Today too, are you 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.
to introduce Doctor myself,

who is the head of division

Malignancy's

Cancer Center so Doctor Funding Bank

is an expert in hematopoietic stem cell

transplantation and he obtained his MD

completed a postdoctoral fellowship at

the Pittsghburgh Cancer Institute and his

residency at Duke University Medical Center.

He has been the head of the Division

of Hematology Malignancies since 2008

is also a professor of medicine and

immunology at Weill Cornell Medical

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 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

In 2010, Doctor Finder brought started the Susan and Peter Solomon Divisional Genomics program, which focuses on targeted therapeutic approaches for patients with less 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
NOTE Confidence: 0.8043628
00:02:27.569 --> 00:02:29.579 us incredibly exciting stories on
NOTE Confidence: 0.8043628
00:02:29.579 --> 00:02:31.694 the intestinal microbiome in stem
NOTE Confidence: 0.8043628
00:02:31.694 --> 00:02:33.332 cell transplantation. So welcome.
NOTE Confidence: 0.8043628
00:02:33.332 --> 00:02:36.104 And we look forward to your presentation.
NOTE Confidence: 0.8666846
00:02:37.240 --> 00:02:38.500 Thank you so much.
NOTE Confidence: 0.8666846
00:02:38.500 --> 00:02:41.336 Thank you so much for these kind kind words.
NOTE Confidence: 0.8666846
00:02:41.336 --> 00:02:44.354 Of course this is again going to be a
NOTE Confidence: 0.8666846
00:02:44.354 --> 00:02:47.587 lecture by zoom and we were just saying how?
NOTE Confidence: 0.8666846
00:02:47.590 --> 00:02:49.578 Slowly but steadily we're getting a little
NOTE Confidence: 0.8666846
00:02:49.578 --> 00:02:52.194 bit tired of that and would like to have
NOTE Confidence: 0.8666846
00:02:52.194 --> 00:02:56.290 some real physical lectures again and see
NOTE Confidence: 0.8666846
00:02:56.290 --> 00:02:59.036 your audience and work with your audience.
NOTE Confidence: 0.8666846
00:02:59.036 --> 00:03:01.506 But no matter what, it is a fantastic honor
NOTE Confidence: 0.8666846
00:03:01.506 --> 00:03:03.832 to be your guest and to speak for you.
NOTE Confidence: 0.8666846
00:03:03.832 --> 00:03:05.510 So the first thing that I have to tell
NOTE Confidence: 0.8666846
you honestly is that I do have a conflict 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, texts are linked to a graft versus host, and I’m giving you one study here from 2015 where we demonstrated in a patients during the time of neutrophil engraftment which is about 14 days out from allogeneic.
transplant that the abundance of a commensal enteric cell called sublaudia 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.

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 at the baseline sample, so 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,

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, except for one and I'll get back to that one later. I told you already that these patients came in with fairly similar diversity and when we analyze that actually against normal healthy folks, what we saw is that all at all of these centers patients come into a transplant with lower diversity, and we speculate that that is because most of them will have gone through a year or so of chemotherapy. Neutropenic fevers treated 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,
00:12:02.938 --> 00:12:05.570 with VRE for instance.

00:12:05.570 --> 00:12:06.886 Bob was very striking.

00:12:06.886 --> 00:12:08.860 Is that at all four centers?

00:12:08.860 --> 00:12:10.738 It was one specific species that

00:12:10.738 --> 00:12:12.614 would do that that would lead

00:12:12.614 --> 00:12:14.553 to a state of a dominance and

00:12:14.553 --> 00:12:16.430 that was Enterococcus aficion.

00:12:16.430 --> 00:12:18.070 As I’m showing you here.

00:12:20.100 --> 00:12:22.236 And that seemed to matter clinically.

00:12:22.240 --> 00:12:24.166 Also because what we know Tist

00:12:24.166 --> 00:12:26.158 is having during the period or

00:12:26.158 --> 00:12:28.084 the post transplant period at one

00:12:28.084 --> 00:12:30.452 point a state of dominance with

00:12:30.452 --> 00:12:32.527 Enterococcus aficion was linked to

00:12:32.527 --> 00:12:34.740 greater risk of graft versus host,
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 here 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,
lethal a graft versus host.

Then you must notice that there are these.

These these red diamonds here, which means that there’s a blooming of Enterococcus happening during the development of a graft versus host.

In these mice, these mice are not getting any type of antibiotic or anything else.

We thought first.

Well, maybe that is just for one strain or for one setting.

so we did different strains in three different settings.
For 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. Those that matter in these mouse models. Well, we test the debt by taking a germ free mice, giving them a minimal flora plus or minus Enterococcus. In these mouse models. By the way we saw blooming with different species was not physione, but Enterococcus faecalis an.
If we did that. If these mice had Enterococcus in their flora, then indeed they had worse a 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
00:14:43.769 --> 00:14:46.355 plus the Elo activated T cells
NOTE Confidence: 0.8248834
00:14:46.355 --> 00:14:48.135 which specifically targets the crypt stem cells and causing a
NOTE Confidence: 0.8248834
00:14:48.135 --> 00:14:50.612 graft versus host within the gut.
NOTE Confidence: 0.8248834
00:14:50.612 --> 00:14:52.754 That will lead to enterocyte damage.
NOTE Confidence: 0.8248834
00:14:52.760 --> 00:14:55.568 The enter sites therefore start
NOTE Confidence: 0.8248834
00:14:55.570 --> 00:14:57.630 to make less of an anti microbial
NOTE Confidence: 0.8248834
00:14:57.630 --> 00:15:00.717 approaching called REC 3 which
NOTE Confidence: 0.8248834
00:15:00.717 --> 00:15:03.067 is known as we and others have demonstrated to be a an
NOTE Confidence: 0.8248834
00:15:03.067 --> 00:15:06.242 anti microbial approaching that can contain Enterococcus.
NOTE Confidence: 0.8248834
00:15:06.242 --> 00:15:08.762 Another thing that also happens is
NOTE Confidence: 0.8248834
00:15:08.770 --> 00:15:10.970 that he enterocytes specifically
NOTE Confidence: 0.8248834
00:15:10.970 --> 00:15:12.730 within the ilium or less,
NOTE Confidence: 0.8248834
00:15:12.730 --> 00:15:15.580 are capable of making electees
NOTE Confidence: 0.8248834
00:15:15.580 --> 00:15:17.480
that will lead them to increase levels within the lumen.

Of lactose and that plus the fact that there’s less of rec rec three will then lead to an Enterococcus bloom.

The Enterococcus Bloom pushes away some of the year.

Commensal flora well.

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.

So if there’s less a butyrates then that will lead to even more
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
00:17:02.832 --> 00:17:04.248 graft versus host me.
NOTE Confidence: 0.7907168
00:17:04.250 --> 00:17:05.980 You’re not curing a graft
NOTE Confidence: 0.7907168
00:17:05.980 --> 00:17:07.364 versus host with this,
NOTE Confidence: 0.7907168
00:17:07.370 --> 00:17:09.575 and he could block the
NOTE Confidence: 0.7907168
00:17:09.575 --> 00:17:10.898 blooming of Enterococcus.
NOTE Confidence: 0.7907168
00:17:10.900 --> 00:17:15.103 So then he took that finding back to humans.
NOTE Confidence: 0.7907168
00:17:15.110 --> 00:17:17.318 And we looked in our patients.
NOTE Confidence: 0.7907168
00:17:17.320 --> 00:17:18.058 A cohort.
NOTE Confidence: 0.7907168
00:17:18.058 --> 00:17:19.903 Are there maybe patients who
NOTE Confidence: 0.7907168
00:17:19.903 --> 00:17:21.010 have lactose intolerance?
NOTE Confidence: 0.7907168
00:17:21.010 --> 00:17:23.600 When we looked at that we hoped,
NOTE Confidence: 0.7907168
00:17:23.600 --> 00:17:24.310 of course,
NOTE Confidence: 0.7907168
00:17:24.310 --> 00:17:26.795 is that that would be linked to
NOTE Confidence: 0.7907168
00:17:26.795 --> 00:17:29.128 increased levels of graft versus host.
NOTE Confidence: 0.7907168
00:17:29.130 --> 00:17:32.442 We didn’t really find that there was a trend,
NOTE Confidence: 0.7907168
00:17:32.450 --> 00:17:35.026 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 of

Enterococcus 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 a 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.

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 tazobactam and imipenem also
mirror mirror Panama’s.

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 that 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. Ecker, Ecker, Mencia and Accra. 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 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 these that will lead to greater activation will lead to greater activation of Elo activated CD 4T cells. In this model that we are using, 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, 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 studies over the last two years,

do seem to indicate that the use 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 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.
00:24:21.825 --> 00:24:24.710 to taking this into trials now.
NOTE Confidence: 0.8515854
00:24:24.710 --> 00:24:26.150 A second major factor,
NOTE Confidence: 0.8515854
00:24:26.150 --> 00:24:29.227 we think that can impact on the dramatic
NOTE Confidence: 0.8515854
00:24:29.227 --> 00:24:32.153 loss of diversity are are the different
NOTE Confidence: 0.8515854
00:24:32.153 --> 00:24:34.669 types of a conditioning regiments.
NOTE Confidence: 0.8515854
00:24:34.670 --> 00:24:37.099 So we took a deep dive here.
NOTE Confidence: 0.8515854
00:24:37.100 --> 00:24:39.557 As all of the different types of
NOTE Confidence: 0.8515854
00:24:39.557 --> 00:24:40.951 air conditioning regiments that
NOTE Confidence: 0.8515854
00:24:40.951 --> 00:24:42.925 we have been using at our center,
NOTE Confidence: 0.8515854
00:24:42.930 --> 00:24:44.550 and as you can see,
NOTE Confidence: 0.8515854
00:24:44.550 --> 00:24:47.268 there are many.
NOTE Confidence: 0.8515854
00:24:47.268 --> 00:24:49.089 You can put them into three
NOTE Confidence: 0.8515854
00:24:49.090 --> 00:24:52.842 Going from my lower blade of two reduced
NOTE Confidence: 0.8515854
00:24:52.842 --> 00:24:55.397 intensity tune on my lower blade.
NOTE Confidence: 0.8515854
00:24:55.400 --> 00:24:58.550 And if you do that as you would expect,
the ones with lower strength indeed curfew less of a drop in the diversity.
And even if you were control for the use of antibiotics, you still keep on finding that same thing.
Another thing that was very interesting when we looked at it in some more detail is that certain regiments and we don’t know why we need to study that further, such as this one with fludarabine, cyclophosphamide and low dose at TV. I seem to be linked to the blooming of certain bacteria, and here I’m pointing out again 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 dietze data, we hired a nutritionist who very carefully monitored exactly what these patients 8. 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 that the calorie intake the moment that these patients are coming goes down dramatically and follows 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 diversity immediately dropped when patients come into a hospital, and that that diversity 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,
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 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 or staying put in that same cluster. And when she did that kind of an analysis, what was very striking is that, of 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 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. 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.
in therapies in four, then you can think about the use of antibiotics, and that is probably the lowest hanging fruit because those are drugs that we given that we can easily monitor. The second category would be. Prebiotics were thinking of there is to maybe give specific nutrients that would help that would feed that would favor texture that we think could be of benefit. The one that most people are focused on is ProBiotic.
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,

So we didn't see much there.

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
much their own flora.

Back so the concept seemed to be working, but in terms of clinically relevant outcomes, the only thing that we saw in this very small series was actually something that we weren’t counting on, and that is that the activation of certain viruses which commonly happens within the context of allogeneic transplant, such as CMV and EBV was somewhat lower in those patients who have been treated with an auto fecal transplant. Another thing that we notice is that auto fecal transplant seemed to favor the engraftment reconstitution of
neutrophils, lymphocytes and monocytes.

A study that we’re working on that is not open yet is to really rationally design a consortia of these bacteria pretty much based upon 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 that what I’ve been trying to show you is 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 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?

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

00:38:07.028 --> 00:38:08.620 know about these markets, then you know of course those are the markets that have been developed by Jamie Ferrara an he is doing these kind of studies.
with Ernst Holler at the moment, within the context of the Magic Consortium, and I haven’t seen direct connections yet between, for instance, which would be really interested rectally, So those are the studies that. They are doing, but I haven’t seen any data from them yet. We have only very limited data because we haven’t used that panel that they are using so much. OK, awesome and I’m gonna read you. The second question from Lewis is one of our transplanters.
00:38:52.356 --> 00:38:53.990 for other sites to study?

00:38:55.590 --> 00:38:58.990 The New York School bank. Well,

00:38:58.990 --> 00:39:02.118 we don’t have a New York school bank.

00:39:02.118 --> 00:39:04.639 I wish actually that we have one

00:39:04.639 --> 00:39:06.810 and the one that most people have

00:39:06.810 --> 00:39:09.446 used is open open Biome and I was

00:39:09.446 --> 00:39:11.542 just reading that they might have

00:39:11.542 --> 00:39:13.702 some trouble and that they are

00:39:13.702 --> 00:39:16.089 closing and that is a company and

00:39:16.089 --> 00:39:18.003 not for profit company in Boston.

00:39:18.003 --> 00:39:20.194 So that’s where a lot of people

00:39:20.194 --> 00:39:22.108 have been getting flora from.

00:39:22.110 --> 00:39:24.784 We at the moment are working with

00:39:24.784 --> 00:39:26.917 some companies also and I put

00:39:26.917 --> 00:39:29.038 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 have tried that for steroids or 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 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 regimen. 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.
some of these fecal transplants where the product wasn’t carefully screened enough for certain bacteria, which led to two patients getting seriously ill and one of them dying. So there are a lot of risks there, so.

Hi, fantastic talk thank you. Do you see similar effects of the microbiome in auto transplants? Yeah, so I showed some of the data. So for autotransplant we see the same drop in the diversity, again starting immediately and
00:41:24.170 --> 00:41:26.390 we see also links to outcomes.
00:41:26.390 --> 00:41:27.542 So for instance,
00:41:27.542 --> 00:41:29.846 for myeloma we could very nicely
00:41:29.846 --> 00:41:31.857 see that patients with a with
00:41:31.857 --> 00:41:34.304 less of a loss in their diversity
00:41:34.304 --> 00:41:36.746 would have better PFS and OS,
00:41:36.750 --> 00:41:40.080 so that that seems to be a real benefit.
00:41:40.080 --> 00:41:42.670 All of this needs to be studied
00:41:42.670 --> 00:41:45.293 in much more detail because now of
00:41:45.293 --> 00:41:47.198 course you’re talking about it.
00:41:47.200 --> 00:41:49.558 Order whatever transplants are not talking
00:41:49.558 --> 00:41:52.318 about a graft versus host or something.
00:41:52.320 --> 00:41:53.313 Things like that,
00:41:53.313 --> 00:41:55.630 but there are signals there that are
00:41:55.693 --> 00:41:57.837 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 to back science articles demonstrating that certain compositions
00:43:07.689 --> 00:43:10.713 of the flora were linked to better
NOTE Confidence: 0.8356063
00:43:10.713 --> 00:43:12.365 outcomes with checkpoint blockade,
NOTE Confidence: 0.8356063
00:43:12.370 --> 00:43:14.200 foreign Melanoma and so on,
NOTE Confidence: 0.8356063
00:43:14.200 --> 00:43:17.395 and that has led to a series of trials
NOTE Confidence: 0.8356063
00:43:17.395 --> 00:43:20.070 that are going on at the moment.
NOTE Confidence: 0.8356063
00:43:20.070 --> 00:43:23.060 It has also and I always tell that
NOTE Confidence: 0.8356063
00:43:23.060 --> 00:43:26.000 story because I want to warn people.
NOTE Confidence: 0.8356063
00:43:26.000 --> 00:43:28.289 It has led to negative outcomes and
NOTE Confidence: 0.8356063
00:43:28.289 --> 00:43:31.515 what I mean by that is that because so
NOTE Confidence: 0.8356063
00:43:31.515 --> 00:43:34.009 many patients heard about these stories?
NOTE Confidence: 0.8356063
00:43:34.010 --> 00:43:36.558 Oh, you can do something with microbiome,
NOTE Confidence: 0.8356063
00:43:36.560 --> 00:43:38.735 and my checkpoint therapy is
NOTE Confidence: 0.8356063
00:43:38.735 --> 00:43:40.475 going to go better.
NOTE Confidence: 0.8356063
00:43:40.480 --> 00:43:43.078 They went to their own pharmacy.
NOTE Confidence: 0.8356063
00:43:43.080 --> 00:43:45.690 They started to buy local Pro,
NOTE Confidence: 0.8356063
00:43:45.690 --> 00:43:46.083 Pro,
Biotic and Drugs etc and A and

A scientist at Anderson had actually carefully analyzed it.

And found that those people who did do it themselves.

Probiotics had worse outcomes from their check.

One blocked then patients who didn’t do that.

So there are certain dangers and I think we have to warn people also about this.

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
00:45:00.840 --> 00:45:02.832 really think the diets are completely different.
00:45:04.330 --> 00:45:06.766 And they will go into these transplant with completely different flora.
00:45:08.200 --> 00:45:10.600 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.
00:45:12.840 --> 00:45:15.114 They come, they come into transplant already having steam for a year or so. So many drugs and antibiotics.
00:45:17.000 --> 00:45:19.406 They come, they come into transplant already having steam for a year or so. So many drugs and antibiotics.
00:45:19.406 --> 00:45:21.927 That is probably why it’s so simple.
00:45:28.180 --> 00:45:29.650 Something something so.
00:45:29.650 --> 00:45:32.994 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 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 that 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, maybe we close on the House and.
Maybe a fantastic collaboration that we could then do with.
You have to do that.
Take that epic interface and put it to use for patient care. That’d be wonderful.
Thank you awesome.
So we’re not getting more questions you have answered.
Everybody’s questions so thank you so much again for giving a fantastic talk and you certainly have my mind spinning and I don’t know if I should drink on my ginger tea now. Let’s see how that goes.
OK, thank you very much.

Much is great.

Thank you.