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, 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 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,

Precision oncology, precision cancer medicine to help us define models to further the research of many of our faculty so.

Marcus, thank you for volunteering to speak at our virtual form.

Great, thanks so much Charlie. Thanks for the kind introduction. Just someone give me an odd that they can hear me and see the alright
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 one 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
00:04:16.327 --> 00:04:18.439 innate immune system to enhance that.

00:04:18.440 --> 00:04:20.864 and I would argue here is that the mechanism of how these drugs work,

00:04:20.864 --> 00:04:22.888 and in general how anti-cancer immune responses happen is really not well understood.

00:04:22.890 --> 00:04:25.212 Just to go back a little bit in terms of what’s innate immunity

00:04:25.212 --> 00:04:27.293 and what’s adaptive immunity.

00:04:27.293 --> 00:04:28.670 Most aspects of immunity have a strong basis in haematopoiesis and the cell types that are derived,

00:04:28.670 --> 00:04:30.782 at least in part from bone marrow and going from pluripotent stem cells

00:04:30.782 --> 00:04:32.854 and from bone marrow and going from pluripotent stem cells

00:04:32.854 --> 00:04:34.818 at least in part from bone marrow and going from pluripotent stem cells

00:04:34.820 --> 00:04:37.130 strong basis in haematopoiesis and going from pluripotent stem cells

00:04:37.130 --> 00:04:39.060 to mile wooden lymphoid precursors,
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. What you’re looking at here is a
00:06:01.375 --> 00:06:03.927 Kaplan Meier plot of a pre clinical.
NOTE Confidence: 0.889917499999999
00:06:03.930 --> 00:06:04.660 Tumor experiment,
NOTE Confidence: 0.889917499999999
00:06:04.660 --> 00:06:07.580 in which a line that we have developed
NOTE Confidence: 0.889917499999999
00:06:07.654 --> 00:06:09.810 number one point 7 is in Grafton,
NOTE Confidence: 0.889917499999999
00:06:09.810 --> 00:06:11.114 subcutaneously in a mouse,
NOTE Confidence: 0.889917499999999
00:06:11.114 --> 00:06:14.227 and if a mouse succumbs to in a large
NOTE Confidence: 0.889917499999999
00:06:14.227 --> 00:06:16.037 tumor that’s resulting survival law.
NOTE Confidence: 0.889917499999999
00:06:16.040 --> 00:06:18.161 So there’s no mice alive in mice
NOTE Confidence: 0.889917499999999
00:06:18.161 --> 00:06:20.190 that have had tumor outgrowth.
NOTE Confidence: 0.889917499999999
00:06:20.190 --> 00:06:20.536 However,
NOTE Confidence: 0.889917499999999
00:06:20.536 --> 00:06:23.650 if you have this line extend out the side,
NOTE Confidence: 0.889917499999999
00:06:23.650 --> 00:06:25.050 as it does here,
NOTE Confidence: 0.889917499999999
00:06:25.050 --> 00:06:28.229 that means that the mouse was cured of its
NOTE Confidence: 0.889917499999999
00:06:28.229 --> 00:06:31.259 tumor and lived life span up to 60 days,
NOTE Confidence: 0.889917499999999
00:06:31.260 --> 00:06:32.331 as illustrated here.
NOTE Confidence: 0.889917499999999
00:06:32.331 --> 00:06:34.116 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.
NOTE Confidence: 0.889917499999999

So what I’m kind of bringing up now
NOTE Confidence: 0.889917499999999

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,
NOTE Confidence: 0.889917499999999

which will talk about second quick
NOTE Confidence: 0.889917499999999

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 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,
NOTE Confidence: 0.90716255
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? 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 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 a lot of 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 fully go into that.

In this session there’s different subsets of dendritic cells which
Neutrophils are granulocytes down the bottom here and then there are some components of cells that are derived from lymphoid precursors, but kind of have some aspects of innate immunity in that they may or may not have the memory response. It's debated with some of these and also they have the ability to. Rapid respond to certain common molecular signatures which typically B&T cells don’t do as regularly, so these are kind of a little bit in between depending on what.
aspect you’re talking about, might fall in between the two. Errands group has also found some really interesting therapies that stimulate NK cells the same. When I was talking about you, wait for his talk to do that more and more depth, and he may have talked a little bit about that during this grand rounds recently. But I think there’s a more of a story there that. And certainly can follow up with. So the question with innate immunity has been for awhile as is it actually 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 once he’s also these changes of 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 is 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 coop that and then grow out and myeloid derived suppressor cells.

Or the probably related M2 quote, Unquote subset of Macrophages 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, zan 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 this 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 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.
factor 1 pathway,

so CSF one and its receptor CSF one R are very very important and Macrophiles Biology. One way this was known as there is the so called osteopetrosis model of the opi model. In which CSF one is an inactive illegal in my so my Sutter home was I get for that particular allele oven on fully. They also lack macrophage related cells like osteoclast, that remodel bone and teeth so these are hard nice to keep around. Then I’ll talk about them in just a second a little bit more but that’s one idea about how this
00:15:27.909 --> 00:15:30.795 pathway is relevant for Macro F ages.

00:15:30.800 --> 00:15:31.176 Uh?

00:15:31.176 --> 00:15:33.432 And so there are small molecule

00:15:33.432 --> 00:15:35.722 inhibitors that this is a receptor

00:15:35.722 --> 00:15:37.900 tyrosine kinase that it can be

00:15:37.900 --> 00:15:39.916 inhibited by small molecules and

00:15:39.916 --> 00:15:41.896 it’s also antibodies that block

00:15:41.896 --> 00:15:43.696 this receptor tyrosine kinase an.

00:15:43.696 --> 00:15:46.567 We’ve used both of these in the context

00:15:46.567 --> 00:15:48.697 of preclinical modeling and I’ll talk

00:15:48.697 --> 00:15:51.097 about a clinical trial at the end.

00:15:51.100 --> 00:15:52.888 It’s currently underway at Yale and

00:15:52.888 --> 00:15:55.364 you could have either of these two

00:15:55.364 --> 00:15:56.996 activities that’s actually inhibited

00:15:56.996 --> 00:15:58.490 and somewhat disappointingly CSF.

28
One R inhibitors as single agents have really not been particularly effective. There’s one indication which I believe their FDA approved for it 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 and 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 with as I mentioned before because. 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 'cause 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 that wasn’t specific just for CSF one R, but that was its highest potency towards that particular receptor. And one thing I’d like to bring your attention to is that 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 filament cells. And CD40 Los results in a B cell class switching defect. But it’s been developed as an agonist.
NOTE Confidence: 0.8683355
00:19:43.467 --> 00:19:45.633 CD 40 antibody, not a blocking.
NOTE Confidence: 0.8683355
00:19:45.633 --> 00:19:46.716 Anybody want it?
NOTE Confidence: 0.8683355
00:19:46.720 --> 00:19:47.803 Stimulates this particular
NOTE Confidence: 0.8683355
00:19:47.803 --> 00:19:49.247 receptor and Bob Vonderheide?
NOTE Confidence: 0.8683355
00:19:49.250 --> 00:19:52.130 Who is the Cancer Center director at Penn,
NOTE Confidence: 0.8683355
00:19:52.130 --> 00:19:55.018 has been developing this for over 10 years.
NOTE Confidence: 0.8683355
00:19:55.020 --> 00:19:56.795 For pancreatic cancer and with
NOTE Confidence: 0.8683355
00:19:56.795 --> 00:19:58.215 the former colleague Sukach
NOTE Confidence: 0.8683355
00:19:58.215 --> 00:20:00.180 and also with Catherine Miller.
NOTE Confidence: 0.8683355
00:20:00.180 --> 00:20:01.158 And more recently,
NOTE Confidence: 0.8683355
00:20:01.158 --> 00:20:02.462 we’ve published preclinical models
NOTE Confidence: 0.8683355
00:20:02.462 --> 00:20:04.150 looking at Agona CD 40 therapy,
NOTE Confidence: 0.8683355
00:20:04.150 --> 00:20:06.590 and I’d say at this point in time,
NOTE Confidence: 0.8683355
00:20:06.590 --> 00:20:08.110 the mechanism isn’t entirely clear.
NOTE Confidence: 0.8683355
00:20:08.110 --> 00:20:10.028 Although we went into that a little
NOTE Confidence: 0.8683355
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, or PD1 plus ETA four 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 even 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
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,
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 grant with Catherine Miller Jensen as the contact and me as a secondary API to evaluate single cell cytokine secretion. 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 spore project for in our skin support and this is a trial that as 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

communicated 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, and 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 ALYSIA,
is the person who is a scientific program director.

She can get you set up so you can join some of these groups should you be interesting.

And with that I'll just acknowledge especially arena quick by Eva, who's in my lab, who has done a lot of the pre clinical work.

All of the trial work and writing and managing.

That’s all Harriet Kluber Inserra wise.

Earlier work with Sue Kevin I mentioned vision with Asami as part of the center precision cancer modeling.

And I’ll stop there and just for,

I guess,
brief minute we can potentially take a question or two. Work is thank you. 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
combinations of immune therapies is
that if you do a standard of care,
so your drug plus PD one blockade
versus PD one blockade alone,
those trials 10, and that's the reference
trial that one might use at the end,
take a very long time to complete
and it takes awhile with.
Follow up to know what those results are.
Sort of the scenarios that I've just
sort of illustrated at these anecdotal
cases give one much better indication of
whether there's some activity of an agent.
And that's basically in the setting of
failure of response to existing therapies.
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. Weather 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
00:29:28.965 --> 00:29:31.117 of how these things work would be

00:29:31.117 --> 00:29:32.853 one step in the second step might

00:29:32.853 --> 00:29:34.916 be doing a more careful evaluation.

00:29:34.920 --> 00:29:35.980 Immediately after you started

00:29:35.980 --> 00:29:36.775 this new therapy,

00:29:36.780 --> 00:29:39.084 do you see the site of kind of response

00:29:39.084 --> 00:29:41.550 that you would expect to see in a patient?

00:29:41.550 --> 00:29:43.116 That’s going to benefit and have

00:29:43.116 --> 00:29:44.737 him earlier cut off if they’re

00:29:44.737 --> 00:29:46.315 not going to along those lines,

00:29:46.320 --> 00:29:47.910 but I think those are some

00:29:47.910 --> 00:29:48.970 of the thoughts that

00:29:48.970 --> 00:29:51.090 people are having at this one time and

00:29:51.090 --> 00:29:52.983 one other question that you sort of

00:29:52.983 --> 00:29:55.060 alluded to at the end of your talk.

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I know you had a recent publication sort of characterizing the sort of non-traditionally son exposed class of.

With respect to the biology and also their potential benefit or lack of benefit for checkpoint editors, can 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,

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

And right now we’re not that great in any level of recognizing which cancers those might be, and it’ll probably be different for every patient,

so you can’t just say well, this person has this particular peptide expressed or so forth.

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

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

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 we’re very fortunate to have doctor more convene speaking to us.