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.
to introduce Doctor myself,

wondering who is the head of division

of hematologic malignancy Malignancy’s

so Doctor Funding Bank

is an expert in hematopoietic stem cell

transplantation and he obtained his MD

completed a postdoctoral fellowship at

the Pittsburgh 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 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 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
us incredibly exciting stories on

the intestinal microbiome in stem cell transplantation. So welcome.

And we look forward to your presentation.

Thank you so much.

Thank you so much for these kind kind words.

Of course this is again going to be a lecture by zoom and we were just saying how slow but steadily we're getting a little bit tired of that and would like to have some real physical lectures again and see your audience and work with your audience. But no matter what, it is a fantastic honor to be your guest and to speak for you. 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 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.

If you do that, then you can paint a cladogram an indicate with a blue color text said 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, 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 where during the time period, of 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 led 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,

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 centers. What we notice is that the moment that they come in for allogeneic transplant,
there is 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,
NOTE Confidence: 0.7821491
as I said already,
NOTE Confidence: 0.7821491
is about 14 days out from allergen
NOTE Confidence: 0.7821491
echo transplant patients who at
NOTE Confidence: 0.7821491
that point had higher diversity,
NOTE Confidence: 0.7821491
that better overall outcomes.
NOTE Confidence: 0.7821491
And this was holding up for
NOTE Confidence: 0.7821491
the New York and patients,
NOTE Confidence: 0.7821491
but also for the combined cohort
NOTE Confidence: 0.7821491
of the other three centers.
NOTE Confidence: 0.7821491
When we took a deeper dive,
NOTE Confidence: 0.7821491
So what makes or what leads
NOTE Confidence: 0.7821491
to that a difference?
NOTE Confidence: 0.7821491
Then it seemed to be mostly linked
NOTE Confidence: 0.7821491
to transplant related mortality,
NOTE Confidence: 0.7821491
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
00:10:06.150 --> 00:10:08.682 at that time point higher diversity
NOTE Confidence: 0.8554378
00:10:08.682 --> 00:10:11.490 is linked to better overall outcomes.
NOTE Confidence: 0.86777544
00:10:13.630 --> 00:10:16.228 Now, Meanwhile, a number of studies,
NOTE Confidence: 0.86777544
00:10:16.230 --> 00:10:18.605 specifically within checkpoints and blockades
NOTE Confidence: 0.86777544
00:10:18.605 --> 00:10:20.980 have also demonstrated that diversity
NOTE Confidence: 0.86777544
00:10:21.041 --> 00:10:23.159 seems to matter for certain outcomes.
NOTE Confidence: 0.86777544
00:10:23.160 --> 00:10:26.304 In this case, responses to checkpoint
NOTE Confidence: 0.86777544
00:10:26.304 --> 00:10:29.883 blockade and we have some early data
NOTE Confidence: 0.86777544
00:10:29.883 --> 00:10:32.649 also that this might matter for
NOTE Confidence: 0.86777544
00:10:32.649 --> 00:10:35.826 the efficacy of car cell therapy.
NOTE Confidence: 0.86777544
00:10:35.830 --> 00:10:37.846 Some studies that were still finishing
NOTE Confidence: 0.86777544
00:10:37.846 --> 00:10:40.301 at the moment seem to indicate also
NOTE Confidence: 0.86777544
00:10:40.301 --> 00:10:42.389 that changes within the gut flora
NOTE Confidence: 0.86777544
00:10:42.389 --> 00:10:44.188 specific texture could be linked with
NOTE Confidence: 0.86777544
00:10:44.188 --> 00:10:46.555 the pace of the CD four and regeneration
NOTE Confidence: 0.86777544
00:10:46.555 --> 00:10:47.855 after an allogeneic transplants.
I don’t want to make too much of a deal here of these various attacks are 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,
with VRE for instance.

Bob was very striking.

Is that at all four centers?

It was one specific species that would do that that would lead to a state of dominance and that was Enterococcus aficion.

As I’m showing you here.

And that seemed to matter clinically.

Also because what we know Tist is having during the period or the post transplant period at one point a state of dominance with Enterococcus aficion was linked to 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,
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 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 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 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
NOTE Confidence: 0.8248834
00:14:48.135 --> 00:14:50.612 crypt stem cells and causing a
NOTE Confidence: 0.8248834
00:14:50.612 --> 00:14:52.754 graft versus host within the gut.
NOTE Confidence: 0.8248834
00:14:52.760 --> 00:14:55.568 That will lead to enterocyte damage.
NOTE Confidence: 0.8248834
00:14:55.570 --> 00:14:57.630 The enter sites therefore start
NOTE Confidence: 0.8248834
00:14:57.630 --> 00:15:00.717 to make less of an anti microbial
NOTE Confidence: 0.8248834
00:15:00.717 --> 00:15:03.067 approaching called REC 3 which
NOTE Confidence: 0.8248834
00:15:03.067 --> 00:15:06.242 is known as we and others have
NOTE Confidence: 0.8248834
00:15:06.242 --> 00:15:08.762 actually demonstrated to be an an
NOTE Confidence: 0.8248834
00:15:08.770 --> 00:15:10.970 anti and anti microbial approaching
NOTE Confidence: 0.8248834
00:15:10.970 --> 00:15:12.730 that can contain Enterococcus.
NOTE Confidence: 0.8248834
00:15:12.730 --> 00:15:15.580 Another thing that also happens is
NOTE Confidence: 0.8248834
00:15:15.580 --> 00:15:17.480 that he enterocytes specifically
NOTE Confidence: 0.8248834
00:15:17.556 --> 00:15:19.326 within the ilium or less,
NOTE Confidence: 0.8248834
00:15:19.330 --> 00:15:21.355 are capable of making electees
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.

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
damage to the enterocytes and now you’re in a downward spiral. And things get worse and worse. So we’re trying to figure out are there ways that we can maybe blocked AT and we thought initially about some bacteriophages and other things. But then the post Doc who was working on this Christof Stein touring are did a very simple thing. He analyzed simply what are the pathways with already nutrients. As I mentioned already, that Enterococcus favors well. As I said already, it likes Electo, 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
00:17:35.026 --> 00:17:36.933 moment that patients come off antibiotics and that is the 0 here.

00:17:39.460 --> 00:17:41.195 Then those patients who are lactose intolerant will have higher levels of Enterococcus.

00:17:46.540 --> 00:17:48.997 So as I’ve been trying to show you here in this part so the Enterococcus can dominate in the post transplant period, it is linked to a graft versus host, lactose is one of the basic nutrients and lactose or or.

00:17:51.445 --> 00:17:54.090 00:18:01.976 for Enterococcus and using lactate or.

00:18:03.830 --> 00:18:06.051 potentially block the bloom of Enterococcus and in that way limit the graft versus host.

00:18:08.840 --> 00:18:11.115 This of course begs for a clinical
00:18:11.115 --> 00:18:13.289 study which we haven’t done yet,
NOTE Confidence: 0.8346875
00:18:13.290 --> 00:18:16.930 so I can’t tell you anything about that.
NOTE Confidence: 0.8346875
00:18:16.930 --> 00:18:18.890 Meanwhile, other centers have also
NOTE Confidence: 0.8346875
00:18:18.890 --> 00:18:20.850 demonstrated that the levels of
NOTE Confidence: 0.8346875
00:18:20.914 --> 00:18:22.784 Enterococcus within the post transplant
NOTE Confidence: 0.8346875
00:18:22.784 --> 00:18:25.788 periods are linked to a graft versus host.
NOTE Confidence: 0.8346875
00:18:25.790 --> 00:18:29.246 I’m just showing you one out of several here.
NOTE Confidence: 0.85659957
00:18:31.310 --> 00:18:32.930 Another disease that we were interested
NOTE Confidence: 0.85659957
00:18:32.930 --> 00:18:35.707 in is the a complication of chronic graft
NOTE Confidence: 0.85659957
00:18:35.707 --> 00:18:37.762 versus host after allogeneic transplant,
NOTE Confidence: 0.85659957
00:18:37.770 --> 00:18:40.686 so we try to figure out if changes within
NOTE Confidence: 0.85659957
00:18:40.686 --> 00:18:43.890 the four I could be relevant for that also.
NOTE Confidence: 0.85659957
00:18:43.890 --> 00:18:45.822 Now, the onset of chronic graft
NOTE Confidence: 0.85659957
00:18:45.822 --> 00:18:47.970 versus host is of course much,
NOTE Confidence: 0.85659957
00:18:47.970 --> 00:18:50.350 much later is about 200 days out,
NOTE Confidence: 0.85659957
00:18:50.350 --> 00:18:53.077 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 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
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
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, 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 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 2020 three 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, 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

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
The blooming of Enterococcus.

The blooming of Enterococcus.

The blooming of Enterococcus.

The blooming of Enterococcus.

The blooming of Enterococcus.

The blooming of Enterococcus.

The blooming of Enterococcus.
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,
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, 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 day by day and almost 100 patients monitored exactly what these patients 8.

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 calorie intake the moment that these patients are coming 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 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 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. These very simple sugars. That they 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, 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
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 cluster. When she did that kind of an analysis, what was very striking is that, of course the antibiotics will have impact if you transition to another cluster or if you stay where you are. And all of these other drugs and she looked at a grand total of 6063 different drugs can have impact also. 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.

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
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. Pre biotics were thinking of those 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 Pro Biotic.
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 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
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, 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 that what I’ve been trying to show 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 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.

to say I coming up with questions and was every next step you answered my first question,
00:36:26.050 --> 00:36:31.178 so maybe I can start with one so.

00:36:31.180 --> 00:36:34.127 Right, so you are receiving these patients

00:36:34.127 --> 00:36:36.662 for transplant after they have gone

00:36:36.662 --> 00:36:39.068 through months and months of treatment.

00:36:39.070 --> 00:36:42.390 And have you looked at how you know?

00:36:42.390 --> 00:36:43.218 For example,

00:36:43.218 --> 00:36:46.068 you know whether patients receive, you know,

00:36:46.068 --> 00:36:48.791 is decided in or targeted therapy or

00:36:48.791 --> 00:36:51.099 chemotherapy before coming to transplant,

00:36:51.100 --> 00:36:52.819 does that effect?

00:36:52.819 --> 00:36:54.946 What you see, then,

00:36:54.946 --> 00:36:56.976 in terms of transplant outcomes,

00:36:56.980 --> 00:36:58.608 yes. So this is

00:36:58.610 --> 00:37:00.645 of course, where we still

00:37:00.645 --> 00:37:02.680 don’t have very good data.

NOTE Confidence: 0.8748975
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 again, 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? Rank 3 S, T2, etc.

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 know about these markets, know of course those are the markets that have been developed by Jamie Ferrara and he 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
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, 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 just reading that they might have

00:39:11.542 --> 00:39:13.702 some trouble and that they are closing and that is a company and not for profit company in Boston.

00:39:13.702 --> 00:39:16.089 So that’s where a lot of people have been getting flora from.

00:39:16.089 --> 00:39:18.003 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 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 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 any kind of bacteria that you give there have a higher likelihood to pass the gut 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.

Then you have a question.

Do you want to ask it directly?

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,
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 there 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 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,
00:43:46.083 --> 00:43:48.834 Biotic and Drugs etc and A and

00:43:48.834 --> 00:43:51.398 a scientist at Anderson had

00:43:51.398 --> 00:43:53.646 actually carefully analyzed it.

00:43:53.650 --> 00:43:55.620 And found that those people

00:43:55.620 --> 00:44:00.345 who did do it do it yourself.

00:44:00.350 --> 00:44:01.710 Probiotics had worse outcomes

00:44:01.710 --> 00:44:02.730 from their check.

00:44:02.730 --> 00:44:04.090 One blockades then patients

00:44:04.090 --> 00:44:05.450 who didn’t do that.

00:44:05.450 --> 00:44:08.242 So there are certain dangers and I think

00:44:08.242 --> 00:44:10.847 we have to warn people also about this.

00:44:10.847 --> 00:44:13.973 This is not sort of a free for all and

00:44:13.973 --> 00:44:17.005 and we still need to understand much more.

00:44:17.010 --> 00:44:18.710 What are the dietary elements?

00:44:18.710 --> 00:44:20.750 What are the bacteria that really
matter for certain outcomes?

As I illustrated also simply telling people to eat a lot of fruit well in certain context it might be a bad thing actually. Who would have thought that?

Dance, it's understand the questions. I think it's fascinating that cross centers you know in the world, whereas diet is probably quite different that you have such homogeneous or similar starting populations. Yeah, yeah, that we found very fascinating, right? I mean, you're talking with patients from by iron versus the North 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 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. 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, I maybe maybe we close on the House and.
Maybe a fantastic collaboration that we would 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.