Today too, are y'all catch Santa grand rounds? Today is a special day. It’s one of our endowed lectureships. This is the blanched Omen lecture series established in 2012 by Marvin Sears, who many of you might remember was a longtime chairman of our Department of Optomology and Visual Sciences. He established his series in honor of his mother Blanched Holman, who eventually succumbed to acute myelogenous leukemia, and this is the first and I’ll lecture series at Yale.
Devoted to hematology, malignancy’s.

It’s intended to bring Yale pioneers that have made major contributions to our understanding of the current trends in hematologic oncology to a very exciting today to have Marcel Vandenbrink as our speaker and to introduce myself today.

I’m going to turn the podium over to Stephanie Helene, the director of our Division of Hematology. So Stephanie, the floor is yours. Thank you, Dan.

So it’s my absolute pleasure
00:00:56.690 --> 00:00:58.106 to introduce Doctor myself,
NOTE Confidence: 0.8043628
00:00:58.110 --> 00:01:00.371 wondering who is the head of division
NOTE Confidence: 0.8043628
00:01:00.371 --> 00:01:01.816 of hematologic malignancy Malignancy’s
NOTE Confidence: 0.8043628
00:01:01.816 --> 00:01:03.500 at Memorial Sloan Kettering.
NOTE Confidence: 0.8043628
00:01:03.500 --> 00:01:05.474 Cancer Center so Doctor Funding Bank
NOTE Confidence: 0.8043628
00:01:05.474 --> 00:01:08.107 is an expert in hematopoietic stem cell
NOTE Confidence: 0.8043628
00:01:08.107 --> 00:01:10.609 transplantation and he obtained his MD
NOTE Confidence: 0.8043628
00:01:10.609 --> 00:01:13.245 and PhD from the University of Leiden,
NOTE Confidence: 0.8043628
00:01:13.250 --> 00:01:15.165 completed a postdoctoral fellowship at
NOTE Confidence: 0.8043628
00:01:15.165 --> 00:01:17.495 the Pittsburgh Cancer Institute and his
NOTE Confidence: 0.8043628
00:01:17.495 --> 00:01:19.625 residency at Duke University Medical Center.
NOTE Confidence: 0.8043628
00:01:19.630 --> 00:01:22.182 He has been the head of the Division
NOTE Confidence: 0.8043628
00:01:22.182 --> 00:01:24.022 of Hematology Malignancies since 2008
NOTE Confidence: 0.8043628
00:01:24.022 --> 00:01:26.661 is also a professor of medicine and
NOTE Confidence: 0.8043628
00:01:26.727 --> 00:01:28.822 immunology at Weill Cornell Medical
NOTE Confidence: 0.8043628
00:01:28.822 --> 00:01:30.906 College as a physician, scientist,
Doctor, Vandenbrink studies, allogeneic stem cell transplantation. Both in the clinic and the laboratory, his research is currently focused on two areas. One is to study the role that microorganisms living in the testing playing in patients undergoing stem cell transplantation and in those receiving cancer immunotherapy. He’s developing strategies to help the body rebuild the immune system after bone marrow transplantation. His research in both of these areas is being translated into clinical
trials that are currently ongoing at Sloan Kettering and beyond. In 2010, Doctor Finder bring started the Susan and Peter Solomon Divisional Genomics program, which focuses on targeted therapeutic therapy approaches for patients with less with blood cancers such as leukemia and this program was actually instrumental in the development of the first genomic profiling test. Pro Haematological malignancy is called Foundation One Heme which we are happy to use, so I’m turning over the podium to Doctor Vandenbrink who will tell
00:02:27.569 --> 00:02:29.579 us incredibly exciting stories on

00:02:29.579 --> 00:02:31.694 the intestinal microbiome in stem

00:02:31.694 --> 00:02:33.332 cell transplantation. So welcome.

00:02:33.332 --> 00:02:36.104 And we look forward to your presentation.

00:02:37.240 --> 00:02:38.500 Thank you so much.

00:02:38.500 --> 00:02:41.336 Thank you so much for these kind kind words.

00:02:41.336 --> 00:02:44.354 Of course this is again going to be a

00:02:44.354 --> 00:02:47.587 lecture by zoom and we were just saying how?

00:02:47.590 --> 00:02:49.578 Slowly but steadily we're getting a little

00:02:49.578 --> 00:02:52.194 bit tired of that and would like to have

00:02:52.194 --> 00:02:56.290 some real physical lectures again and see

00:02:54.260 --> 00:02:56.290 your audience and work with your audience.

00:02:56.290 --> 00:02:58.918 But no matter what, it is a fantastic honor

00:02:58.918 --> 00:03:01.506 to be your guest and to speak for you.

00:03:01.510 --> 00:03:03.832 So the first thing that I have to tell
you honestly is that I do have a conflict

of interest because some of the data,

some of the studies that I

will be showing were actually

sponsored by the company serious.

I’m not sure if I still need

to show these kind of slides.

I think that most of us will have

a concept now that the microbiome

that lives inside of us and on us is

definitely relevant for a lot of the

Physiology and one way of looking

at that is what is summarized here.

That one should start thinking about

a human multi species symbiotic

supra Organism with a constant
interaction between microbes.

And human human cells.

So we’ve been doing that basically since 2009 and our focus was very much when we started on allogeneic transplant patients, but since then we have broadened our whole scope.

These are the current leaders of our group and the original gangster, Eric Pamer. As since then left us and has bolted for the University of Chicago, so these are the folks within my lap that are working on this, and I will mention some of their names.
When we get to their studies.

So an easy way to summarize about 10 years of work by our group and by others within the context of allogeneic bone marrow transplantation and trying to see if there's a clinical relevance to it.

Changes within the gut flora is to take as a starting point the causes of death within the first year after allogeneic transplants. And if you do that, then you can paint a cladogram an indicate with a blue color text said that are linked to good outcomes, that are linked to good outcomes, and with red color text editor linked with bad outcomes.
And you can differentiate the various clinically relevant outcomes 1st and most of all, of course, the overall survival rate, where you can see that certain texts are linked in a positive or a negative way. Then of course the second one that we have focused on very much is if certain texts are linked to a graft versus host, and I’m giving you one study here from 2015 where we demonstrated in a patient's neutrophil engraftment which is about 14 days out from allogeneic.
transplant that the abundance of a commensal enercell called sub laudia was clinically relevant. It seemed because patients who at that point had low levels of that of that texture had a greater incidence of little a graph versus host which is marked here with these red bars and that leads to overall worse outcomes. Many other clinically relevant outcomes can also be linked to changes within the flora, such as infections, organ toxicity, and even relapse. So now you can start to paint a picture really of what the different taxa could be linked to an.
In some cases we have some mechanism also, and I will show you some of that. Now, many of these studies that we did and that others who did were limited by small group sizes. For instance, here I am showing a study early on where we demonstrated that if you look again at the time of neutrophil engraftment after an allogeneic transplant at the diversity within the gut flora that patients who had that point had higher diversity had a better overall outcome, and that seemed to be linked.
to the incidence of lethal.

A graft versus host.

But again, this was a single center small study.

So we felt very fortunate when some of our dear friends and colleagues from all over the world were willing to work with us, so that now we could do a much larger study looking at 1300 plus patients. These patients were getting allogeneic transplants for AML and DS NHL. And the first thing that really struck us that if we looked at the baseline sample, the samples when patients come
in for their allogeneic transplant, that the composition of the flora was not that different between those centers. And I’ll give you some reasons for that later, an SEC that in all four in all four centers. What we notice is that the moment that they come in for allogeneic transplant, there is a. A dramatic drop within the diversity of the gut flora. And thus that matter a clinically yes it does, as I’m showing here again, taking as a time point around neutrophil engraftment,
which, as I said already, is about 14 days out from allergen echo transplant patients who at that point had higher diversity, that better overall outcomes. And this was holding up for the New York and patients, but also for the combined cohort of the other three centers. When we took a deeper dive, So what makes or what leads to that a difference? Then it seemed to be mostly linked to transplant related mortality, not so much relapse and within
that category it actually seems to be mostly a difference in lethal graft versus host again. You can go one step further and you can start to think about certain attacks are that are linked to more favorable or worse outcomes and that you can validate. Then again by taking all of the patients of the other three cohorts, and indeed see that certain a consortia would be linked to better or worse outcomes. As you can tell we’re not so focused on really zooming in
too much on certain attacks,

NOTE Confidence: 0.8554378

certain attacks, except for one and I’ll

NOTE Confidence: 0.8554378

get back to that one later.

NOTE Confidence: 0.8554378

I told you already that these patients

NOTE Confidence: 0.8554378

came in with fairly similar diversity

NOTE Confidence: 0.8554378

and the composition of their flora,

NOTE Confidence: 0.8554378

and when we analyze that actually

NOTE Confidence: 0.8554378

against normal healthy folks,

NOTE Confidence: 0.8554378

what we saw is that all at all of

NOTE Confidence: 0.8554378

these centers patients come into

NOTE Confidence: 0.8554378

a transplant with lower diversity,

NOTE Confidence: 0.8554378

and we speculate that that is

NOTE Confidence: 0.8554378

because most of them will have gone

NOTE Confidence: 0.8554378

through a year or so of chemotherapy.

NOTE Confidence: 0.8554378

Neutropenic fevers treated

NOTE Confidence: 0.8554378

with all kinds of antibiotics.
And so on.

But what was interesting is that coming in with an even lower diversity coming into a transplant was again linked to worse outcomes. Similar findings we have now also for Ottawa transplant where we see a similar drop within the diversity which starts at the moment that these patients come in for a transplant. And again if we take asmark the time point of neutrophil.

So engraftment, which is about 9 days out from Ottawa transplants we see again that having
at that time point higher diversity is linked to better overall outcomes.

Now, Meanwhile, a number of studies, specifically within checkpoints and blockades have also demonstrated that diversity seems to matter for certain outcomes. In this case, responses to checkpoint blockade and we have some early data that this might matter for the efficacy of car cell therapy. Some studies that were still finishing at the moment seem to indicate also that changes within the gut flora specific texture could be linked with the pace of the CD four and regeneration after an allogeneic transplants.
I don’t want to make too much of a deal here of these various attacks because we still want to take that into a germ free mouse.

Models and study data further, but this gives us hints of which assault apps might be or which text that might be relevant.

Another critical feature is that with the loss of diversity, what happens also is that in some of these patients specifically within the post transplant period, there is a moment that their whole flora is being dominated by a single taxer.
If you use as a definition that domination is when more than 1/3 of your flora is dominated by a certain attacks, and then we actually notice that in all patients at all centres they will have. At a certain at time points, a dominance or almost all, and what was very striking is that all four centers had all former centers that the most prominent bacteria that would do that is Enterococcus an. We knew already from studies at our center that having a state of dominance with Enterococcus within the post transplant period was linked to a 9 faults of risk for bacteremia,
NOTE Confidence: 0.86777544
00:12:02.938 --> 00:12:05.570 with VRE for instance.
NOTE Confidence: 0.86777544
00:12:05.570 --> 00:12:06.886 Bob was very striking.
NOTE Confidence: 0.86777544
00:12:06.886 --> 00:12:08.860 Is that at all four centers?
NOTE Confidence: 0.86777544
00:12:08.860 --> 00:12:10.738 It was one specific species that
NOTE Confidence: 0.86777544
00:12:10.738 --> 00:12:12.614 would do that that would lead
NOTE Confidence: 0.86777544
00:12:12.614 --> 00:12:14.553 to a state of a dominance and
NOTE Confidence: 0.86777544
00:12:14.553 --> 00:12:16.430 that was Enterococcus aficion.
NOTE Confidence: 0.86777544
00:12:16.430 --> 00:12:18.070 As I’m showing you here.
NOTE Confidence: 0.8248834
00:12:20.100 --> 00:12:22.236 And that seemed to matter clinically.
NOTE Confidence: 0.8248834
00:12:22.240 --> 00:12:24.166 Also because what we know Tist
NOTE Confidence: 0.8248834
00:12:24.166 --> 00:12:26.158 is having during the period or
NOTE Confidence: 0.8248834
00:12:26.158 --> 00:12:28.084 the post transplant period at one
NOTE Confidence: 0.8248834
00:12:28.084 --> 00:12:30.452 point a state of dominance with
NOTE Confidence: 0.8248834
00:12:30.452 --> 00:12:32.527 Enterococcus aficion was linked to
NOTE Confidence: 0.8248834
00:12:32.527 --> 00:12:34.740 greater risk of graft versus host,
NOTE Confidence: 0.8248834
worse overall outcomes, and specifically an increased incidence of lethal graft versus host that was true for all of the New York of patients and also held up when we took the three cohorts from the other centers together. So we took that into mouse models and what I’m showing you here is every box is 1 mouse where we did sequential a sequencing an in this case if we add some of T cells to the allograft with which these mice were being transplanted which will lead to a graft versus host. As you can see here,
NOTE Confidence: 0.8248834
00:13:11.100 --> 00:13:12.770 lethal a graft versus host.
NOTE Confidence: 0.8248834
00:13:12.770 --> 00:13:15.450 Then you must notice that there are these.
NOTE Confidence: 0.8248834
00:13:15.450 --> 00:13:17.120 These these red diamonds here,
NOTE Confidence: 0.8248834
00:13:17.120 --> 00:13:19.292 which means that there’s a blooming
NOTE Confidence: 0.8248834
00:13:19.292 --> 00:13:21.097 of Enterococcus happening during the
NOTE Confidence: 0.8248834
00:13:21.097 --> 00:13:22.879 development of a graft versus host.
NOTE Confidence: 0.8248834
00:13:22.880 --> 00:13:23.840 In these mice,
NOTE Confidence: 0.8248834
00:13:23.840 --> 00:13:26.080 these mice are not getting any type
NOTE Confidence: 0.8248834
00:13:26.145 --> 00:13:28.130 of antibiotic or anything else.
NOTE Confidence: 0.8248834
00:13:28.130 --> 00:13:29.150 We thought first.
NOTE Confidence: 0.8248834
00:13:29.150 --> 00:13:29.490 Well,
NOTE Confidence: 0.8248834
00:13:29.490 --> 00:13:31.961 maybe that is just for one strain
NOTE Confidence: 0.8248834
00:13:31.961 --> 00:13:33.377 or for one setting,
NOTE Confidence: 0.8248834
00:13:33.380 --> 00:13:35.130 so we did different strains
NOTE Confidence: 0.8248834
00:13:35.130 --> 00:13:36.530 in three different settings.
NOTE Confidence: 0.8248834
For monitoring a graft versus host causing a graft versus host in all of these cases, we kept on finding about seven days out from Allergan Aker transplant during the development of a graft versus host. There's a blooming of Enterococcus. Well, we test the debt by taking a germ free mice, giving them a minimal flora giving them a minimal flora plus or minus Enterococcus. In these mouse models. By the way we saw blooming with different species was not physiome, but Enterococcus faecalis an.
If we did that.

If these mice had Enterococcus in their flora, then indeed they had worse graft versus host, and again had a blooming of Enterococcus. So we took that further into these mouse models and analyzed mechanisms, and since this is published, I’m only going to summarize it here with Soma schematics. So what we think is happening and what kind of data we have so far is that the damage caused by chemo and by the conditioning regiments.
plus the Elo activated T cells

which specifically targets the crypt stem cells and causing a graft versus host within the gut.

That will lead to enterocyte damage.

The enter sites therefore start to make less of an anti microbial approaching called REC 3 which is known as we and others have actually demonstrated to be a an anti and anti microbial approaching anti and anti microbial approaching that can contain Enterococcus.

Another thing that also happens is that he enterocytes specifically are capable of making electees
00:15:21.355 --> 00:15:23.962 that will lead them to increase levels within the lumen.

00:15:23.962 --> 00:15:30.378 Of lactose and that plus the fact that there's less of rec rec three will then lead to an Enterococcus blue.

00:15:30.378 --> 00:15:32.825 The Enterococcus Bloom pushes away some of the year.

00:15:32.825 --> 00:15:35.033 The Enterococcus Bloom pushes away some of the year.

00:15:35.040 --> 00:15:36.078 The Enterococcus Bloom pushes away some of the year.

00:15:36.078 --> 00:15:38.154 pushes away some of the year.

00:15:38.160 --> 00:15:39.228 Commensal flora well.

00:15:39.228 --> 00:15:41.720 One of the beneficial things that the commensal flora does is we and others have demonstrated is that it makes a butyrate and butyrate is an intraluminal nutrient for these intro sites.

00:15:41.789 --> 00:15:44.389 commensal flora does is we and others have. A demonstrated is that it makes a butyrate and butyrate is an intraluminal nutrient for these intro sites.

00:15:44.390 --> 00:15:46.644 A demonstrated is that it makes a butyrate and butyrate is an intraluminal nutrient for these intro sites.

00:15:46.644 --> 00:15:48.774 So if there's less a butyrates then that will lead to even more nutrient for these intro sites.
00:15:55.062 --> 00:15:56.822 damage to the enterocytes and
NOTE Confidence: 0.7907168
00:15:56.822 --> 00:15:58.998 now you’re in a downward spiral.
NOTE Confidence: 0.7907168
00:15:59.000 --> 00:16:01.826 And things get worse and worse.
NOTE Confidence: 0.7907168
00:16:01.830 --> 00:16:04.168 So we’re trying to figure out are
NOTE Confidence: 0.7907168
00:16:04.168 --> 00:16:06.717 there ways that we can maybe blocked
NOTE Confidence: 0.7907168
00:16:06.717 --> 00:16:08.925 AT and we thought initially about
NOTE Confidence: 0.7907168
00:16:09.003 --> 00:16:11.528 some bacteriophages and other things.
NOTE Confidence: 0.7907168
00:16:11.530 --> 00:16:13.917 But then the post Doc who was
NOTE Confidence: 0.7907168
00:16:13.917 --> 00:16:15.885 working on this Christof Stein
NOTE Confidence: 0.7907168
00:16:15.885 --> 00:16:18.895 touring are did a very simple thing.
NOTE Confidence: 0.7907168
00:16:18.900 --> 00:16:21.228 He analyzed simply what are the
NOTE Confidence: 0.7907168
00:16:21.228 --> 00:16:22.780 pathways with already nutrients.
NOTE Confidence: 0.7907168
00:16:22.780 --> 00:16:24.332 As I mentioned already,
NOTE Confidence: 0.7907168
00:16:24.332 --> 00:16:25.884 that Enterococcus favors well.
NOTE Confidence: 0.7907168
00:16:25.890 --> 00:16:28.599 As I said already, it likes Electo,
NOTE Confidence: 0.7907168
00:16:28.600 --> 00:16:31.218 so in his culture system for intro
Enterococcus he simply poured some lactaid.
From the local pharmacy and demonstrated that with that.
Of course he could block the growth of these bacteria.
He then went back to these mouse models and what he did there, he’s bought Chow without electrons, which is actually difficult because lactose is everywhere in many different nutrients. But he was able to get that mate and when he put these mice in two different models on the child, it was lactose free. Who could get somewhat less a
You’re not curing a graft versus host with this, and he could block the blooming of Enterococcus. So then he took that finding back to humans. And we looked in our patients. Are there maybe patients who have lactose intolerance? When we looked at that we hoped, of course, that that would be linked to increased levels of graft versus host. We didn’t really find that there was a trend, but what we did notice is the
NOTE Confidence: 0.7907168
00:17:35.026 --> 00:17:36.933 moment that patients come off
NOTE Confidence: 0.7907168
00:17:36.933 --> 00:17:39.453 antibiotics and that is the 0 here.
NOTE Confidence: 0.7907168
00:17:39.460 --> 00:17:41.195 Then those patients who are
NOTE Confidence: 0.7907168
00:17:41.195 --> 00:17:42.583 lactose intolerant will have
NOTE Confidence: 0.7907168
00:17:42.583 --> 00:17:44.260 higher levels of Enterococcus.
NOTE Confidence: 0.8346875
00:17:46.540 --> 00:17:48.997 So as I’ve been trying to show you here
NOTE Confidence: 0.8346875
00:17:48.997 --> 00:17:51.445 in this part so the Enterococcus can
NOTE Confidence: 0.8346875
00:17:51.445 --> 00:17:54.090 dominate in the post transplant period,
NOTE Confidence: 0.8346875
00:17:54.090 --> 00:17:56.826 it is linked to a graft versus host,
NOTE Confidence: 0.8346875
00:17:56.830 --> 00:17:59.702 and lactose is one of the basic nutrients
NOTE Confidence: 0.8346875
00:17:59.702 --> 00:18:01.976 for Enterococcus and using lactate or or.
NOTE Confidence: 0.8346875
00:18:01.980 --> 00:18:03.830 Basically strategies like that could
NOTE Confidence: 0.8346875
00:18:03.830 --> 00:18:06.051 potentially block the bloom of Enterococcus
NOTE Confidence: 0.8346875
00:18:06.051 --> 00:18:08.832 an in that way limit the graft versus host.
NOTE Confidence: 0.8346875
00:18:08.840 --> 00:18:11.115 This of course begs for a clinical
NOTE Confidence: 0.8346875
study which we haven’t done yet, so I can’t tell you anything about that. Meanwhile, other centers have also demonstrated that the levels ofEnterococcus within the post transplant periods are linked to a graft versus host. I’m just showing you one out of several here. Another disease that we were interested in is the complication of chronic graft versus host after allogeneic transplant, so we try to figure out if changes within the four I could be relevant for that also. Now, the onset of chronic graft versus host is of course much, much later is about 200 days out, and what we did in this case is we
looked at the samples about 100 days out and try to see if there were certain texts on maybe that could be linked. In a favorable or an unfavorable way with the onset of chronic graft versus host much, much later, and indeed we have some hints now such as Streptococcus in Accra Mencia. That seems to favor the onset of chronic graft versus host. So of course that this needs much more work. Another feature in this article that I’m not summarizing is that there might be also a role for certain short chain.
fatty fatty acids that might limit the incidence of chronic graft versus host.

Now I mentioned already a few times that this drop in the diversity within the gut flora is pretty dramatic in all patients who have an allogeneic bone marrow transplantation. So we went back and we try to analyze what are possible factors that might cause that dramatic loss, and the first one of course, that we looked at was antibiotics. And indeed, if you look at the use of broad spectrum antibiotics, so those type of antibiotics that...
we typically give when a patient has fever and neutropenia, and specifically will do damage to their commensal enter up flora, then indeed the exposure to those types of antibiotics will lead to a greater drop in the diversity. We analyzed over a period about 10 years the use of antibiotics in our allogeneic transplants patients and try to see if certain types of antibiotics were linked to greater incidence of lethal graft versus host an we came up with two piperacillin and imipenem also
We're using it now, but for this study we could only look at me Pennant and those are indeed two types of antibiotics that do more damage to the commensal anaerobic flora, then many other types of broad spectrum antibiotics, such as it's ever been. As I'm showing you here that was LinkedIn D2, higher incidence of lethal graft versus host. We took that again into a mouse model and we could see indeed that these two broad spectrum antibiotics damage the analog flora would lead to worse graft versus host.
And to make a Long story short, because this is all published when we studied this further in this mouse model we saw a few things. First of all, we saw a change within the gut flora that there was a blooming of a bacteria. Mencia lives very close to the mucus layer and has mucolytic enzymes and therefore will lead to a greater breakdown. We actually speculate of the mucus layer and we could to demonstrate that the gut barrier function.
More impaired in these mice treated with this broad spectrum antibiotic than not, and that again, might set up a cascade of a number of things, more stimulation of potentially of certain dendritic cells that I won’t get into now. They will make higher levels of aside account that we know is linked to gut a graft versus host, which is all three that will lead to greater activation will give you a graph versus host, those are the driving donor T cells that will give you a graph versus host, leading to worse overall graph versus host.
Specifically within the column. So a number of studies have looked now over the last decades or so. If the use of broad spectrum antibiotics has any impact on outcomes after allogeneic transplant, and as we were chatting earlier the first studies looking at the use of antibiotics, at the use of antibiotics, broad spectrum antibiotics in humans in the 1970s and 80s actually seemed to indicate that wiping out the whole flora would lead to better outcomes. Specifically, less graft versus host, and there are some pediatric studies.
that still seem to indicate that, but the bulk of the stories, the bulk of the studies over the last two years, do seem to indicate that the use of broad spectrum antibiotics is linked to worse outcomes, specifically, increased levels of lethal graft versus host or graft versus host overall.

So what can we do about that? Well, one of the things that we have been looking at is a beta lactamase that you would give orally so that within the lumen you can block any kind of effects of whatever
type of antibiotic you are using. So these are some early studies with such a compound, so if we get gift that then indeed we can block in a normal mouse the change within the diversity. The blooming of Enterococcus. When you treat a mouse with both an antibiotic and this beta beta lactamase, and if you take it to a mouse model for graft versus host, similarly you can somewhat block the worsening of graft versus host that you would get with the antibiotics. Of course, we're looking forward
to taking this into trials now.

A second major factor, we think that can impact on the dramatic loss of diversity are the different types of conditioning regiments.

So we took a deep dive here. As all of the different types of air conditioning regiments that we have been using at our center, and as you can see, there are many.

Going from my lower blade of two reduced intensity tune on my lower blade.

And if you do that as you would expect,
00:24:58.550 --> 00:25:01.136 the ones with lower strength indeed
00:25:01.136 --> 00:25:04.777 curfew less of a drop in the diversity.
00:25:04.780 --> 00:25:06.484 And even if you were control
00:25:06.484 --> 00:25:08.490 for the use of antibiotics,
00:25:08.490 --> 00:25:12.570 you still keep on finding that same thing.
00:25:12.570 --> 00:25:14.640 Another thing that was very interesting
00:25:14.640 --> 00:25:17.653 when we looked at it in some more detail
00:25:17.653 --> 00:25:19.873 is that certain regiments and we don’t
00:25:19.873 --> 00:25:22.193 know why we need to study that further,
00:25:22.200 --> 00:25:24.126 such as this one with fludarabine,
00:25:24.130 --> 00:25:26.050 cyclophosphamide and low dose at TV.
00:25:26.050 --> 00:25:28.080 I seem to be linked to the
00:25:28.080 --> 00:25:29.580 blooming of certain bacteria,
00:25:29.580 --> 00:25:31.218 and here I’m pointing out again
00:25:31.218 --> 00:25:33.439 the one that I mentioned earlier,
Another factor that hasn’t been studied with that much detail yet, but we know is a major factor for changes within the flora is diet.

So to be able to get accurate diet data, we hired a nutritionist who very carefully monitored exactly what these patients day by day and almost 100 patients.

The first thing that he notices if he looked at the onset when patients come into transplant that calculating the Nutrition risk index.

Patients coming in with lower levels for that index have already a lower diversity within their flora.
Another thing that he notices is that the calorie intake the moment that these patients are coming goes down dramatically and follow sort of the same pattern as that drop within diversity. And he first would have analyzed the usual aspects that people look at when they're studying a diet, so calories, protein, fats, fiber and swim. And he found indeed that calorie intake was positively correlated with the diversity fiber also and also positively with blodia. And that is a true for both calories and fiber and negatively for Enterococcus so.
That was interesting, but what I actually found even more interesting is a different way to look at a diet, and that is to look at it as a taxonomy. So now you look at all of the fruits of products more than these categories like protein, fat and so on. And when we analyzed our data like that, what we saw was that the footer diversity immediately dropped when patients come into a hospital, and that that diversity. Again, drops more for those patients who get a stronger type of a conditioning regiment.
You can then start to look at certain food groups and how they are linked to a diversity, and that was very interesting because then you find something that we didn’t really thought of and that is that the intake of fruits and sugars and sweets linked negatively to the diversity. So we’re still trying to figure out why that is and one of the theories that we have is that these very simple sugars actually might feed some of the pathogens or the bacteria that are...
taking over in times of low diversity.
And in that case might make matters worse,
as has been shown.
For instance, for an enteritis,
ferrea colitis model.
And again you see there if you feed
these mice while they’re getting DSS.
Also, simple sugars and you
see him blossoming of again and
bug like Accra Mencia.
So now we can start to make these kind
of tables where we can see what food
groups might have impact on certain tax.
And of course this can.
This can help us to start to a compose,
maybe a diet that would be a beneficial
for specific patients in specific settings and that is of course our ultimate goal with all of this.

Another category is drugs and. Patients who are getting an allogeneic bone marrow transplantation at any given moment are probably on seven or eight different drugs. And it was a very nice study a couple of years back where it was demonstrated that many drugs that weren’t antibiotics that actually could also impact on many of the bacteria that are part of the commensal flora and just to highlight some of these drugs.
These are all drugs that we frequently give to our patients, including things like slight cyclosporin. So a very talented, say, graduate student. She took all of the data that we have from all of the samples on 1100 patients. And she put them in a you map and therefore could see all these clusters. She came up with 10 different clusters and labeled them and then analyze. Since we had to kinetic data if...the starting or stopping of a
certain drug would have impact on the flora in these patients,
moving from one cluster to another cluster or staying put in that same a cluster.
And when she did that kind of an analysis, what was very striking is that,
what was very striking is that, course the antibiotics will have impact if you a transition to another cluster or if you stay where you are
so you can see here from this data.
But all of these other drugs and
she looked at a grand total of 6063
different drugs can have impact also.
So it’s a little bit early to show you data yet,
but we have we have some data now that seem to indicate a certain. Pain medicines might have impact on changes within the gut flora, so there’s a lot of work still that we can expand on. Now of course, the ultimate goal for many people is to take this back into the clinic, and we’ve been thinking, of course, about that. Also, I’m still very cautious because I feel that we’re in the early going, so we still need to know much, much more. But if you categorize the difference
00:31:27.124 --> 00:31:28.330 in therapies in four,
NOTE Confidence: 0.89225054
00:31:28.330 --> 00:31:30.298 then you can think about the
NOTE Confidence: 0.89225054
00:31:30.298 --> 00:31:33.733 use of antibiotics,
NOTE Confidence: 0.89225054
00:31:31.290 --> 00:31:33.733 and that is probably the lowest hanging
NOTE Confidence: 0.89225054
00:31:33.733 --> 00:31:35.753 fruit because those are drugs that
NOTE Confidence: 0.89225054
00:31:35.753 --> 00:31:37.867 we given that we can easily monitor.
NOTE Confidence: 0.89225054
00:31:37.870 --> 00:31:39.570 The second category would be.
NOTE Confidence: 0.89225054
00:31:39.570 --> 00:31:41.454 Pre biotics were thinking of there
NOTE Confidence: 0.89225054
00:31:41.454 --> 00:31:43.523 is to maybe give specific nutrients
NOTE Confidence: 0.89225054
00:31:43.523 --> 00:31:45.773 that would help that would feed
NOTE Confidence: 0.89225054
00:31:45.773 --> 00:31:47.577 that would favor texture that
NOTE Confidence: 0.89225054
00:31:47.577 --> 00:31:49.545 we think could be of benefit.
NOTE Confidence: 0.89225054
00:31:49.550 --> 00:31:51.482 The one that most people are
NOTE Confidence: 0.89225054
00:31:51.482 --> 00:31:53.330 focused on is Pro Biotic.
NOTE Confidence: 0.89225054
00:31:53.330 --> 00:31:55.790 So now we’re talking bout fecal
NOTE Confidence: 0.89225054
transplant engineered microbes and so on and so on and there certainly with an allergen Aker transplant there's a lot of work going on within that field and then a fourth category would be post biotics so those could be certain products made. By bacteria I mentioned already short chain fatty acids such as a butyrate, and there are trials going on with that. What are we doing at the moment? Well, as I said already, for us the lowest hanging fruit is antibiotic stewardship avoids the use as much as possible of these broad spectrum antibiotics that do damage
to the commensal enrolled flora.

So we have a trial open at the moment where patients who get fever neutropenia will be.

A randomized to either getting our standard of care which is piperacillin tazobactam versus cefepime and try to win these patients as quickly as possible off antibiotics.

A second study that we have finished already as an auto fecal transplant.

So the thinking there was when patients come off antibiotics which is about 14 days out from the allergen acre transplants, why don’t we give them back their
original flora from pre transplant?

And since this was led by Eric

Pamer Ann Young Tower our primary focus was the prevention of C diff.

So we looked at that mostly,

the incidence of a C diff was actually relatively low,

But what we did notice is first of all that’s the concept worked.

You could indeed this is the pre transplant and diversity pattern of a patient,

who then was transplant again with an auto fecal transplant, and indeed would get pretty
00:33:50.070 --> 00:33:51.686 much their own flora.

00:33:51.690 --> 00:33:54.714 Back so the concept seemed to be working,

00:33:54.720 --> 00:33:57.380 but in terms of clinically relevant outcomes,

00:33:57.380 --> 00:33:59.868 the only thing that we saw in this

00:33:59.868 --> 00:34:01.903 very small series was actually

00:34:01.903 --> 00:34:04.579 something that we weren’t counting on,

00:34:04.580 --> 00:34:06.841 and that is that the activation of

00:34:06.841 --> 00:34:08.754 certain viruses which commonly happens

00:34:08.754 --> 00:34:11.394 within the context of allogeneic transplant,

00:34:11.400 --> 00:34:13.990 such as CMV and EBV was somewhat

00:34:13.990 --> 00:34:17.111 lower in those patients who have been

00:34:17.111 --> 00:34:19.997 treated with an auto fecal transplant.

00:34:20.000 --> 00:34:23.290 Another thing that we notice is that

00:34:23.290 --> 00:34:26.667 auto fecal transplant seemed to favor

00:34:26.667 --> 00:34:29.179 the engraftment reconstitution of

00:34:30.000 --> 00:34:32.399
neutrophils, lymphocytes and monocytes.

A study that we’re working on that is not open yet is to really rationally design consortia of these bacteria pretty much based upon that, we’ll that I started out with that whole a cladograms where I indicated how certain flora elements were linked to good or bad outcomes and based upon that we have created a consortium and we want to give these bacteria back again at that time which is about 14 days out from allogeneic transplant. As I’ve said many times by now.
So with that I would like to stop.

I would like to summarize basically what I've been trying to show that changes within the gut flora are linked to overall survival.

Lethal graft versus host bacteremia, sepsis, engraftment and even a relapse.

I gave you a specific story about how the dominance with Enterococcus within the post transplant period is linked both in mouse and men to lethal graft versus host.

And I told you about the various factors that we think can have impact on the gut flora,
such as the use of antibiotics, but also other types of drugs, diet and conditioning regiments. So with that I would like to of course thank all of my funding agencies in my fantastic lap and the many folks who we have worked with at other centers. So with that I would like to stop and I should probably stop sharing also. If I can do that? It seems to be. But thank you myself for this really, really fascinating talk. I have to say I coming up with questions and was every next step you answered my first question,
so maybe I can start with one so. Right, so you are receiving these patients for transplant after they have gone through months and months of treatment. And have you looked at how you know? For example, you know whether patients receive, you know, is decided in or targeted therapy or chemotherapy before coming to transplant, does that effect? What you see, then, in terms of transplant outcomes, yes. So this is of course, where we still don’t have very good data.
We do have some collection also of samples from patients before transplant, specifically with AML. We see a bit of the same patterns, but it hasn’t been analyzed that well yet that we see with allogeneic bone marrow transplantation that an AML patient getting in induction regiment will have the same pattern of the loss of a diversity dominance with certain tax are specifically with Enterococcus, but we need much more work to analyze that, and as I hinted at, almost every drug that they might have seen in the year prior to a transplant,
00:37:39.650 --> 00:37:40.050 potentially.

00:37:40.050 --> 00:37:42.450 Could have impacted on their floor, so it’s very worthwhile to look at that.

00:37:46.260 --> 00:37:48.732 OK, awesome. So we have questions from the audience from Lucas Cauda, who says great talk in his first question is how well does this correlate with amino acid magic biomarkers?

00:37:53.860 --> 00:37:56.949 Rank 3 S, T2, etc.

00:37:53.860 --> 00:37:59.364 Then you know of course those are the markets that have been developed by Jamie Ferrara and he is doing these kind of studies.

00:37:59.370 --> 00:38:01.490 So as you know, since you know about these markets, know about these markets, then you know of course those are the markets that have been developed by Jamie Ferrara and he is doing these kind of studies.

00:38:04.640 --> 00:38:07.028 So as you know, since you know about these markets, then you know of course those are the markets that have been developed by Jamie Ferrara and he is doing these kind of studies.

00:38:07.028 --> 00:38:08.620 So as you know, since you know about these markets, then you know of course those are the markets that have been developed by Jamie Ferrara and he is doing these kind of studies.

00:38:08.620 --> 00:38:11.329 then you know of course those are the markets that have been developed by Jamie Ferrara and he is doing these kind of studies.

00:38:11.329 --> 00:38:13.759 the markets that have been developed by Jamie Ferrara and he is doing these kind of studies.

00:38:13.759 --> 00:38:16.524 by Jamie Ferrara and he is doing these kind of studies.

00:38:16.606 --> 00:38:18.976 is doing these kind of studies.

00:38:18.976 --> 00:38:21.372 is doing these kind of studies.
00:38:18.976 --> 00:38:21.356 with Ernst Holler at the moment,
NOTE Confidence: 0.8281397
00:38:21.356 --> 00:38:24.140 within the context of the Magic Consortium,
NOTE Confidence: 0.8281397
00:38:24.140 --> 00:38:26.528 and I haven’t seen direct connections
NOTE Confidence: 0.8281397
00:38:26.528 --> 00:38:28.124 yet between, for instance,
NOTE Confidence: 0.8281397
00:38:28.124 --> 00:38:30.506 which would be really interested rectally,
NOTE Confidence: 0.8281397
00:38:30.510 --> 00:38:31.728 gamma and form.
NOTE Confidence: 0.8281397
00:38:31.728 --> 00:38:34.164 So those are the studies that.
NOTE Confidence: 0.8281397
00:38:34.170 --> 00:38:35.181 They are doing,
NOTE Confidence: 0.8281397
00:38:35.181 --> 00:38:38.249 but I haven’t seen any data from them yet.
NOTE Confidence: 0.8281397
00:38:38.250 --> 00:38:40.356 We have only very limited data
NOTE Confidence: 0.8281397
00:38:40.356 --> 00:38:42.148 because we haven’t used that
NOTE Confidence: 0.8281397
00:38:42.148 --> 00:38:44.367 panel that they are using so much.
NOTE Confidence: 0.8043221
00:38:45.080 --> 00:38:46.739 OK, awesome and I’m gonna read you.
NOTE Confidence: 0.8043221
00:38:46.740 --> 00:38:48.615 The second question from Lewis
NOTE Confidence: 0.8043221
00:38:48.615 --> 00:38:50.490 is one of our transplanters.
NOTE Confidence: 0.8043221
00:38:50.490 --> 00:38:52.356 Is the New York poupan commercialized
for other sites to study?

The New York School bank. Well, we don’t have a New York school bank. I wish actually that we have one and the one that most people have used is open open Biome and I was just reading that they might have some trouble and that they are closing and that is a company and not for profit company in Boston. So that’s where a lot of people have been getting flora from.

We at the moment are working with some companies also and I put didn’t put that into my slide 2.
Potentially do a sequel transplant

for Graft versus host and you might

have seen very small series from

all over the world where people

tried that for steroids or

have tried that for refractory graft versus host.

They would do a fecal transplant.

Different concepts sometimes that

you just do a normal donor or even

one company is sponsoring a trial

where they take a whole bunch of

healthy healthy folks and literally

mix all of the feces.

And give One Giants and

transplants with that,

and they seem to have some benefit,
so there is a lot of focus at the moment on doing fecal transplant for steroids. Refractory graft versus host and with small series showing showing benefits, but we need much more work and I want to emphasize that there are also risks because we all realize you’re dealing with patients where the gut barrier is negatively impacted by the conditioning regiment. I’m so any kind of bacteria that you give there have a higher likelihood to pass the gut Scott Barrier and you might know of the negative outcomes that we’re seeing with.
00:40:44.784 --> 00:40:46.569 some of these fecal transplants
NOTE Confidence: 0.8375062
00:40:46.569 --> 00:40:48.608 where the product wasn’t carefully
NOTE Confidence: 0.8375062
00:40:48.608 --> 00:40:50.868 screened enough for certain bacteria,
NOTE Confidence: 0.8375062
00:40:50.870 --> 00:40:53.732 which led to two patients getting
NOTE Confidence: 0.8375062
00:40:53.732 --> 00:40:56.949 seriously ill and one of them dying.
NOTE Confidence: 0.8375062
00:40:56.950 --> 00:40:58.455 So there there are a lot of
NOTE Confidence: 0.8375062
00:40:58.455 --> 00:41:00.120 a lot of risks there, so.
NOTE Confidence: 0.8816916
00:41:01.690 --> 00:41:02.790 Then you have a question.
NOTE Confidence: 0.8816916
00:41:02.790 --> 00:41:04.316 Do you want to ask it directly?
NOTE Confidence: 0.73999095
00:41:06.880 --> 00:41:10.660 Hi, fantastic talk thank you.
NOTE Confidence: 0.73999095
00:41:10.660 --> 00:41:13.124 Do you see similar effects of the
NOTE Confidence: 0.8718298
00:41:13.130 --> 00:41:15.660 microbiome in auto transplants?
NOTE Confidence: 0.8167996
00:41:15.660 --> 00:41:18.593 Yeah, so I showed some of the data.
NOTE Confidence: 0.8167996
00:41:18.593 --> 00:41:20.308 So for autotransplant we see
NOTE Confidence: 0.8167996
00:41:20.308 --> 00:41:22.690 the same drop in the diversity,
NOTE Confidence: 0.8167996
00:41:22.690 --> 00:41:24.170 again starting immediately and
we see also links to outcomes. So for instance, for myeloma we could very nicely see that patients with less of a loss in their diversity would have better PFS and OS, so that seems to be a real benefit. All of this needs to be studied in much more detail because now of course you’re talking about it. Order whatever transplants are not talking about a graft versus host or something. but there are signals that are absolutely worthwhile studying for.
Now, so I think it’s fascinating where that in this population you are studying the immune system so intricately and. And can some of this work trying to be transplanted? You know their translator to patients who are not in the transplant setting in terms of you know immune interaction. I think you were mentioning the effects on immunotherapy. So I think that is of course where a number of companies and number of centers and number of scientists are going with this.
The general concept being that the gut flora can modulate immunity, which it almost has to write because you’re in a constant interaction there with God for us. So it’s very clear that T cell repertoire and activation of innate cells is very much modulated by changes within the floor. That is obvious. So people have taken this, of course within the field of a checkpoint blockade much much further. You might know there was a back to back science articles demonstrating that certain compositions
of the flora were linked to better outcomes with checkpoint blockade,
and that has led to a series of trials that are going on at the moment.
It has also and I always tell that story because I want to warn people.
It has led to negative outcomes and
what I mean by that is that because so many patients heard about these stories?
Oh, you can do something with microbiome,
and my checkpoint therapy is going to go better.
They went to their own pharmacy.
They started to buy local Pro,
Biotic and Drugs etc and A and

a scientist at Anderson had actually carefully analyzed it. And found that those people who did it themselves had worse outcomes from their check. So there are certain dangers and I think this is not sort of a free for all and we still need to understand much more. What are the dietary elements? What are the bacteria that really
00:44:20.750 --> 00:44:22.110 matter for certain outcomes?
NOTE Confidence: 0.8356063
00:44:22.110 --> 00:44:23.915 As I illustrated also simply
NOTE Confidence: 0.8356063
00:44:23.915 --> 00:44:26.460 telling people to eat a lot of
NOTE Confidence: 0.8356063
00:44:26.460 --> 00:44:28.458 fruit well in certain context it
NOTE Confidence: 0.8356063
00:44:28.458 --> 00:44:30.660 might be a bad thing actually.
NOTE Confidence: 0.8356063
00:44:30.660 --> 00:44:31.770 Who would have thought that?
NOTE Confidence: 0.7930988
00:44:33.360 --> 00:44:35.650 Dance, it’s understand the questions.
NOTE Confidence: 0.7930988
00:44:35.650 --> 00:44:38.494 I think it’s fascinating that cross
NOTE Confidence: 0.7930988
00:44:38.494 --> 00:44:41.598 centers you know in in the world,
NOTE Confidence: 0.7930988
00:44:41.600 --> 00:44:43.545 whereas diet is probably quite
NOTE Confidence: 0.7930988
00:44:43.545 --> 00:44:46.144 different that you have such homogeneous
NOTE Confidence: 0.7930988
00:44:46.144 --> 00:44:48.468 or similar starting populations.
NOTE Confidence: 0.7930988
00:44:48.470 --> 00:44:51.676 Yeah, yeah, that we found very fascinating,
NOTE Confidence: 0.7930988
00:44:51.680 --> 00:44:54.416 right? I mean, you’re talking with
NOTE Confidence: 0.7930988
00:44:54.416 --> 00:44:57.628 patients from by iron versus the North
NOTE Confidence: 0.7930988
00:44:57.630 --> 00:45:00.836 of and of Japan, and you would
really think the diets are completely different.
And they will go into these transplant with completely different flora.
But as I mentioned during my talk, also, we really think that that is because most of these people have injured microbiomes to start with.
They come, they come into transplant already having steam for a year or so. So many drugs and antibiotics.
That is probably why it’s so simple.
Something something so.
Do you have a? Do you have a suggestion of a simple measure?
So we ask our hospital to change the diet.
What food is served in the cafeteria?
Well, I think first of all, when we started to look at the diet, I don’t know how it is at your center. But on our transplants floor we it’s almost like an ICU, right?
We have such detailed data about everything finals every eight hours and and daily chemistries.
and blood counts and everything. But when it comes to what do patients actually eat? Most of what we saw is?
Eight half sandwich or something like that,
so we have no detail about what we're actually eating, so I think that is a moment where we need to operate. We need to take that a little bit more serious now that we know that it's a major factor that can have impacts on microbiome microbiome. I hope that you got that out of this lecture. Really seems to impact on clinically relevant outcomes, so that's one of the things that I'm trying to fight for within our hospital so that we take a little bit more serious.
We really need to know what our patients eat, not just nurses scribbling down like well, and then we can learn a lot from it. And then we need to understand in much more detail which of dietary elements do what. OK, that’s fascinating, so I’m not going to get more questions, so I get to have all the questions in the entire conversation here for everybody. But you know that that seems like a fantastic project where you could potentially engage the patient right in documenting using Epic using. Well, I maybe maybe we close on the House and.
NOTE Confidence: 0.842861
00:47:19.340 --> 00:47:20.452 Maybe a fantastic collaboration
NOTE Confidence: 0.842861
00:47:20.452 --> 00:47:22.410 that we would could then do with.
NOTE Confidence: 0.842861
00:47:22.410 --> 00:47:23.801 You have to do that.
NOTE Confidence: 0.842861
00:47:23.801 --> 00:47:25.172 Take that epic interface and
NOTE Confidence: 0.842861
00:47:25.172 --> 00:47:27.150 put it to use for patient care.
NOTE Confidence: 0.842861
00:47:27.150 --> 00:47:28.207 That’d be wonderful.
NOTE Confidence: 0.842861
00:47:28.207 --> 00:47:29.698 Thank you awesome.
NOTE Confidence: 0.842861
00:47:29.700 --> 00:47:31.686 So we’re not getting more questions
NOTE Confidence: 0.842861
00:47:31.686 --> 00:47:32.679 you have answered.
NOTE Confidence: 0.842861
00:47:32.680 --> 00:47:34.550 Everybody’s questions so thank you
NOTE Confidence: 0.842861
00:47:34.550 --> 00:47:37.196 so much again for giving a fantastic
NOTE Confidence: 0.842861
00:47:37.196 --> 00:47:39.326 talk and you certainly have my
NOTE Confidence: 0.842861
00:47:39.326 --> 00:47:41.620 mind spinning and I don’t know if I
NOTE Confidence: 0.842861
00:47:41.620 --> 00:47:44.191 should drink on my ginger tea now.
NOTE Confidence: 0.842861
00:47:44.191 --> 00:47:46.776 Let’s see how that goes.
NOTE Confidence: 0.842861

80
OK, thank you very much.

Much is great.

Thank you.