out, you know.
And just like we would profile
a tumor in genetically,
we need to profile the immune
microenvironment and these cold tumors.
These tumors that might not be driven.
PDL one or perhaps ticket is involved
as we heard tomorrow we need to start
thinking about the right combinations,
but you know the biggest problem
is we're just flying blind and
the clinical world will do. That.
Will go on for years if not stopped.
You know just combining different
00:46:40.605 --> 00:46:41.785 drugs and using them,

00:46:41.790 --> 00:46:43.827 but I think you know right now

00:46:43.827 --> 00:46:45.933 it’s a perfect time and you and

00:46:45.933 --> 00:46:47.395 I have talked about this.

00:46:47.395 --> 00:46:49.165 It’s very complicated in refractory setting.

00:46:49.165 --> 00:46:50.345 Someone gets chemo immunotherapy

00:46:50.345 --> 00:46:51.230 and then refractory.

00:46:51.230 --> 00:46:52.886 There could be thousands of different

00:46:52.886 --> 00:46:54.344 mechanisms put in the frontline

00:46:54.344 --> 00:46:55.544 setting primary resistance and

00:46:55.544 --> 00:46:57.420 we know that with Ateez Alisme,

00:46:57.420 --> 00:46:57.996 Abbott Pembrolizumab.

00:46:57.996 --> 00:46:59.672 Half the patients about will respond

00:46:59.672 --> 00:47:01.528 when you have the high PD L1 Group,

00:47:01.528 --> 00:47:02.456 the other half don’t.
I would suggest that the group to look for some of the mechanisms we've heard about today. I can't wait to get my hands on Aaron's drug, you know, and look at that and things like that. You know, maybe I can ask her to comment, because obviously that's a major. You need to know what the mechanisms of resistance are in Biomarkers for development of your drugs. So how do you approach that internally? And also in collaboration with academic institutions? I think you know the problem of resistance has even a
00:47:32.639 --> 00:47:34.167 darker aspect to it,
00:47:34.170 --> 00:47:36.080 which is we don’t really,
00:47:36.080 --> 00:47:38.655 truly understand the mechanism of
00:47:38.655 --> 00:47:41.760 why things work when they work.
00:47:41.760 --> 00:47:43.720 Someone’s were diluted to this,
00:47:43.720 --> 00:47:45.670 but our understanding of how
00:47:45.670 --> 00:47:47.230 these checkpoint inhibitors work.
00:47:47.230 --> 00:47:48.794 Even Witcher vision Lee
00:47:48.794 --> 00:47:50.749 was framed by off bias,
00:47:50.750 --> 00:47:53.806 all based in the series of assumptions as
00:47:53.806 --> 00:47:56.616 reversing this process of T cell exhaustion,
00:47:56.620 --> 00:47:58.575 thereby acting in the tumor
00:47:58.575 --> 00:48:00.139 to reactivate T cells,
00:48:00.140 --> 00:48:02.870 either certainly is not the whole story.
00:48:02.870 --> 00:48:04.825 In fact, maybe only marginally
true in some patients.

So if in fact the PD one PD, L1 or Tigit Axis along with simulate 4C28 Axis.

Full works in lymphoid tissues to expand the T cell compartment. Then that means we have the entire mechanism of how PD one blockade works. Not quite right if not incorrect. If that’s the case, it’s very difficult to know how to improve upon that or how to understand resistance mechanisms. If you don’t really know the mechanism of immune mechanism that Modulated as a consequence of your drug.
So I think it’s important to.
You know, even just as a basic science project,
be sure that we really understand
that all of the predictions associated
with a presumed mechanism of action
are actually correct before we
can really understand resistance,
and you know.
That said, there’s certain aspects of
resistance that are that are
finding increasingly important.
We’ve invested very heavily
in tumor antigens,
particularly mutant knew antigens as well as.

Endogenous elements that Akiko is setting.

Chloe Arbiser line elements and transposable elements as potential antigens, 'cause they certainly a great antigens in mice, but we find that you know the context of our vaccine programs you see as significant debilitating amount of MSE loss.

Sometimes it’s a hard loss which means loss of heterozygosity for particular MA serial. Other times it means soft loss which is just simply transcriptional repression.

And you need to workout computational workflows so that you could
actually examine patients on a patient by patient basis to find not only what the range of antigens are that they’re making, so that you can design an appropriate Vaccine in fact, that was that’s your goal. Or design an appropriate type of cell therapy, but also to know how that patient is reacting, whether the patient responds or doesn’t respond at the genetic level in the tumor in terms of whether transcriptional patterns are different
00:50:21.251 --> 00:50:23.699 that now create a resistance environment,
NOTE Confidence: 0.8751713
00:50:23.700 --> 00:50:27.408 perhaps by losing irrelevant MSE molecule.
NOTE Confidence: 0.8751713
00:50:27.410 --> 00:50:29.510 Or again bye bye genetic loss,
NOTE Confidence: 0.8751713
00:50:29.510 --> 00:50:31.960 which is something that the tumors do.
NOTE Confidence: 0.8751713
00:50:31.960 --> 00:50:34.606 Unfortunately very very well and has been
NOTE Confidence: 0.8751713
00:50:34.606 --> 00:50:37.628 a real problem even be targeted therapies.
NOTE Confidence: 0.8751713
00:50:37.630 --> 00:50:38.602 So you know,
NOTE Confidence: 0.8751713
00:50:38.602 --> 00:50:38.926 again,
NOTE Confidence: 0.8751713
00:50:38.926 --> 00:50:41.968 I think this type of work can really only
NOTE Confidence: 0.8751713
00:50:41.968 --> 00:50:44.850 be done on a patient by patient basis,
NOTE Confidence: 0.8751713
00:50:44.850 --> 00:50:47.279 and it’s not something if we use
NOTE Confidence: 0.8751713
00:50:47.279 --> 00:50:49.330 clinical sites just to run trials.
NOTE Confidence: 0.8751713
00:50:49.330 --> 00:50:51.730 And if you use us just to give
NOTE Confidence: 0.8751713
00:50:51.730 --> 00:50:54.139 you drugs to run clinical trials,
NOTE Confidence: 0.8751713
00:50:54.140 --> 00:50:55.860 that’s not going to work.
NOTE Confidence: 0.8751713
00:50:55.860 --> 00:50:57.930 That’s not new advanced the field.
I think there really does need to be.

An interface which is developing but really needs to be.

Advanced around the science, even forgetting about the clinical development issues for the moment, but just, you know, really concentrated on the science that that is controlling response and lack of response, either as primary resistance or acquired resistance.

Thank you, I mean, you know. Obviously I followed your work obviously I followed your work about the way PD one worked and
the effects on CD 28 signaling,
and there’s been a lot of data about
the need for new for it’s the early
stem cells that are generating the
anti tumor response and not the
terminally differentiated cells.
There’s a lot of data out there that
makes the whole mechanism of how anti
PD one works relatively confusing,
but I just want to address maybe
a couple of issues ’cause we have
some expertise on the panel,
one based on errands,
work on our 18 and again going back to Akiko.
And maybe grace on on innate immunity.
How do you?
How do you view the in patients who lose class one and maybe don’t have a lot of T cells? How do you think that we can Co opt innate immunity to treat those patients? Let me just start with them because I think he has some interesting data with I’ll 18 and it may be good at Grayson Akiko and see what their thoughts are about this. And this is obviously a topic that here at Yale, we have a really keen an intense interest. You know from some of the initial observations that that loss of
beta 2 micro Glenn was for current theme of patients who acquired secondary resistance immunotherapy. So Marcus and I have been working on this problem looking for preclinical agents that could treat mouse tumors where we have deleted MHT class one or take tumors that naturally have loss of other components like tapasin. As well and then we see you know, Immunological dogma is that NK cells should recognize these cells that have lost image C Class one this marker itself. But we know that the truthfully NK cells,
particularly the tumor micro environment, become rapidly energetic or exhausted, depending on what terminology want to use. This is work by David Relay and others. And so it is clear preclinically that we can reinvigorate some of those NK cell response. But we started kind therapies. Others have started to use. Agents against NK cell receptors, like agonists of the NK G2D. That’s like sort of as best you could say, TC are equivalent and NK cells or inhibiting key receptors like the anti NK G2A. That’s the Mona Lisa map drug. It actually has some activity when
combined with monoclonal antibodies.

I think one thing that is underexplored, but it’s going to be a major challenge in harnessing NK cell activity, particularly against these tumors.

Last class one is a lot of these preclinical models and work guilty of it here at Yale are not amino edited. So in the same way that tumors become amino edited against T cells they can become Immuno edited against NK cells.

In loss of self antigens is not enough to drive killing.

Lots of markers himself like image C Class one is not enough to drive killing.
You need other signals. NK, activator signals antagonist signals in tumor cells appear to edit those out. For a great example of that has been seen in lymphoma where we know that class one loss is common. But what usually occurs almost always is loss of CD 2, which is an important molecule that drives NK cell killing, and so I think really we need to think about how can we do more than just this inhibit or activate NK cells. But how do we really direct the
00:54:40.001 --> 00:54:40.607 tumor engagement?
NOTE Confidence: 0.7817753
00:54:40.610 --> 00:54:42.344 I think there’s some really exciting
NOTE Confidence: 0.7817753
00:54:42.344 --> 00:54:44.259 programs like the dragon fight programs,
NOTE Confidence: 0.7817753
00:54:44.260 --> 00:54:44.942 monoclonal antibodies.
NOTE Confidence: 0.7817753
00:54:44.942 --> 00:54:47.670 Of course we’re good at that and something
NOTE Confidence: 0.7817753
00:54:47.731 --> 00:54:49.723 that we really keenly have our eye on,
NOTE Confidence: 0.7817753
00:54:49.730 --> 00:54:51.266 something that Marcus and I are
NOTE Confidence: 0.7817753
00:54:51.266 --> 00:54:53.125 working on at the Center for
NOTE Confidence: 0.7817753
00:54:53.125 --> 00:54:54.286 precision cancer modeling.
NOTE Confidence: 0.8589774
00:54:55.840 --> 00:54:59.116 And Grace, What do you think about your rig?
NOTE Confidence: 0.8589774
00:55:01.660 --> 00:55:03.480 Y eah, I think these are really important
NOTE Confidence: 0.8589774
00:55:03.480 --> 00:55:06.224 questions and highlights the point
NOTE Confidence: 0.8589774
00:55:06.224 --> 00:55:08.076 that I read brought up about coupling
NOTE Confidence: 0.8589774
00:55:10.225 --> 00:55:12.499 the basic science with the translation
all aspects right because we think that there are potentially new types of science that’s happening within different types of immune cells, either in response to new antigens or under normal conditions, and that would be important to understand. So, for example, there’s pulmonary evidence that RNA modifications, specifically the N6 methyl adenosine that I mentioned. The levels are different in, you know, cancer situations versus healthy situations and that they change in.
different types of immune cells.

So given that Arnie modifications is like an epic transcriptomic regulator, it controls all sorts of different aspects and within a cell.

M6A has been shown to control the transcript stability as well as its cellular localization, as well as its ability to be translated. So we have data showing that depending on the level of M6A, the Genomic Architecture is different, and the Genomic confirmation then affects the types of transcripts and subsequently the proteins that
could be expressed from those transcripts and stuff we can identify. Key aspects that are differentially changing between cancer states or healthy states and or the different types of immune cells in a cancer state. Potentially, we have new targets to then go after in sort of difficult situations. Let me let Akiko and Marcus comment 'cause I know this is an area that's become a substantial interest to us, including the myeloid component. So maybe you can comment a little bit on that. Akiko and Marcus.
Thank you so since the NK issue is so nicely covered by air and I’m just going to sort of mention another thing that it’s fundamental to immuno oncology Ann yet really hasn’t garnered enough attention, which is the sort of immunosuppressive state. Of tumor burden and this I learned kind of, you know, through experiment. So the rest of my lab does antiviral immunity, and so we’ve been looking at what happens to antiviral immunity in mice that are bearing tumors an they are really immuno suppressed. They cannot generate diesel immunity. In case else you know their dendritic cells are wacky.
So I think before we can even start thinking about how to improve immune oncology, we have to deal with this impact of tumor burden and what it’s doing to the immune system. I don’t think we understand that very well. Or maybe I’m just being ignorant, but I feel like that’s something we need to deal with no matter what the immunotherapy is going to be in order to really elicit a robust immunity against tumors.
Sure, yeah. I think it’s really interesting.

IRA also had kind of touched on this to talking about how I mean 1 version of MHT class losses, sort of by allelic beta, two microglobulin loss and everything is gone and you expect NK cells perhaps to hit those, but it’s probably more subtle than that. Frequently have specific MHT class, one alleles or even specific antigens that are really important. Antigens that are lost and it’s really hard to know how that happens along the way, but I think one of the things that’s been surprising too. I think many immuno oncology field.
Is the demonstration by a lot of different approaches that interferon gamma reception or interferon reception and tumor cells is really critical for being able to be killed by the immune system? And it seems that one of the principle things that that does is upregulate MHC class one in the tumor cells so the transcriptional regulation of MHC class one in tumor cells is really really important and some of the approaches that people have been referring to with innate immunity and even things like cytosolic nucleic acid sensing like Regai agonism.
And things like that were in our hands.

Irv reactivation is great at Reactivating.

You know interferon secretion and sometimes type.

One interferon can substitute for Interferon Gamma at least an upregulation of MFC Class 1 SI think things that are locally going to be inducing the T cell tumor cell interaction in that fashion.

An override whatever local immunosuppressive effects that are there will really be critical.

I think one of the difficulties that we’ve had.

In studying.

The tumor microenvironment is that
it's been very difficult. For instance, I mean T regs have a very well established role, but other aspects, like whatever versions one will call different MD. Yes, sees things like that, so myeloid derived factors that can be suppressive than tumor environment or hard to entirely get rid of in most contexts. And you can’t really study them adequately in human. So I think their roles an exactly what they’re doing has been harder to determine,
but.

I’d refer back to some comments about the personalized immunotherapy and how you know, with these explant assays you can actually do these things and we can keep tumors alive for over a month with all the sto kiamat re preserved and one could reconstitute tumors to take out my load components. So I think I’m very enthusiastic about this approach to actually evaluate how different cell types contribute to localized immune suppression, which hopefully will lead to mechanistic advances, an understanding.
Let me just ask you one more question before I want to turn out back to Iran. Ask him a couple of questions but the do you think that there’s a role for purely non T cell dependent mechanisms in cancer treatment? Do you think that we could without getting any T cell response, activate NK cells, myeloid cells, macrophages in a sufficient way or modulate their function that you could see significant anti tumor activity in the clinic? I think you know there’s a couple examples, so at the NK approaches, ankhar.
NK and things like that, I think that it is likely to be possible to do that. Other things that, for instance, one of our researchers here at Yale Allies, who is looking at using Carty with myeloid cells, like with basophils, another Excel types, and that this approach might be really could work well, and that’s oppressive pathways. Might not actually work as well against a non T cell because that’s typically how the suppression would be expected to work. I think there’s still some work.
to be done in those areas,

but you know I’m open to the possibility that other things can work and I think it’s worth.

Pursuing it based on the preliminary data that you’re seeing in those areas. So I am enthusiastic about that.

Interesting, so I just want to ask you a question you know you lead development in a company and I wonder you know that when you look at combinations, all the combinations that we’ve done. One is not overwhelmed by the by the level of activity that’s been observed. Maybe it’s because we don’t
01:02:23.125 -- 01:02:24.377 have the right biomarkers.

01:02:24.380 -- 01:02:26.200 Have you taken home any any lessons

01:02:26.200 -- 01:02:28.276 from the the three that seemed to

01:02:28.276 -- 01:02:29.821 have worked CTA for chemotherapy

01:02:29.821 -- 01:02:31.599 and veg receptor Inhibitors,

01:02:31.600 -- 01:02:33.616 which seem to be the ones that

01:02:33.616 -- 01:02:36.000 are sort of at the forefront now,

01:02:36.000 -- 01:02:37.256 notwithstanding the early Dec

01:02:37.256 -- 01:02:39.140 with digit but but but those?

01:02:39.140 -- 01:02:41.024 Those seem to have sort of

01:02:41.024 -- 01:02:42.280 moved to the front,

01:02:42.280 -- 01:02:44.512 which are not the ones that other than

01:02:44.512 -- 01:02:47.013 CTA four chemotherapy and the veg F

01:02:47.013 -- 01:02:48.888 Receptor Inhibitors would have been.

01:02:48.890 -- 01:02:51.095 The top ones on my list 10 years ago.

01:02:52.640 -- 01:02:54.616 No, you’re actually right.
Mario. I mean when we decided to go into using chemotherapy. Theoretical pieces for that was not well, Gee, maybe some of them if they’re not. Therefore, blade, if you can choose those properties, maybe they’ll cause some type of information or immunogenic cell death that will somehow synergized with immunotherapy. I think that’s turned out not to be the case. That my guess is now. No looking having book for epitope spreading and. Expansion of TC Arts Fonality and stuff. In lot of these patients.
I just think that’s an additive effect that you get a certain amount of tumor debulking associated with chemotherapy that then allows the immunotherapy to do what it’s going to do almost separately.

So I think that the idea that at least most conventional chemo Immunotherapy combinations are synergistic. That’s that’s still waiting for good evidence that case of.

Antagonist is an interesting one where I think that is. That’s one of the examples where I think we really need to look into that. From a mechanistic POV in HTC for example,
the that particular combination is really quite effective from surprisingly so, especially considering that in renal it’s not. So what’s with that? Because both of the system app on it by itself is supposed to have. Activity and in both of those indications, so I take that to suggest that it’s not necessarily an additive phenomenon there, necessarily an additive phenomenon there, but there’s something that specific that’s going on in ACC that is being addressed by the definition, which could actually have to do with myeloid cell suppression or
overcoming mile itself suppressions, and certainly by Jeff is one way that one can use to turn off dendritic cell activity and antigen presentation, so perhaps. That’s slowing down what aspect of the problem. So there again, is just a plea for saying, You know, we need to look into that from a mechanistic point of view, better than we have thus far. In terms of no future combinations. My. What I keep trying to push is to take a mechanistic approach, look at the tumors and figure
out what’s wrong with them.

What is the rate limiting step here?

What is the rate limiting step there and then try and pick apart mechanisms associated with them, and I think it increasing number of cases.

It does look like the myeloid compartment is playing a. Important, but as yet poorly understood, role in a lot of this, and I think it’s more than high time to go back and look more seriously at the myeloid compartment. The whole field of so-called mileage.
derived suppressor cells that I think is, still very very sketchy in terms of the precision with which those cells are described. What they do and who they are and how to modulate them. So I think we have to kind of back off in some way, at least as scientists and understand the basic immunology and cell biology before really designing and knowing precisely what agents to bring forward in the interim. Obviously we don’t as. Conditions don’t want to wait around for the basic scientists.
01:06:33.889 --> 01:06:35.830 to figure it all out for us,
01:06:35.830 --> 01:06:38.548 assuming that they’ll even do that.
01:06:38.550 --> 01:06:41.398 But agents are coming out all the time
01:06:41.398 --> 01:06:45.120 and I think crafting combinations of them,
01:06:45.120 --> 01:06:47.310 which I find in companies,
01:06:47.310 --> 01:06:49.938 is often akin to just throwing
01:06:49.938 --> 01:06:51.690 spaghetti against the wall.
01:06:51.690 --> 01:06:54.798 Still has to be.
01:06:54.800 --> 01:06:57.334 In a fashion that has some some
01:06:57.334 --> 01:06:58.840 logic associated with that,
01:06:58.840 --> 01:07:01.129 and I think that’s that’s a struggle
01:07:01.129 --> 01:07:03.439 in both of our communities to
01:07:03.439 --> 01:07:05.947 just keep people from doing stuff
01:07:05.947 --> 01:07:08.482 because it can be done and instead
01:07:08.482 --> 01:07:10.610 spending your time and effort and
the commitment of patients to doing those things that have the best chance of working based on the science as we currently understand it.

Thanks, Alright, I’m glad you mentioned mileage, so you’re interested. Also were very interested. I think Marcus is prioritizing. That is one of the areas of research for the El Senor de mean onkologie and we have. You know, we can’t bring everybody onto the phone conversation. We have a lot of expertise here in immunobiology,
in that area that again we just can’t fit everybody into one hour and a half session. 

So I just want to maybe just turn to Roy for a second before you go back to more of the basic science. 

Well, there’s a question about rare tumor initiatives, so I wanted to ask you 2 questions. 

What do we do about rare tumors and what? What are the efforts that we have? And the other question that I have for you is, you know.
where?

Where do you think the field is headed in lung cancer?

For Immunobiology and even on Koleji.

Well, the second question is a lot easier for me to answer than the first rare tumors we send them to Pat Larusso in phase one.

So we know where we’re growing.

You know, the yell when I row is the director of the deputy director of science.

You know we’re seeing a couple of 1000 patients now.

We have about eight 9000 a year and we have a large number of care centers 15 around the state,
so we are seeing you know, like sarcoma is an issue. You know we see enough of those now that we probably need to form more certainly even more rare tumors. You know, skin tumors you know you see some of those, right? Merkel cell tumor approved. You know agents so as this happens, we’re getting to do more and more of that where we’re at the point now. We’re probably going to have to set up an unknown tumor clinic or something for the everything else,
'cause we’re seeing more and more of that.

And we are moving towards a tumor agnostic, you know, sort of treatment with some of these agents. You know, the Pember Lizum app was just approved based on AT MB, so I think with more advanced Genomic profiling and immune profiling. I think that might be one way to deal with the more we are tumors. As far as lung cancer. I’ve been doing this now for almost 25 years, certainly in the area of targeted therapy. I think we’ve done.
We're doing what we need to do.

I remember when we first with

John Mendelsohn started to look

EGFR inhibitors.

We treated everyone we saw a 10% response.

We were thrilled drugs became approved.

It was seven years before the

EGFR mutation was developed,

and then once that happened, of course.

Still not a home run.

'cause of resistance.

But then we started to treat

patients in the frontline setting.

And now just recently there are

data now in the agement setting
with some of these agents where perhaps they’ll be more potent or.

Early on, before resistance develops, I think we’re at a point in lung cancer immunotherapy. We have to take a deep breath, and it’s hard because Iris said, it’s very hard for a company or group not to just add on and start to build combinations. Who would have thought chemotherapy combinations would have worked? In fact, no. I led the trial of a Tesla might as a single agent. I was offered the combo.
I didn’t want it. I talked to a few people here. I didn’t think chemotherapy would be the reason. And I totally agree with IRA, I think it’s an additive approach. They’re not. They’re not antagonistic, but but still. The thing that bothers me is in lung cancer. We those are the agents, We have some with Carla Rothlin. We have some with Carla Rothlin. We have some some expertise there. A little bit vague, Jeff, you know their number of Axl Mer TK. We have some some expertise there.
I think some of these approaches that we heard from Aaron, you know, 50% of lung cancers, maybe 60% when the ping and David rim and Kurt look at them have no tail. So there’s clearly a need to. Personalized this therapy and I think the next step really has to be, and I know I was actually going to ask you a question, Mario, why don’t we do more of this? Why five years now after chemo immunotherapy? I mean, do we not know what’s going on? What’s the sweet spot? Went to work when patients become have primary resistance,
we need to obtain more samples and it’s very hard because those studies are very labor intensive. Specially now in this covid area. Or we just want to survive. But we need samples, we need biopsies. We need to take him to our labs pressing. We need to be quick, but you know I reset the best model sort of human and all the animal models we’ve mentioned are fraught with issues. So I would say right now. Lung cancer. It’s amazing. You know you know therapy. I just got the.
Five year results now with drugs 30% survival in an untreated metastatic lung cancer, no PDL 1 high but you know PDL 1 low. It’s a lot different and many patients don’t benefit klemen they want what they see in the commercials and many patients have acquired resistance. This field is perfect for the alliance between industry and academia to know of course you’ve got to do the big phase three trials. I would do that too if I was in the company, but we’ve got it in. Have a few studies. That are really focusing on the mechanism
and either taking the new drugs and like you know with Aaron’s drug, you know the first trials will have to be just to show some activity in safety, but then they have to move forward with liepins drug, the cyclic 15. There have been responses in the phase one. But are there enough well that time will tell, but now it’s time to develop an assay. So what we’ve been able to do here at Yale in partnership is we early on got David Rimm working closely with next. David Rimm working closely with next. You’re one of the companies that John will tell you was developed
here and it’s taken a few years

But now we can start to treat patients

Based on the biomarker because

Science is going to prevail otherwise.

No, it’s going to be random and there’s just,

You and I talk about this all the time

It’s going to be random and there’s just,

You now and I see each other.

Occasionally now,

’cause we’re all locked in their offices,

But every once in awhile

We bump into each other.

That’s going to be the key thing.

How do we figure out resistance
and be proactive about it?

Yeah, by the way, I was wondering once we told you not to bother with chemotherapy, and I think that just reflects how humbling it is to where you are. The biggest influence bending and mad at you for awhile. Yeah yeah, yeah, the so we. You know it’s the biology is very complex and one of the reasons why I started that question is when I look at CTA four I can think of 10 different reasons why
it might make anti PD one better. But in any individual patient I can’t tell which of those mechanisms might be active for chemotherapy. I mean you could do 10 different things. I think the exploration of email object is really important and that’s why I like this focus on really going back to the tumor, immunobiology and actually to thank Charlie for his commitment to recruiting people who are focusing on that area because I think as we build our strength and continue to build our strength in that
and were very strong already, we may actually get the answer to some of these questions. So let me just ask one question here that I can answer because I don’t know is you know the there was a question related to nano particles in an Atom. Articles fit in into the world of of baby no. Biology and Immuno Oncology or any of you in the capable of addressing that question. I’m not. I can take a stab at it. I don’t know it entirely,
but I do know I think John is also put some comments in the chat for attendees to look at as well.

So Mark Salzman’s been a central player in the Nanoparticle area at Yale, and more broadly for a very long time, and I believe with Mike Gerardi is also recently started. A company called stratify that also Anna particle based approaches to enhance immunotherapy’s. So there certainly are efforts along those lines and it’s not just mark that are additional people at Yahoo are doing these things.
All the platforms tend to be quite different and I think if one actually follows up and looks at Akiko’s paper related to the rig immune with Anna pile and we help with some of those studies. But looking at EPS copal affects for nanoparticles I think part of the difficulty has been getting trafficking to tumors are not like T cells which seem to be really good at finding tumors. Nanoparticles have a harder time and tend to end up in macrophages, so a lot of those efforts tended
to be intratumoral and then trying to see these so-called abscopal effects or distant effects for intratumoral agents is one of the challenges that frequently happens, and again at the center position, counseling were particularly well set up to help those folks evaluate whether they're seeing these abscopal affects, but that's kind of a broader scope across yell as to what's happening. I think Mario is in the back scene area, not a particles have been in use.
and are increasingly being in use.

It certainly the RNA vaccine we’re developing with buying tech.

Is it basically an added particle based approach, as is the cold vaccine that they’re developing as well as.

Maderna there are a number of ways of using them?

I think the first incarnation was to try and use that particles.

That’s kind of surrogate or artificial antigen presenting cells so far that hasn’t really worked out that well because Antigen presenting cells.
are more than simply inert surface.

Is that present antigens.

They actually act and perform a complex

POD to do with the T cells and B

cells that they are presenting too,

but using them as delivery vehicles for

RNA has actually worked out pretty well,

but it also turns out.

Surprisingly,

when they work well,

they can also be quite toxic,

and I think a lot of the adverse

events associated with either the

cancer vaccines over the covid

vaccines can be attributed as much

to the data particle themselves and
its ability to trigger inflammasome responses as the RNA another adjutants that data particles contain.

I’ve worked with Mark and with Tarek Fahmi and I actually get a princely sum every month for being on the patent that controls these princely sum I think gets me coffee at the corner coffee store. But nevertheless, you know, I think they’re very interesting platforms, but they haven’t really been put into play in a way that’s really establishes what the future is going to be.
That’s not to say they shouldn’t be studied.

One thing it hasn’t come up that in this context I’d like to make bring up for the group’s consideration is actually self therapy.

When we think of cell therapy, we think of car T cells, which I think are extraordinarily effective in heme onc setting, certain of them, but thus far less so in solid tumor settings, and it’s probably wide variety.

We have only ourselves recently started getting into this area.

I’m not sure what Yale’s involvement has been,
but I do think despite my reluctance to embrace cartis in our own shop, I do think that. Cells engineered cells are the nanoparticles of the future in terms of being able to engineer and design them in ways that will allow them not only to be therapeutic agents, but also delivers of therapeutic agents such that you can. Get them to use. Make use of their of the cells. ability to find out where it is you would like it to go.
01:19:21.740 --> 01:19:24.212 Get to that spot and then turn it
NOTE Confidence: 0.8830849
01:19:24.212 --> 01:19:26.980 on to generate other activities,
NOTE Confidence: 0.8830849
01:19:26.980 --> 01:19:28.995 possibly even the release and
NOTE Confidence: 0.8830849
01:19:28.995 --> 01:19:30.204 secretion of Biotherapeutics,
NOTE Confidence: 0.8830849
01:19:30.210 --> 01:19:32.195 which would change entirely business
NOTE Confidence: 0.8830849
01:19:32.195 --> 01:19:35.440 of how we make drugs and the patients.
NOTE Confidence: 0.8830849
01:19:35.440 --> 01:19:41.110 So I think this is this is an area that.
NOTE Confidence: 0.86137027
01:19:41.110 --> 01:19:43.100 I find personally very exciting.
NOTE Confidence: 0.86137027
01:19:43.100 --> 01:19:46.600 We are investing heavily in.
NOTE Confidence: 0.86137027
01:19:46.600 --> 01:19:49.966 Looking at how to do I
NOTE Confidence: 0.86137027
01:19:49.966 --> 01:19:51.649 PSC technology perhaps?
NOTE Confidence: 0.86137027
01:19:51.650 --> 01:19:54.650 Diane sender at the Yelton can help push
NOTE Confidence: 0.86137027
01:19:54.650 --> 01:19:56.863 this forward collaboratively because this
NOTE Confidence: 0.86137027
01:19:56.863 --> 01:20:00.437 is just again at the very beginning, but.
NOTE Confidence: 0.86137027
01:20:00.437 --> 01:20:02.519 But this is a place right?
NOTE Confidence: 0.86137027
01:20:02.520 --> 01:20:04.760 I do see a very remarkable future.
Thank you for making it.

As a matter of fact, we do have a large clinical Carty program. We’ve done a great deal of work with TIL cells actually sending. This sells out and infusing them here so we have a very well oiled machine for administering self therapy.

We’ve also done some cell generation of our own and there’s a huge amount of work in Immunobiology looking at targets within T cells that could be used as intellectual property for T cell Engineering. So there is a nascent program here in...
In some areas, in some well developed. Well developed in other areas and we are very interested in that. And I mean we only have about, I think 10 more minutes and I just want to spend a few minutes on an area that I think is a particular strength here at Dale, which is the animal modeling and how important it is towards Immunooncology and Marcus. And perhaps you might make some comments again, because you just mentioned some of the resource, but there's a huge number of resources.
related to animal modeling and how it fits in with testing. Well, this has been a tough crowd for traditional animal model I. No IRA’s point of view and respected an remember seeing him at the back of a city workshop that I organized on animal modeling in IO. I view that as a compliment even if it wasn’t intended to be one. But what I would say is our lab has developed a number of immuno genic syngeneic lines that are used widely including by Pharma. These Yale University mouse, Melanoma,
Yum and Yum are lines that enable people to see responses to checkpoints. And sort of tune your system so you can see either additive or synergistic effects by adding a second agent. Obviously that’s harder to tell whether that will happen in humans, in which humans that will happen. But to get some kind of enthusiasm or not for your agent certainly has been used on those purposes.

One of the things I’d like to focus on is there’s a recent nature biotechnology paper by Nick Joshi’s lab, so Joshi and it uses a very controlled way of antigen delivery.
Digital model antigens from LCMV.

Both class one and Class 2,

but it allows for modeling of

immune related adverse events in

ways that we haven’t really been

able to do to this point in time,

so you can specifically turn antigens on,

either in the context of a cancer

either elsewhere or even without that,

and look at immune checkpoint

inhibitor induced.

IR A’s that I think that has

been a big lack in this area.

There was recently an NCI

meeting related to that.
Also sort of suggesting the same Katie Palitti who was had been at yell out for about 10 years as well as very active and lung cancer modeling. So I do agree that we have great strengths. Yeah I would again for this particular group as well. As for I think these other groups that are developing these patients arrive explant models including. The National Cancer Institute in Amsterdam and Daniella Talmon and Tom Schumacher the big challenge in this area has been A to keep things alive, and I’ve mentioned that we can do that. But also what the readouts are that
correspond to responses in human patients.

I think there’s all sorts of biology you can do in those systems,

but there’s obviously a lot of interest in personalized therapy.

To see how those responses are,

and they haven’t published yet,

it will be interesting to see when people do.

Right now, it seems to be elicited cytokines.

Of certain profiles that seem to be the best answer,

but I think there’s more work to be done on those areas,

but I would agree,

and the other thing that Yale
01:23:50.232 --> 01:23:52.314 has an advantage is for these
NOTE Confidence: 0.81051123
NOTE Confidence: 0.81051123
01:23:53.360 --> 01:23:54.880 We’ve developed many crisper derived
NOTE Confidence: 0.81051123
01:23:54.880 --> 01:23:56.710 genetic mutants like beta two microglia
NOTE Confidence: 0.81051123
01:23:56.710 --> 01:23:58.790 knockout so forth that make it easy
NOTE Confidence: 0.81051123
01:23:58.790 --> 01:24:00.941 for Pharma to come in and just
NOTE Confidence: 0.81051123
01:24:00.941 --> 01:24:03.397 establish an SRA to look at class one.
NOTE Confidence: 0.81051123
01:24:03.400 --> 01:24:05.388 Deficient models of a variety of types
NOTE Confidence: 0.81051123
01:24:05.388 --> 01:24:07.650 that can be responsive to mu agent,
NOTE Confidence: 0.81051123
01:24:07.650 --> 01:24:09.940 so it’s kind of a broader swath of
NOTE Confidence: 0.81051123
01:24:09.940 --> 01:24:11.949 and that’s all centered really through
NOTE Confidence: 0.81051123
NOTE Confidence: 0.81051123
NOTE Confidence: 0.8158064
01:24:16.150 --> 01:24:18.322 Could you just mention briefly the
NOTE Confidence: 0.8158064
01:24:18.322 --> 01:24:20.369 humanized mouse models and with what
NOTE Confidence: 0.8158064
01:24:20.370 --> 01:24:23.114 they will might be, so that was a

01:24:25.300 --> 01:24:27.406 So Richard Flavelle is probably developed.

01:24:27.410 --> 01:24:29.930 You know, the I would argue amongst the most advanced humanized mouse models.

01:24:29.930 --> 01:24:31.990 You know, the I would argue amongst the most advanced humanized mouse models.

01:24:31.990 --> 01:24:34.742 These so called Mr G mice which have not kins of human cytokines for various cytokines that are really important for.

01:24:34.742 --> 01:24:38.029 not kins of human cytokines for various cytokines that are really important for.

01:24:38.029 --> 01:24:40.940 Full development and re engraftment of different components of the hematopoetic system,

01:24:40.940 --> 01:24:42.650 Full development and re engraftment of different components of the hematopoetic system,

01:24:42.650 --> 01:24:44.018 and I think the real strength with the Mr. and I think the real strength with the Mr.

01:24:44.018 --> 01:24:45.449 G model is that it in graphs various components of the myeloid derivatives G model is that it in graphs various components of the myeloid derivatives

01:24:45.450 --> 01:24:48.834 much better than most other models much better than most other models

01:24:48.840 --> 01:24:51.624 have up to this point in time. have up to this point in time.
So there’s two papers of note related to that, so one is related to modeling multiple human multiple myeloma and mice, which was done with MoD adopt carp a couple years back. And they would Stephanie Hellena they’ve modeled MD’s AML, engraftment into these models. The difficulty with a lot of these models has been that to actually test whether agents work on them, they’ve been very, very good to show that you can re in Grafton get these different things to work and you can look at additional
genetic changes that happen in those models, but the remaining challenges to use these to then say how is, say an immune checkpoint or a new therapy going to help in that context. But the other issue until more recently was that Regenerx on had participated in the generation of those models which made. A little bit complex to work with other companies and outside of Richard’s lab, but I think that’s at least possibly being solved, and I wouldn’t view that as an impediment now.
OK, I’m going to ask one more question. I don’t see a whole lot of the questions from the chat before I turn it back over to Charlie for closing comments. One challenging question, you know every day I read a new paper about another T cell checkpoint inhibitor and you know, how many things actually block T cell function in the tumor microenvironment? Or peripherally, how does one know which those are the critical non redundant targets? For therapy.
How do you know well? I mean, I just have how OK I’ll give you a hug.

You approach it. How do you approach it?

Because I you know. I mean, I can list 15 in the back of my head.

I don’t know how to decide is it. I don’t know how to decide is it.

Is it true that they’re all important? It’s just an individual patients?

Or are they are some of them redundant or in the same pathway?

Or is biology not important that some of this biology is just not important in cancer but may be

160
important in other settings like infectious disease or something else?

I’m. I mean, how do you know is I think it’s all tide up with the beginning theme of this whole meeting, which is you have to understand mechanism and understand the science so. Back and how long ago. 10 years ago when these things were first being laid out. I remember you know, constructing a diagram with the negative and positive regulators that were known at the time and which one should we look out, which one should we look at?
And I think a lot of investigators and companies went off just to look at them all without really understanding what the relative contributions of them were. We decided to look at one which was tight. And you know, that emerged as a consequence of perhaps we're deluding ourselves into this, but that emerged as a consequence of increased understanding as to how it is that PD one works. So if the current hypothesis is that PD one blockade causes an increase in the number of this self renewing stem light compartment.
That generates effector T cells.

Then what else is there?

If you’re trying to add to that and forget about the reversal of exhaustion business, if you do that, it turns out that the only other negative regulator that’s expressed on the SCM compartment engine, and so if that and it also turns out that we haven’t published this yet, that PD one is actually enzymatically and tigit with a regular C226. Only by competing for like end. OK so that means that there’s a close Functional Association.
And so if you want to enhance the function then you have to go after both of those things. Assuming you correct with respect to understanding what is the target cell type that you’re dealing with. No interesting if you look at the exhausted cells. There’s lots of digit on them, but there’s no CD226, so unless you know there’s another element of the mechanism that we missing, which is entirely possible. Blockade in exhaust itself can’t be expected to reactivate its client.
A positive rate costimulatory molecule that's a costimulatory molecule isn’t even there. So you know those types of considerations. I think you know one really needs to think them through, not just believe what’s in the literature, but set up your own systems, often in mice to figure out. Whether you doing it in an academ. Lab or industrial lab. You know it takes 2 years at least
01:30:05.484 --> 01:30:07.497 to select the best antibody and then
01:30:07.497 --> 01:30:09.839 to grow it up and then you know,
01:30:09.840 --> 01:30:11.550 put it in patients you’re out.
01:30:11.550 --> 01:30:12.086 You know,
01:30:12.086 --> 01:30:13.694 with a huge investment of money
01:30:13.694 --> 01:30:15.791 and time at least five years before
01:30:15.791 --> 01:30:16.694 you know anything.
01:30:17.930 --> 01:30:19.225 Yeah, we’re actually gonna validating
01:30:19.225 --> 01:30:20.965 some of those targets with some of
01:30:20.965 --> 01:30:22.177 the resources that we have here.
01:30:22.180 --> 01:30:22.885 Thank you. Alright,
01:30:22.885 --> 01:30:24.295 it’s always been a vexing question.
01:30:24.300 --> 01:30:26.188 I could talk to you all all day.
01:30:26.190 --> 01:30:27.835 Actually, it’s my favorite thing to do,
01:30:27.840 --> 01:30:29.233 but I think at this point I
01:30:29.233 --> 01:30:30.969 want to turn it over back over
NOTE Confidence: 0.85898066
01:30:30.969 --> 01:30:32.324 to Charlie for closing remarks,
NOTE Confidence: 0.85898066
01:30:32.330 --> 01:30:34.185 and I want to thank all the
NOTE Confidence: 0.85898066
01:30:34.185 --> 01:30:35.870 participants for all their comments.
NOTE Confidence: 0.85898066
01:30:35.870 --> 01:30:37.028 Charlie, please go
NOTE Confidence: 0.84907657
01:30:37.030 --> 01:30:39.702 ahead. Thank you and I just want to
NOTE Confidence: 0.84907657
01:30:39.702 --> 01:30:42.757 thank all of our panelists for superb
NOTE Confidence: 0.84907657
01:30:42.757 --> 01:30:45.478 discussion and obviously think IRA for
NOTE Confidence: 0.84907657
01:30:45.478 --> 01:30:48.182 taking the time out to join us today.
NOTE Confidence: 0.84907657
01:30:48.190 --> 01:30:50.120 You know, as you’ve heard,
NOTE Confidence: 0.84907657
01:30:50.120 --> 01:30:51.656 we’ve had great advances,
NOTE Confidence: 0.84907657
01:30:51.656 --> 01:30:53.576 probably unprecedented advances in io,
NOTE Confidence: 0.84907657
01:30:53.580 --> 01:30:56.010 but clearly the next generation is
NOTE Confidence: 0.84907657
01:30:56.010 --> 01:30:58.401 going to require innovation at a
NOTE Confidence: 0.84907657
01:30:58.401 --> 01:31:00.507 level that builds on terrific science.
NOTE Confidence: 0.84907657
01:31:00.510 --> 01:31:02.820 Outstanding science moves into the clinic,
and I’m so proud of the fact that everyone of our panelists is innovating in that space and many others who we said they couldn’t include in the forum. In fact I’ll mention a city Chen, one of our leading investigators who company being launched tomorrow, evolve immune therapeutics. Just one of the many things that are our investigators are leading. You know, I want to thank all the attendees for joining us today and again.
01:31:37.216 --> 01:31:39.932 want to emphasize this should be
NOTE Confidence: 0.84907657
01:31:39.932 --> 01:31:42.307 the beginning of the conversation.
NOTE Confidence: 0.84907657
01:31:42.310 --> 01:31:44.210 Please reach out to us.
NOTE Confidence: 0.84907657
01:31:44.210 --> 01:31:46.826 We will be following up with you because
NOTE Confidence: 0.84907657
01:31:46.826 --> 01:31:49.528 we want to build more collaborations,
NOTE Confidence: 0.84907657
01:31:49.530 --> 01:31:50.470 more conversations.
NOTE Confidence: 0.84907657
01:31:50.470 --> 01:31:53.760 And finally want to thank Kathy Lynch
NOTE Confidence: 0.84907657
01:31:53.760 --> 01:31:56.621 and her team for organizing this and
NOTE Confidence: 0.84907657
01:31:56.621 --> 01:31:59.467 remind all of you that we actually
NOTE Confidence: 0.84907657
01:31:59.467 --> 01:32:02.323 have two more forms of cancer engage
NOTE Confidence: 0.84907657
01:32:02.330 --> 01:32:04.736 on November 5th or novel cancer
NOTE Confidence: 0.84907657
01:32:04.736 --> 01:32:06.340 therapeutics and delivery system.
NOTE Confidence: 0.84907657
01:32:06.340 --> 01:32:08.340 And then on December 9th,
NOTE Confidence: 0.84907657
01:32:08.340 --> 01:32:09.916 defining mechanisms and biomarkers
NOTE Confidence: 0.84907657
01:32:09.916 --> 01:32:11.886 of sensitivity and resistance to
NOTE Confidence: 0.84907657
So really key topics beyond IO that our investigators are leading.

So again thank all of you.

Mario, thank you for your leadership.

Any final. Large meal.

No, I want to thank you Charlie.

Thanks to all the panelists, all the people who participated today.

Please contact us.

We are very interested in developing collaborations.

We have an enormous wealth of talent here.

Hope will be working with you in the future.

Thank you again.