You know the areas that we’re going to focus on today, or two critical ones, namely mute on Koleji, for which we really committed you centers and resources as well as computational work, which I think is critical in this next phase of Cancer Research in the 21st century. Anile open with our first speaker, as many of you know, doctor Marcus bosenberg is a leader in our Cancer Center professor of dermatology, pathology and Immunobiology. Co leader of the genomics genetics and epigenetics research program.
Director of the else boren kins skin cancer, as well as a very active member of the faculty in theology. Enough leading nationally internationally recognized amount of pathologists and most most recently serving, really quite brilliantly as our interim leader and director of the L centerview know. Marcus is research has been, as you know, prolific, focused. I pour it on the genetics and cellular changes that result in Melanoma while concurrently building innovative new laboratory models.
animal models to understand cancer,

00:01:18.920 --> 00:01:21.260 to define our immune response,

00:01:23.132 --> 00:01:24.536 responding and also even launching new centers.

00:01:25.650 --> 00:01:28.425 Precision oncology,

00:01:28.425 --> 00:01:31.381 us define models to further the research of many of our faculty so.

00:01:34.200 --> 00:01:34.568 Marcus,

00:01:34.568 --> 00:01:36.408 thank you for volunteering to speak at our virtual form.

00:01:40.020 --> 00:01:41.830 Great, thanks so much Charlie.

00:01:41.830 --> 00:01:43.630 Thanks for the kind introduction.

00:01:43.630 --> 00:01:46.507 Just someone give me an odd that

00:01:46.507 --> 00:01:49.977 they can hear me and see the alright they.

00:01:49.977 --> 00:01:52.750 sounds good great so I'll start.
Today’s topic will be targeting innate immunity to enhance anti-cancer immune responses and I think you know. What we’ve seen, even in the last decade, has been a remarkable transformation about how we think about treating cancer. A decade ago. You know, aside from area snow, if you look around Yale and other institutions, and there are a number of other people as well. But there wasn’t that much interested in Koleji. There have been longstanding efforts in a couple of cancer types,
including Melanoma, such as IO2, systemic therapy, and adaptive transferring to Myrtle trading lymphocytes. On both of those sort of pioneered by Steve Rosenberg at NCI and then over the early 2000s CLI four and PD L1 checkpoint blocking therapies were developed and if you look at the impact that this is had in terms of the number of cancer types where these are now standard of care therapies, you could argue that this is amongst the greatest advances ever and cancer therapeutics and resulted in
sort of the first large decline.

And cancer mortality over the last year, especially with the effects in lung cancer attributed to, for instance, the PD one PD, L1 blockade and this breakthrough was awarded the Nobel Prize in 2018. There’s a nice video, the PBS that’s made about Jim Allison. Related to that. That’s just been out and following on that initial success, a lot of companies change their portfolios to try to do PD one blockade plus. Other drugs as the new sort of
standard clinical trial that was instituted in disappointingly the success of these approaches, was not really what had been anticipated. PD one blockade continued to have low, but real levels of effects in a variety of cancer types, but the addition of 2nd drugs almost overwhelmingly did not have significant benefit beyond PD one blockade, so there's a lot of interest in developing combination therapy approaches. In which cancer, me know therapy is a component of that and will focus a little bit more about targeting components of the
NOTE Confidence: 0.876604
00:04:16.327 --> 00:04:18.439 innate immune system to enhance that.
NOTE Confidence: 0.876604
00:04:18.440 --> 00:04:20.864 and I would argue here is that the mechanism of how these drugs work,
NOTE Confidence: 0.876604
00:04:20.864 --> 00:04:22.888 and in general how anti cancer immune responses happen is really not well understood.
NOTE Confidence: 0.876604
00:04:22.890 --> 00:04:25.212 Just to go back a little bit in terms of what’s innate immunity and what’s adaptive immunity.
NOTE Confidence: 0.876604
00:04:25.212 --> 00:04:27.293 Most aspects of immunity have a strong basis in haematopoiesis and the cell types that are derived,
NOTE Confidence: 0.876604
00:04:27.293 --> 00:04:28.670 going from pluripotent stem cells to mile wooden lymphoid precursors,
NOTE Confidence: 0.876604
00:04:28.670 --> 00:04:30.782 at least in part from bone marrow and at least in part from bone marrow and
NOTE Confidence: 0.876604
00:04:30.782 --> 00:04:32.854 strong basis in haematopoiesis and going from pluripotent stem cells
NOTE Confidence: 0.876604
00:04:32.854 --> 00:04:34.818 to mile wooden lymphoid precursors,
NOTE Confidence: 0.876604
00:04:34.820 --> 00:04:37.130 and what’s adaptive immunity.
NOTE Confidence: 0.876604
00:04:37.130 --> 00:04:39.060 Most aspects of immunity have a strong basis in haematopoiesis and
NOTE Confidence: 0.876604
00:04:39.060 --> 00:04:40.980 the cell types that are derived,
pretty much everything in the myeloid side, so the mass cells and all of these guys over here on the right are part of the innate immune system and T cells and B cells. Make up the primary component of adaptive immune immunity and so what are the characteristics of the adaptive immune system to sort of to get that out of the way while we’re talking about innate immunity, well, somatic hypermutation of the T Cell Receptor, an amino globulin loci and recombination of those loci allow for billions of different clones within every human that have distinct reactivity set
allow for the recognition of almost countless and diverse sets of Antigens for which one can have a response that’s either Pisati Seller B cell mediated and these responses typically associated with what’s called memory, which typically means that after an initial exposure to a particular antigen, something that’s recognizable by these cells, there’s an increased response the next time that Amazon is encountered. How do you know whether T cells are B? Cells are actually important in any of these processes.
Kaplan Meier plot of a preclinical tumor experiment, in which a line that we have developed number one point 7 is in Grafton, subcutaneously in a mouse, and if a mouse succumbs to in a large tumor that's resulting survival law. So there's no mice alive in mice. However, if you have this line extend out the side, that means that the mouse was cured of its tumor and lived life span up to 60 days, as illustrated here. Well, what can be done?
In mice, which is not really typically ethical in humans, is that you can actually deplete certain components of the immune system or in graph tumors. In mice that are deficient for those components of the immune system. In this case, what you can see is treatment with the drug that was developed here at Yale by Aaron Rings Group. This is a cloud of project that’s now in press in nature through owners group. This drug annihilating derivative
result in about a 30% cure,

NOTE Confidence: 0.889917499999999

depleting with CD8 anti CD 8 antibody.

NOTE Confidence: 0.889917499999999

Prevented that cure rate and CD four

NOTE Confidence: 0.889917499999999

also did at a little bit longer latency

NOTE Confidence: 0.889917499999999

while blockade of NK cells didn’t

NOTE Confidence: 0.889917499999999

result in any extended survivals.

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So what I'm kind of bringing up now

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is a concept that if you really want

NOTE Confidence: 0.889917499999999

to understand how these things work,

NOTE Confidence: 0.889917499999999

it’s typically useful to have a

NOTE Confidence: 0.889917499999999

system to evaluate what functional

NOTE Confidence: 0.889917499999999

components are at play here,

NOTE Confidence: 0.889917499999999

and that’s been a difficulty with

NOTE Confidence: 0.889917499999999

the innate immune system,

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which will talk about second quick

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segue here to B cells and anti
cancer immune responses which.

Had a big splash earlier in the year where there were three papers in nature in January suggesting that the cells have a role in anti cancer immunity and I would say that this issue is still not really fully resolved. All of those patient papers tended to be a correlative and weren’t really functional. Studies now show example of that in a bit what is known and has been known for awhile is that when you have elevated number of T cells and cancer, you tend to have elevated B cells as well.
Uh, that correlation coefficient from an RNA POV is about a row of about .7, so it’s a pretty high correlation in terms of be selling T celko infiltration into tumors, but that doesn’t necessarily say that they’re actually doing things there, and clinically we typically it’s very common to use a drug called Rituxan Mab, which is a CD20 anti CD 20 in a body which results in depletion of B cells and the patients that are treated that way. And typically these patients don’t have really much higher rates of cancers you might anticipate. If that were a primary method of restraining that particular arm
NOTE Confidence: 0.90716255
00:08:46.324 --> 00:08:47.816 of the immune system, however,
NOTE Confidence: 0.90716255
00:08:47.816 --> 00:08:50.308 I think there’s still more work that
NOTE Confidence: 0.90716255
00:08:50.308 --> 00:08:52.328 hopefully will be done in this area.
NOTE Confidence: 0.90716255
00:08:52.330 --> 00:08:54.493 This is an experiment that I was
NOTE Confidence: 0.90716255
00:08:54.493 --> 00:08:56.803 referring to in which you can actually
NOTE Confidence: 0.90716255
00:08:56.803 --> 00:08:59.167 graph the same kind of tumor into
NOTE Confidence: 0.90716255
00:08:59.167 --> 00:09:00.777 a B cell deficient mouse.
NOTE Confidence: 0.90716255
00:09:00.780 --> 00:09:01.758 Here at LAX,
NOTE Confidence: 0.90716255
00:09:01.758 --> 00:09:03.714 the heavy chain that’s needed prior
NOTE Confidence: 0.90716255
00:09:03.714 --> 00:09:05.764 to class switching of these cells
NOTE Confidence: 0.90716255
00:09:05.764 --> 00:09:08.258 and in a normal mouse say with PD,
NOTE Confidence: 0.90716255
00:09:08.260 --> 00:09:09.880 one therapy or spontaneous rejection.
NOTE Confidence: 0.90716255
00:09:09.880 --> 00:09:12.950 This is this curve here, or black sticks in.
NOTE Confidence: 0.90716255
00:09:12.950 --> 00:09:15.925 Black them you empty mice which lack B
NOTE Confidence: 0.90716255
00:09:15.925 --> 00:09:18.508 cells actually reject as well or better,
while rag mice that lack both B&T cells. So a second way of evaluating whether lymphocytes more generally are needed results an outgrowth of the tumors so that you don’t have that. This is a collaborative project with Harriet clickers lab by Bill Damski, who is going to be a new faculty member in dermatology in July. So what are the characteristics of the innate immune system? So it’s typically a rapid response of system in which it’s kind of hard wired to wrecking sentries, certain pathogen or pathogen molecular patterns that viruses or bacteria.
Might happen or not typically present in eukaryotes, so it allows for almost like a barrier or reflex. If response to these type of molecules one recognize, but also the innate immune system can regulate enhance activation of the adaptive immune system. This has been known in vaccine biology and it’s also known or understood the role within dirt excels. Play Witcher view to be part of the innate immune system. And their activation of T cells
and T cell responses.

So the question really is is what’s the role of these various components in anti cancer immune responses and?

It’s useful to have an idea of what we’re talking about here in terms of what the components might be.

There’s a lot of confusion and debate as to what.

Sort of subsets of things that are related to macrophyllus.

I’m not going to get into that.

It’s not enough time to really go into that.

In this session there’s different subsets of dendritic cells which
00:11:01.524 --> 00:11:03.246 a few of which are labeled here.

00:11:03.250 --> 00:11:04.490 Neutrophils are granulocytes down

00:11:04.490 --> 00:11:06.350 the bottom here and then there

00:11:06.400 --> 00:11:08.110 are some components of cells that

00:11:08.110 --> 00:11:09.250 are derived from lymphoid

00:11:09.307 --> 00:11:11.724 precursors, but kind of have some aspects

00:11:11.724 --> 00:11:13.963 of innate immunity in that they may

00:11:13.963 --> 00:11:16.112 or may not have the memory response.

00:11:16.120 --> 00:11:18.034 It’s debated with some of these

00:11:18.034 --> 00:11:20.338 and also they have the ability to.

00:11:20.340 --> 00:11:22.090 Rapid respond to certain common

00:11:22.090 --> 00:11:23.490 molecular signatures which typically

00:11:23.490 --> 00:11:25.249 B&T cells don’t do as regularly,

00:11:25.250 --> 00:11:27.126 so these are kind of a little

00:11:27.126 --> 00:11:29.195 bit in between depending on what

NOTE Confidence: 0.9131504
00:11:29.195 --> 00:11:30.795 aspect you’re talking about,
NOTE Confidence: 0.9131504
00:11:30.800 --> 00:11:32.768 might fall in between the two.
NOTE Confidence: 0.9131504
00:11:32.770 --> 00:11:34.822 Errands group has also found some
NOTE Confidence: 0.9131504
00:11:34.822 --> 00:11:36.190 really interesting therapies that
NOTE Confidence: 0.9131504
00:11:36.241 --> 00:11:37.666 stimulate NK cells the same.
NOTE Confidence: 0.9131504
00:11:37.670 --> 00:11:39.626 When I was talking about you,
NOTE Confidence: 0.9131504
00:11:39.630 --> 00:11:41.786 wait for his talk to do that
NOTE Confidence: 0.9131504
00:11:41.786 --> 00:11:43.230 more and more depth,
NOTE Confidence: 0.9131504
00:11:43.230 --> 00:11:45.732 and he may have talked a little bit about
NOTE Confidence: 0.9131504
00:11:45.732 --> 00:11:48.139 that during this grand rounds recently.
NOTE Confidence: 0.9131504
00:11:48.140 --> 00:11:50.144 But I think there’s a more
NOTE Confidence: 0.9131504
00:11:50.144 --> 00:11:51.950 of a story there that.
NOTE Confidence: 0.9131504
00:11:51.950 --> 00:11:54.266 And certainly can follow up with.
NOTE Confidence: 0.9131504
00:11:54.270 --> 00:11:56.520 So the question with innate immunity
NOTE Confidence: 0.9131504
00:11:56.520 --> 00:11:59.487 has been for awhile as is it actually
NOTE Confidence: 0.9131504
00:11:59.487 --> 00:12:01.575 fighting cancer or is it promoting
cancer with certain aspects?
and I think most people would view most components of the innate immune system to be promoting cancer, at least in some level. And how might we know that? Well, in certain cancer types where as a pathologist one sees something called metaplasia. So at the junction. Of the posterior aspect of the vagina and cervix. There’s typically there can be inflammation, depending on the status of HP. The other things like that,
which results in inflammation being chronically present at that site and for gastroesophageal reflux inflammation and alteration of the cell types that are there that are associated with higher rates of cancer in those particular spots.

Also in a variety of models where when you induce inflammation, it tends to be cancer promoting. And the thought process that few people feel is at at work there is that some of these inflammatory cells, like macrophages, secrete things like veg, F or other factors that are associated
with growth or angiogenesis which then allow cancers to Co op that and then grow out and myeloid derived suppressor cells.

Or the probably related M2 quote, Unquote subset of Macro Fages and in certain cases, neutrophils, which might also be viewed as the granulocytic MDC’s, have been described as being potentially tumor, promoting by growth restriction, but also that they actively suppress the function of the adaptive immune system.
And there are ways you can test this ex vivo and looking at T cell proliferation assay, secretion of cytokines, things that these cells might do against tumors. It’s well established that natural killer cells have a large role. Uh, in eliminating cells that don’t have MHC class one expressed on their surface and this is a little bit variable in terms of the balance between inhibitory and activating receptors. But there are thought to be the primary way where this occurs, and obviously they’re called natural killer cells for a reason.
They actually kill in a variety of contexts, so some of those contexts can be against cancer, and there's also the thought that a certain subtype of macrophages can also participate in killing responses. Either through respiratory burst activity or secretion of cytokines locally in the micro environments. And so it's been an attractive hypothesis for a while to try to target cells that seem to be promoting cancer formation and a few ways of doing that have been.
00:14:45.380 --> 00:14:46.595 factor 1 pathway,
NOTE Confidence: 0.9082676
00:14:46.600 --> 00:14:49.700 so CSF one and its receptor CSF one R are
NOTE Confidence: 0.9082676
00:14:49.784 --> 00:14:53.120 very very important and Macrophiles Biology.
NOTE Confidence: 0.9082676
00:14:53.120 --> 00:14:56.510 One way this was known as there is the so
NOTE Confidence: 0.9082676
00:14:56.602 --> 00:15:00.249 called osteopetrosis model of the opi model.
NOTE Confidence: 0.9082676
00:15:00.250 --> 00:15:03.026 In which CSF one is an inactive illegal
NOTE Confidence: 0.9082676
00:15:03.026 --> 00:15:06.694 in my so my Sutter home was I get for
NOTE Confidence: 0.9082676
00:15:06.694 --> 00:15:09.417 that particular allele oven on fully
NOTE Confidence: 0.9082676
00:15:09.417 --> 00:15:11.812 functional CSF one Lac macrophages?
NOTE Confidence: 0.9082676
00:15:11.820 --> 00:15:13.810 They also lack macrophage related
NOTE Confidence: 0.9082676
00:15:13.810 --> 00:15:15.004 cells like osteoclast,
NOTE Confidence: 0.9082676
00:15:15.010 --> 00:15:17.368 that remodel bone and teeth so
NOTE Confidence: 0.9082676
00:15:17.368 --> 00:15:20.199 these are hard nice to keep around.
NOTE Confidence: 0.9082676
00:15:20.200 --> 00:15:22.671 Then I’ll talk about them in just
NOTE Confidence: 0.9082676
00:15:22.671 --> 00:15:25.418 a second a little bit more but
NOTE Confidence: 0.9082676
00:15:25.418 --> 00:15:27.824 that’s one idea about how this
pathway is relevant for Macrophages.

And so there are small molecule inhibitors that this is a receptor tyrosine kinase that it can be inhibited by small molecules and it’s also antibodies that block this receptor tyrosine kinase. We’ve used both of these in the context of preclinical modeling and I’ll talk about a clinical trial at the end. It’s currently underway at Yale and you could have either of these two activities that’s actually inhibited and somewhat disappointingly CSF.
One R inhibitors as single agents have really not been particularly effective. There’s one indication which I believe their FDA approved for it to so-called giant cell tumor, which is really composed of macrophages. But I think they’ve been negative in all or nearly all other single-agent indications.

There typically also negative in combination with anti-PD one blockade. One of the issues with studies of this type is did the drug actually affectively inhibit macrophages or even deplete macrofossils were typically very hard to deplete and so this is also called pharmacodynamics to see.
if your drug had the intended effect,
and I think sometimes it’s been a little less clear that it’s been full effect as opposed to a partial effect for some of these drugs.
So can we use preclinical models to help define a role for makefiles in cancer?
I had described an approach before with those Kaplan Meier plots where we use.
Antibodies to deplete,
for instance CDA, positive T cell, CD 4 positive T cells, or NK cells.
Well, those approaches don’t tend to work very well for macro fibers,
and even using the anti CSF one R and
nobody even with the right type of IgG, that would be typically more depleting, doesn’t really tend to work in this subset. The genetic models which are actually probably not bad for this, and the Mets it off lab and others have used these in a cancer context. These are very hard models to work even the teeth don’t form properly, they don’t breed particularly well suited to feed themselves Chow. You have to really, really baby them, like a watch them very closely to actually do a full experiment and then doing cohort type work.
It is difficult because they don’t tend to live particularly long, even postnatally. And you can deplete in macrophages from spleen and peripheral blood, but within the tumor, if you look at them pretty carefully, they tend not to have been depleted in those areas, so this is an area obviously of interest in growth, so it’s hard to know what the real role of these things are, but we have done some work looking at CSF.
years back with Mark Smith from Brisbane, Australia. A drug that Plexxikon had developed wasn’t specific just for CSF one R, but that was its highest potency towards that particular receptor. Wouldn’t it be great if there were human models where you could actually see an effective anti cancer immune response and you could actually deplete macrophages? And we think, and we hope that we may have developed something like that. And this is with my colleague vision.
with zombie who directs the Center
for precision cancer modeling at Yale,
sort of preclinical testing core at Yale,
in which we’ve taken tumor fragments.
And we were seeing full checkpoint inhibitor response,
including elimination of tumor cells within four or five days
in a fully indietro model, this has been mouse first,
but we’re trying to build this up
and towards a human setting an the overall goal is to, for instance.
Flow sort the cells that make up these tumors and deplete macrophages that way,
which will work in terms of getting rid of those and putting back the components that you think will be important for these anti-cancer immune responses. So stupid too and hopefully that will be something else. Hear more about with overtime.

So one thing I talk about briefly now too is CD40 as a target which is on dendritic cells, macrophages and to some extent other cells, including in the filial cells. And CD40 los results in a B cell class switching defect. But it’s been developed as an agonist.
CD 40 antibody, not a blocking. Anybody want it? Stimulates this particular receptor and Bob Vonderheide? Who is the Cancer Center director at Penn, has been developing this for over 10 years. For pancreatic cancer and with the former colleague Sukach and also with Catherine Miller. And more recently, we’ve published preclinical models looking at Agona CD 40 therapy, and I’d say at this point in time, the mechanism isn’t entirely clear. Although we went into that a little
bit with both of these manuscripts.

But one thing that we can see here is that agonist, CD 40 plus anti PD one blockade in CSF one R blockade works a lot better than any of the other drugs alone, so it has almost 80% cure rates and this is the younger model as well. And then the doublet therapies were PD one plus CD 40 and so forth. Also, don't work as well as the triple, although in humans will see in a second that may be slightly different, but we're seeing this is pretty promising. Prickly on clinical evidence to support using combination therapies with CD40.
One of the things that striking
with this particular therapy
relative to PD one blockade,
Here's the T sne plot of a single cell RNA
seq experiment where you have two samples,
one of which is a mouse which had an
injection subcutaneously of a tumor model.
Seven day or eight days before and
then one day prior to this harvest,
mice for either treated with the
three drug therapeutic protocol.
This-is Agassi, 40 anti PD,
one anti CSF 1R versus not treated and
for those of you who look at TI sneak lots.
What’s striking here is that there’s almost no overlap. The T cell areas are down here. You can see by the Vijay areas over here and here that there’s really huge expression profiling differences between. The various components of these tumor micro environments and we’re currently chasing that down. There’s also differences in clona type representation, which I won’t have time to go into here. And so just to show a little bit of pathology as well. PD one treat tumors don’t look that different from this,
which is one day after initiation of

there might be some slightly increased lymphocytes but not really extensive death,

but with the CD 40 agonist containing therapies,

we see Thromboses.

We see extensive cell death

ev en within one day,

and the regression profile is you

can see over here on the right is

different from what we see with.

Uh Anti CTF War anti PD one

sort of combination therapies?

So there’s something that’s unique here

which also seems to have a vascular

40
component which we don’t see the
typically with those other therapies.
So an interesting thing too is that we tend
to think about effects of immune therapies.
We tend to think mostly on
adaptive immune therapies.
This is an image and a rag.
My switch when we gave CD
40 agonist therapy issues,
we actually saw more toxicity in rag
mice then we saw on while typing.
I’m trying to figure out why that might be,
including in Forks in the liver,
and so he’s her F 480 positive
kupfer cells in the control rag,
mouse liver and one day after treatment
with Agnes CD 40 you can see that extensive.
A mini granuloma formation of discover
cells was slightly larger granulomas as well.
Interesting high dose steroid treatment prevents this from happening
even in the absence of lymphocytes,
so there’s a innate immune dependent
aggregation of histiocytes.
Also seeing large differences in
the histiocyte expression profiles
on a single seller,
and I see,
but I'd say that’s a work in progress.
One of the things we do see
systemically is you can see here’s
cry about a 1000 to 10,000 fold.

Increase in the chemo kind CX CL-10, which is a factor that recruits lymphocytes to the tumor microenvironment and you’re seeing a large extension that, with the triple therapy and so some mechanism for the CD 40 agonist therapy, it’s more rapid than what we’re seeing elsewhere. We see a real big up regulation and systemic cytokines from Serum. We’re not sure exactly which cell type yet, although macrophages and Dicesar certainly candidates. We’re interested in the vascular effects were seeing next to endothelial cells,
and I would say that this sort of suggests that cytokine cycling is obsolete. Very important in these responses, and that we will be getting a new you 01 grant with Catherine Miller Jensen as the contact P and me as a secondary API to evaluate single cell cytokine secretion. So RNA levels don’t typically aren’t very accurate for these. An actual looking at each cell and what cytokines it makes will be helpful in the last minute or so. I will briefly discuss.
This is part of the spore project for in skin support and this is a trial led by Harriet cougar and Sarah Wise, in which an agonist CD 40 therapy is combined with anti PD one and then an anti CSF one R therapy and this is in patients that have progressed on PD one blockade in Melanoma and also non small cell lung cancer and renal cell carcinoma and I will kind of go through this so we make sure we have enough time for the second talk as well. Here's a brief description of the cohorts that are here, and we're going to move through this relatively rapidly and get to some of
the neat stuff and mucosal Melanoma
is notoriously hard to treat,
tends not to have really high
mutation burdens, and here is a
patient who had progressed on C5,
four plus PD one blockade,
and you can see multiple liver
lesions that actually cleared by the
addition of giving an agonist CD 40,
so the two patients I’m showing here
didn’t necessarily have the anti CSF 1 R.
It had very clear responses after a PD,
one failure or PD1 Pussy clip for further.
So here’s a couple more cases where
there’s a lesion here that’s disappeared
in a couple other lesions here that are not present at a later time. So this is a trial again by Harriet cougar and Sara Weiss. Part export project for the phase one is moving forward. I think the decisions now or whether or not to have the CSF one R inhibitor around for the next phases of the trial. But one thing that was interesting is that we are seeing a similar cytokine. Profiling is what we see in the mice with dramatic elevations. Avxl 10 in the triple therapy group with some elevations. In Co works that happened to have
higher levels of agonist CD 40, and so these are the conclusions that I've already mentioned to you along the way.

One thing I’d really briefly like to say is that as part of the Yale Center for me on Koleji, we’re starting a list of a set of working groups which are smaller groups around particular complex, and we’re trying to be inclusive and I would suggest that you go to the website through Yale Cancer Center and. Elisa Matthews, which was ALLYSIA,
00:26:52.340 --> 00:26:54.818 is the person who is a scientific
NOTE Confidence: 0.8776111
00:26:54.818 --> 00:26:55.526 program director.
NOTE Confidence: 0.8776111
00:26:55.530 --> 00:26:58.864 She can get you set up so you can join some
NOTE Confidence: 0.8776111
00:26:58.864 --> 00:27:01.916 of these groups should you be interesting.
NOTE Confidence: 0.8776111
00:27:01.920 --> 00:27:04.086 And with that I’ll just acknowledge
NOTE Confidence: 0.8776111
00:27:04.086 --> 00:27:05.830 especially arena quick by Eva,
NOTE Confidence: 0.8776111
00:27:05.830 --> 00:27:07.066 who’s in my lab,
NOTE Confidence: 0.8776111
00:27:07.066 --> 00:27:10.800 who has done a lot of the pre clinical work.
NOTE Confidence: 0.8776111
00:27:10.800 --> 00:27:12.924 All of the trial work and
NOTE Confidence: 0.8776111
00:27:12.924 --> 00:27:13.986 writing and managing.
NOTE Confidence: 0.8776111
00:27:13.990 --> 00:27:16.120 That’s all Harriet Kluber Inserra wise.
NOTE Confidence: 0.8776111
00:27:16.120 --> 00:27:18.542 Earlier work with Sue Kevin I mentioned
NOTE Confidence: 0.8776111
00:27:18.542 --> 00:27:21.100 vision with Asami as part of the
NOTE Confidence: 0.8776111
00:27:21.100 --> 00:27:22.556 center precision cancer modeling.
NOTE Confidence: 0.8776111
00:27:22.560 --> 00:27:24.345 And I’ll stop there and just for,
NOTE Confidence: 0.8776111
00:27:24.350 --> 00:27:25.048 I guess,
brief minute we can potentially take a question or two.

That's a terrific body of work.

Yet let me ask a somewhat complicated question.

Instead of multiple parts, which is, you know,

you've clearly shown that targeting an innate immunity for this sort potentially moves the needle higher, realizing that within that cohort there are patients who may respond.
to just PD one alone or PT1 hippie, or things like that.
And so how do you? How do you see the work you’re doing help differentiate that? Or do we just give everyone sort of the combination? Then Secondly, is a related note for the tumors that are not actually really benefiting and meaningfully from the current checkpoint inhibitors you know? Where do you see this approach working in that subset of tumors as well? But I think right now the difficulty in evaluating new
00:28:24.789 --> 00:28:26.404 combinations of immune therapies is
NOTE Confidence: 0.9162716
00:28:26.404 --> 00:28:28.897 that if you do a standard of care,
NOTE Confidence: 0.9162716
00:28:28.900 --> 00:28:30.881 so your drug plus PD one blockade
NOTE Confidence: 0.9162716
00:28:30.881 --> 00:28:32.699 versus PD one blockade alone,
NOTE Confidence: 0.9162716
00:28:32.700 --> 00:28:35.087 those trials 10, and that's the reference
NOTE Confidence: 0.9162716
00:28:35.087 --> 00:28:37.458 trial that one might use at the end,
NOTE Confidence: 0.9162716
00:28:37.460 --> 00:28:39.532 take a very long time to complete
NOTE Confidence: 0.9162716
00:28:39.532 --> 00:28:41.259 and it takes awhile with.
NOTE Confidence: 0.9162716
00:28:41.260 --> 00:28:43.796 Follow up to know what those results are.
NOTE Confidence: 0.9162716
00:28:43.800 --> 00:28:45.949 Sort of the scenarios that I've just
NOTE Confidence: 0.9162716
00:28:45.949 --> 00:28:47.895 sort of illustrated at these anecdotal
NOTE Confidence: 0.9162716
00:28:47.895 --> 00:28:50.156 cases give one much better indication of
NOTE Confidence: 0.9162716
00:28:50.217 --> 00:28:52.520 whether there’s some activity of an agent.
NOTE Confidence: 0.9162716
00:28:52.520 --> 00:28:54.711 And that’s basically in the setting of
NOTE Confidence: 0.9162716
00:28:54.711 --> 00:28:56.898 failure of response to existing therapies.
NOTE Confidence: 0.9162716
So in these cases it was PD one plus ETA 4 in one case, which we use more commonly in Melanoma. But also just with PD, one failure in and of itself. So in those clinical context, which regrettably are still pretty common in many cancer types, you have the opportunity to add on something like agonist CD 40 to evaluate. Whether is what would really be nice to have a biomarker to know when it would be useful to use these other therapies, and that’s sort of lacking at the this time point I would say, but having a better understanding.
How these things work would be one step in the second step might be doing a more careful evaluation. Immediately after you started this new therapy, do you see the site of kind of response that you would expect to see in a patient? That’s going to benefit and have him earlier cut off if they’re not going to along those lines, but I think those are some people are having at this one time and one other question that you sort of alluded to at the end of your talk.
I know you had a recent publication, sort of characterizing the sort of non-traditionally sun exposed class of. With respect to the biology and also their potential benefit or lack of benefit for checkpoint editors, you just to share a little bit of insight from that work? Yeah, I mean this was kind of nice here 'cause the mucosal Melanoma here 'cause the mucosal Melanoma that was the first case that we had shown in this would be an example of a relatively low mutation burden of Melanoma is a pretty clear, at least correlation with tumors with higher mutation version being
a little bit more responsive
to mean checkpoint hitters,
but it turns out that.
There’s a number of people in different venues that are looking for tumors that might have chromosomal changes, which are typically more common in low sun damage melanomas that those might induce translocations and sort of not like transcripts.
That sort of have random proteins that are expressed at reasonably high levels that might be very good targets for immune therapies, so it’s not just whether you
have mutation burn or not,

NOTE Confidence: 0.88166106

it just whether you have antigens that your T cells can recognize or not.

NOTE Confidence: 0.88166106

And right now we’re not that great in any level of recognizing which cancers those might be,

NOTE Confidence: 0.88166106

and it’ll probably be different for every patient,

NOTE Confidence: 0.88166106

so you can’t just say well,

NOTE Confidence: 0.88166106

this person has this particular peptide expressed or so forth.

NOTE Confidence: 0.88166106

It’s also their HLA haplotype and there’s a lot of things along that that go into.

NOTE Confidence: 0.88166106

Whether or not they’ll be able to form a productive response.

NOTE Confidence: 0.9102248

Well, thank you and thank you for that talk.
Why don’t we turn it over now to our second speaker?

As I mentioned, you know, clear area of priority for the Cancer Center has been in computational biology and were really very fortunate to have doctor more convene speaking to us.