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.
NOTE Confidence: 0.9024154
00:00:37.070 --> 00:00:40.766 Director of the else boren kins skin cancer,
NOTE Confidence: 0.9024154
00:00:40.770 --> 00:00:43.787 as well as a very active member
NOTE Confidence: 0.9024154
00:00:43.787 --> 00:00:46.309 of the faculty in theology.
NOTE Confidence: 0.9024154
00:00:46.310 --> 00:00:48.194 Enough leading nationally internationally
NOTE Confidence: 0.9024154
00:00:48.194 --> 00:00:50.078 recognized amount of pathologists
NOTE Confidence: 0.9024154
00:00:50.078 --> 00:00:52.320 and most most recently serving,
NOTE Confidence: 0.9024154
00:00:52.320 --> 00:00:55.146 really quite brilliantly as our interim
NOTE Confidence: 0.9024154
00:00:55.146 --> 00:00:58.780 leader and director of the L centerview know.
NOTE Confidence: 0.9024154
00:00:58.780 --> 00:01:02.497 Cology is really part of that launch.
NOTE Confidence: 0.9024154
00:01:02.500 --> 00:01:04.850 Marcus is research has been,
NOTE Confidence: 0.9024154
00:01:04.850 --> 00:01:07.190 as you know, prolific, focused.
NOTE Confidence: 0.9024154
00:01:07.190 --> 00:01:09.696 I pour it on the genetics and
NOTE Confidence: 0.9024154
00:01:09.696 --> 00:01:11.950 cellular changes that result in
NOTE Confidence: 0.9024154
00:01:11.950 --> 00:01:14.166 Melanoma while concurrently building
NOTE Confidence: 0.9024154
00:01:14.166 --> 00:01:16.382 innovative new laboratory models
NOTE Confidence: 0.9024154
animal models to understand cancer,

NOTE Confidence: 0.9024154

to define our immune response,

NOTE Confidence: 0.9024154

responding and also even

NOTE Confidence: 0.9024154

launching new centers.

NOTE Confidence: 0.9024154

Precision oncology,

NOTE Confidence: 0.9024154

precision cancer medison to help

NOTE Confidence: 0.9024154

us define models to further the

NOTE Confidence: 0.9024154

research of many of our faculty so.

NOTE Confidence: 0.9024154

Marcus,

NOTE Confidence: 0.9024154

thank you for volunteering to

NOTE Confidence: 0.9024154

speak at our virtual form.

NOTE Confidence: 0.876604

Great, thanks so much Charlie.

NOTE Confidence: 0.876604

Thanks for the kind introduction.

NOTE Confidence: 0.876604

Just someone give me an odd that

NOTE Confidence: 0.876604

ey can hear me and see the alright

NOTE Confidence: 0.876604

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 on Koleji. There have been longstanding efforts in a couple of cancer types,
including Melanoma, such as IO2,

00:02:31.860 --> 00:02:32.688 systemic therapy,

00:02:32.688 --> 00:02:34.344 and adaptive transferring to

00:02:34.344 --> 00:02:35.586 Myrtle trading lymphocytes.

00:02:35.590 --> 00:02:38.257 On both of those sort of pioneered

00:02:38.257 --> 00:02:40.766 by Steve Rosenberg at NCI and then

00:02:40.766 --> 00:02:43.221 over the early 2000s CLI four and

00:02:43.221 --> 00:02:45.849 PD one PD L1 checkpoint blocking

00:02:45.849 --> 00:02:47.828 therapies were developed and if

00:02:47.828 --> 00:02:50.131 you look at the impact that this

00:02:50.131 --> 00:02:53.171 is had in terms of the number of

00:02:53.171 --> 00:02:55.752 cancer types where these are now

00:02:55.752 --> 00:02:57.584 standard of care therapies,

00:02:57.590 --> 00:03:00.271 you could argue that this is amongst

00:03:00.271 --> 00:03:02.224 the greatest advances ever and

00:03:02.224 --> 00:03:04.069 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
inmate immune system to enhance that.

and I would argue here is that the mechanism of how these drugs work,

Just to go back a little bit in terms of what’s innate immunity

Most aspects of immunity have a strong basis in haematopoiesis and

the cell types that are derived, at least in part from bone marrow and going from pluripotent stem cells

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 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...
Kaplan Meier plot of a pre clinical.

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.

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.
NOTE Confidence: 0.889917499999999

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,
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.
00:08:09.410 --> 00:08:11.345 Uh, that correlation coefficient from
NOTE Confidence: 0.90716255
00:08:11.345 --> 00:08:14.568 an RNA POV is about a row of about .7,
NOTE Confidence: 0.90716255
00:08:14.570 --> 00:08:17.207 so it’s a pretty high correlation in terms of
NOTE Confidence: 0.90716255
00:08:17.207 --> 00:08:20.066 be selling T celko infiltration into tumors,
NOTE Confidence: 0.90716255
00:08:20.070 --> 00:08:22.128 but that doesn’t necessarily say that
NOTE Confidence: 0.90716255
00:08:22.128 --> 00:08:23.860 they’re actually doing things there,
NOTE Confidence: 0.90716255
00:08:23.860 --> 00:08:25.816 and clinically we typically it’s very
NOTE Confidence: 0.90716255
00:08:25.816 --> 00:08:28.670 common to use a drug called Rituxan Mab,
NOTE Confidence: 0.90716255
00:08:28.670 --> 00:08:31.290 which is a CD20 anti CD 20 in a body
NOTE Confidence: 0.90716255
00:08:31.367 --> 00:08:34.511 which results in depletion of B cells and
NOTE Confidence: 0.90716255
00:08:34.511 --> 00:08:37.270 the patients that are treated that way.
NOTE Confidence: 0.90716255
00:08:37.270 --> 00:08:39.020 And typically these patients don’t
NOTE Confidence: 0.90716255
00:08:39.020 --> 00:08:41.178 have really much higher rates of
NOTE Confidence: 0.90716255
00:08:41.178 --> 00:08:42.578 cancers you might anticipate.
NOTE Confidence: 0.90716255
00:08:42.580 --> 00:08:44.960 If that were a primary method of
NOTE Confidence: 0.90716255
00:08:44.960 --> 00:08:46.324 restraining that particular arm
of the immune system, however, I think there's still more work that hopefully will be done in this area. This is an experiment that I was referring to in which you can actually graph the same kind of tumor into a B cell deficient mouse. Here at LAX, the heavy chain that's needed prior to class switching of these cells and in a normal mouse say with PD, one therapy or spontaneous rejection. This is this curve here, or black sticks in. Black them you empty mice which lack B 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 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 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 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
a few of which are labeled here. 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
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.
There's typically there can be inflammation,
metaplasia. So at the junction.
Of the posterior aspect of the
vagina and cervix.
There's typically there can be inflammation,
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 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, 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 eliminate ING cells that don’t have MHT 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 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
pathway is relevant for Macro F ages.

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 an.

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 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, CD4 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.
NOTE Confidence: 0.8768581
00:18:41.129 --> 00:18:43.167 with zombie who directs the Center
NOTE Confidence: 0.8768581
00:18:43.167 --> 00:18:45.339 for precision cancer modeling at Yale,
NOTE Confidence: 0.8768581
00:18:45.340 --> 00:18:47.657 sort of preclinical testing core at Yale,
NOTE Confidence: 0.8768581
00:18:47.660 --> 00:18:49.646 in which we’ve taken tumor fragments.
NOTE Confidence: 0.8768581
00:18:49.650 --> 00:18:51.300 And we were seeing full
NOTE Confidence: 0.8768581
00:18:51.300 --> 00:18:52.290 checkpoint inhibitor response,
NOTE Confidence: 0.8768581
00:18:52.290 --> 00:18:53.666 including elimination of tumor
NOTE Confidence: 0.8768581
00:18:53.666 --> 00:18:55.730 cells within four or five days
NOTE Confidence: 0.8768581
00:18:55.792 --> 00:18:57.257 in a fully indietro model,
NOTE Confidence: 0.8768581
00:18:57.260 --> 00:18:58.910 this has been mouse first,
NOTE Confidence: 0.8768581
00:18:58.910 --> 00:19:01.136 but we’re trying to build this up
NOTE Confidence: 0.8768581
00:19:01.136 --> 00:19:03.513 and towards a human setting an the
NOTE Confidence: 0.8768581
00:19:03.513 --> 00:19:05.518 overall goal is to, for instance.
NOTE Confidence: 0.8768581
00:19:05.518 --> 00:19:08.110 Flow sort the cells that make up these
NOTE Confidence: 0.8768581
00:19:08.181 --> 00:19:10.677 tumors and deplete macrophages that way,
NOTE Confidence: 0.8768581
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.

One thing I talk about briefly now too is CD 40 as a target which is on dendritic cells, macrophages and to some extent other cells, including in the filial cells. And CD 40 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

36
bit with both of these manuscripts.

00:20:12.080 --> 00:20:13.730 But one thing that we can

NOTE Confidence: 0.8683355

00:20:13.730 --> 00:20:15.430 see here is that agonist,

NOTE Confidence: 0.8683355

00:20:15.430 --> 00:20:17.630 CD 40 plus anti PD one blockade in

NOTE Confidence: 0.8683355

00:20:17.630 --> 00:20:20.021 CSF one R blockade works a lot better

NOTE Confidence: 0.8683355

00:20:20.021 --> 00:20:22.448 than any of the other drugs alone,

NOTE Confidence: 0.8683355

00:20:22.450 --> 00:20:24.885 so it has almost 80% cure rates and

NOTE Confidence: 0.8683355

00:20:24.885 --> 00:20:27.020 this is the younger model as well.

NOTE Confidence: 0.8683355

00:20:27.020 --> 00:20:28.976 And then the doublet therapies were

NOTE Confidence: 0.8683355

00:20:28.976 --> 00:20:31.398 PD one plus CD 40 and so forth.

NOTE Confidence: 0.8683355

00:20:31.400 --> 00:20:34.040 Also, don’t work as well as the triple,

NOTE Confidence: 0.8683355

00:20:34.040 --> 00:20:36.070 although in humans will see in a

NOTE Confidence: 0.8683355

00:20:36.070 --> 00:20:38.330 second that may be slightly different,

NOTE Confidence: 0.8683355

00:20:38.330 --> 00:20:40.640 but we’re seeing this is pretty promising.

NOTE Confidence: 0.8683355

00:20:40.640 --> 00:20:42.650 Prickly on clinical evidence to support

NOTE Confidence: 0.8683355

00:20:42.650 --> 00:20:44.270 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 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.
00:22:56.852 --> 00:22:59.835 with Agnes CD 40 you can see that extensive.

00:22:59.840 --> 00:23:02.036 A mini granuloma formation of discover

00:23:02.036 --> 00:23:04.648 cells was slightly larger granulomas as well.

00:23:04.650 --> 00:23:06.206 Interesting high dose steroid

00:23:06.206 --> 00:23:08.151 treatment prevents this from happening

00:23:08.151 --> 00:23:10.199 even in the absence of lymphocytes,

00:23:10.200 --> 00:23:12.420 so there’s a innate immune dependent

00:23:12.420 --> 00:23:13.530 aggregation of histiocytes.

00:23:13.530 --> 00:23:15.465 Also seeing large differences in

00:23:15.465 --> 00:23:17.013 the histiocyte expression profiles

00:23:17.013 --> 00:23:18.340 on a single seller,

00:23:18.340 --> 00:23:19.309 and I see,

00:23:19.309 --> 00:23:22.410 but I’d say that’s a work in progress.

00:23:22.410 --> 00:23:25.021 One of the things we do see

00:23:25.021 --> 00:23:27.339 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 P and me. As 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

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 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 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.

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,

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 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. We hope to have a biomarker to know when it would be useful to use these other therapies, and that’s sort of lacking at the 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.
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,
NOTE Confidence: 0.88166106
it just whether you have antigens that
NOTE Confidence: 0.88166106
your T cells can recognize or not.
NOTE Confidence: 0.88166106
And right now we’re not that
great in any level of recognizing
NOTE Confidence: 0.88166106
which cancers those might be,
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and it’ll probably be different
NOTE Confidence: 0.88166106
for every patient,
NOTE Confidence: 0.88166106
so you can’t just say well,
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this person has this particular
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peptide expressed or so forth.
NOTE Confidence: 0.88166106
It’s also their HLA haplotype and there’s
NOTE Confidence: 0.88166106
a lot of things along that that go into.
NOTE Confidence: 0.88166106
Whether or not they’ll be able
NOTE Confidence: 0.88166106
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.