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 was 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

Doctor F unding 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

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, and 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 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 slowly 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 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, and with red color text editor linked with bad outcomes.
And you can differentiate the various clinically relevant outcomes 1st and most of all, of course, the overall survival rate, where you can see that certain texts are linked in a positive or a negative way. Then of course the second one that we have focused on very much is if certain texts are linked to a graft versus host, and I’m giving you one study here from 2015 where we demonstrated in a patients that 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 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.
NOTE Confidence: 0.7821491

A graft versus host.
NOTE Confidence: 0.7821491

But again,
NOTE Confidence: 0.7821491

this was a single center small study.
NOTE Confidence: 0.7821491

So we felt very fortunate when
NOTE Confidence: 0.7821491

some of our dear friends and
NOTE Confidence: 0.7821491

colleagues from all over the world
NOTE Confidence: 0.7821491

were willing to work with us,
NOTE Confidence: 0.7821491

so that now we could do a much larger
NOTE Confidence: 0.7821491

study looking at 1300 plus patients.
NOTE Confidence: 0.7821491

These patients were getting allogeneic
NOTE Confidence: 0.7821491

transplants for AML and DS NHL.
NOTE Confidence: 0.7821491

And the first thing that really
NOTE Confidence: 0.7821491

struck us if we looked at
NOTE Confidence: 0.7821491

the at baseline sample,
NOTE Confidence: 0.7821491

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 focused on really zooming in.
too much on certain attacks,
NOTE Confidence: 0.8554378
except for one and I’ll get back to that one later.
NOTE Confidence: 0.8554378
I told you already that these patients came in with fairly similar diversity
NOTE Confidence: 0.8554378
and the composition of their flora,
NOTE Confidence: 0.8554378
and when we analyze that actually against normal healthy folks,
NOTE Confidence: 0.8554378
what we saw is that all at all of these centers patients come into a transplant with lower diversity,
NOTE Confidence: 0.8554378
and we speculate that that is because most of them will have gone through a year or so of chemotherapy.
NOTE Confidence: 0.8554378
Neutropenic fevers treated
NOTE Confidence: 0.8554378
with all kinds of antibiotics.
And so on. But what was interesting is that coming in with an even lower diversity coming into a transplant was again linked to worse outcomes. Similar findings we have now also for Ottawa transplant where we see a similar drop within the diversity which starts at the moment that these patients come in for a transplant. And again if we take asmark the time point of neutrophil. So engraftment, which is about 9 days out from Ottawa transplants we see again that having
at that time point higher diversity is linked to better overall outcomes. Now, Meanwhile, a number of studies, specifically within checkpoints and blockades have also demonstrated that diversity seems to matter for certain outcomes. In this case, responses to checkpoint blockade and we have some early data that this might matter for the efficacy of car cell therapy. Some studies that were still finishing at the moment seem to indicate also that changes within the gut flora could be linked with 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 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.
NOTE Confidence: 0.86777544
00:12:02.938 --> 00:12:05.570 with VRE for instance.
NOTE Confidence: 0.86777544
00:12:05.570 --> 00:12:06.886 Bob was very striking.
NOTE Confidence: 0.86777544
00:12:06.886 --> 00:12:08.860 Is that at all four centers?
NOTE Confidence: 0.86777544
00:12:08.860 --> 00:12:10.738 It was one specific species that
NOTE Confidence: 0.86777544
00:12:10.738 --> 00:12:12.614 would do that that would lead
NOTE Confidence: 0.86777544
00:12:12.614 --> 00:12:14.553 to a state of a dominance and
NOTE Confidence: 0.86777544
00:12:14.553 --> 00:12:16.430 that was Enterococcus aficion.
NOTE Confidence: 0.86777544
00:12:16.430 --> 00:12:18.070 As I’m showing you here.
NOTE Confidence: 0.8248834
00:12:20.100 --> 00:12:22.236 And that seemed to matter clinically.
NOTE Confidence: 0.8248834
00:12:22.240 --> 00:12:24.166 Also because what we know Tist
NOTE Confidence: 0.8248834
00:12:24.166 --> 00:12:26.158 is having during the period or
NOTE Confidence: 0.8248834
00:12:26.158 --> 00:12:28.084 the post transplant period at one
NOTE Confidence: 0.8248834
00:12:28.084 --> 00:12:30.452 point a state of dominance with
NOTE Confidence: 0.8248834
00:12:30.452 --> 00:12:32.527 Enterococcus aficion was linked to
NOTE Confidence: 0.8248834
00:12:32.527 --> 00:12:34.740 greater risk of graft versus host,
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 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,
For monitoring a graft versus host causing a graft versus host in all of these cases, we kept on finding about seven days out from Allergan Aker transplant during the development of a graft versus host. There’s a blooming of Enterococcus. Well, we test the debt by taking a germ free mice, giving them a minimal flora plus or minus Enterococcus. In these mouse models. By the way we saw blooming with different species was not physiome, but Enterococcus faecalis.
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.
plus the Elo activated T cells which specifically targets the crypt stem cells and causing a graft versus host within the gut. That will lead to enterocyte damage. The enterocytes therefore start to make less of an anti microbial approaching called REC 3 which is known as we and others have actually demonstrated to be an anti microbial that can contain Enterococcus. Another thing that also happens is that the enterocytes specifically within the ilium or less, are capable of making electees.
NOTE Confidence: 0.8248834
00:15:21.355 --> 00:15:23.962 that will lead them to increase
NOTE Confidence: 0.8248834
00:15:23.962 --> 00:15:25.978 levels within the lumen.
NOTE Confidence: 0.8248834
00:15:25.980 --> 00:15:30.378 Of lactose and that plus the fact that
NOTE Confidence: 0.8248834
00:15:30.378 --> 00:15:32.825 there’s less of rec rec three will
NOTE Confidence: 0.8248834
00:15:32.825 --> 00:15:35.033 then lead to an Enterococcus blue.
NOTE Confidence: 0.7907168
00:15:35.040 --> 00:15:36.078 The Enterococcus Bloom
NOTE Confidence: 0.7907168
00:15:36.078 --> 00:15:38.154 pushes away some of the year.
NOTE Confidence: 0.7907168
00:15:38.160 --> 00:15:41.720 Commensal flora well.
NOTE Confidence: 0.7907168
00:15:41.789 --> 00:15:44.389 One of the beneficial things that the
NOTE Confidence: 0.7907168
00:15:44.390 --> 00:15:46.644 commensal flora does is we and others have.
NOTE Confidence: 0.7907168
00:15:46.644 --> 00:15:48.774 and butyrate is a nutrient for these intro sites.
NOTE Confidence: 0.7907168
00:15:48.774 --> 00:15:50.604 So if there’s less a butyrates
NOTE Confidence: 0.7907168
00:15:50.610 --> 00:15:52.602 then that will lead to even more
NOTE Confidence: 0.7907168
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
00:18:53.077 --> 00:18:55.729 looked at the samples about 100 days out
00:18:55.729 --> 00:18:58.665 and try to see if there were certain
00:18:58.665 --> 00:19:01.292 texts on maybe that could be linked.
00:19:01.292 --> 00:19:03.518 In a favorable or an unfavorable
00:19:03.518 --> 00:19:06.291 way with the onset of chronic graft
00:19:06.291 --> 00:19:08.126 versus host much, much later,
00:19:08.126 --> 00:19:10.750 and indeed we have some hints now such
00:19:10.815 --> 00:19:12.980 as Streptococcus in Accra Mencia.
00:19:10.815 --> 00:19:15.152 That seems to favor the onset
00:19:15.152 --> 00:19:17.010 of chronic graft versus host.
00:19:17.010 --> 00:19:19.579 So of course that this needs much
00:19:19.579 --> 00:19:20.680 much more work.
00:19:20.680 --> 00:19:23.014 Another feature in this article that
00:19:23.014 --> 00:19:25.605 I’m not summarizing is that there might
00:19:25.605 --> 00:19:28.307 be also a role for certain short chain
00:19:28.307 --> 00:19:30.307
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
00:20:07.312 --> 00:20:09.635 we typically give when a patient
00:20:09.635 --> 00:20:11.207 has fever and neutropenia,
00:20:11.210 --> 00:20:13.454 and specifically will do damage to
00:20:13.454 --> 00:20:15.400 their commensal enter up flora,
00:20:15.400 --> 00:20:18.472 then indeed the exposure to those
00:20:18.472 --> 00:20:21.476 types of antibiotics will lead to
00:20:21.476 --> 00:20:24.080 a greater drop in the diversity.
00:20:24.080 --> 00:20:26.418 We analyzed over a period about 10
00:20:26.418 --> 00:20:28.825 years the use of antibiotics in
00:20:28.825 --> 00:20:30.605 our allogeneic transplants patients
00:20:30.605 --> 00:20:34.029 and try to see if certain types of
00:20:34.029 --> 00:20:36.044 antibiotics were linked to greater
00:20:36.050 --> 00:20:37.988 incidence of lethal graft versus host
00:20:37.988 --> 00:20:40.747 an we came up with two piperacillin
00:20:40.747 --> 00:20:42.619 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. 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 demonstrate that the gut barrier function.
More impaired in these mice treated with this broad spectrum antibiotic than not, and that again, might set up a cascade of a number of things, more stimulation of potentially of certain dendritic cells that I won’t get into now. They will make higher levels of aside account that we know is linked to gut a graft versus host, which is all three that will lead to greater activation will give you a graph versus host, those are the driving donor T cells leading to worse overall graph versus host.
00:22:32.750 --> 00:22:34.070 Specifically within the column.

00:22:36.340 --> 00:22:39.189 So a number of studies have looked

00:22:39.189 --> 00:22:42.150 now over the last decades or so.

00:22:44.286 --> 00:22:46.303 If the use of broad spectrum

00:22:46.303 --> 00:22:48.379 outcomes after allogeneic transplant,

00:22:48.380 --> 00:22:50.630 and as we were chatting earlier

00:22:50.630 --> 00:22:53.130 the the the first studies looking

00:22:53.130 --> 00:22:55.425 at the use of antibiotics,

00:22:55.430 --> 00:22:57.445 broad spectrum antibiotics in humans

00:22:57.445 --> 00:23:00.371 in the 1970s and 80s actually seemed

00:23:00.371 --> 00:23:03.290 to indicate that wiping out the whole

00:23:03.290 --> 00:23:05.906 flora would lead to better outcomes.

00:23:05.910 --> 00:23:07.870 Specifically, less graft versus host,

00:23:07.870 --> 00:23:10.084 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

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 --> 00:24:45.456 there are many.
NOTE Confidence: 0.8515854
00:24:45.456 --> 00:24:47.268 You can put them into three
NOTE Confidence: 0.8515854
00:24:47.268 --> 00:24:49.089 categories based upon their strength.
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 diet data, we hired a nutritionist who very carefully monitored exactly what these patients ate. 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 goes down dramatically and follows 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. 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 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, that they actually might feed some of the pathogens or the bacteria that are the pathogens or the bacteria that are
taking over in times of low diversity.

And in that case might make matters worse, as has been shown.

For instance, for an enteritis, ferrea colitis model.

And again you see there if you feed these mice while they’re getting DSS.

Also, simple sugars and you see him blossoming of again and bug like Accra Mencia.

So now we can start to make these kind of tables where we can see what food groups might have impact on certain tax.

And of course this can.

This can help us to start to a compose, maybe a diet that would be a beneficial
00:29:00.628 --> 00:29:02.677 for specific patients in specific
00:29:02.677 --> 00:29:05.498 settings and that is of course our
00:29:05.576 --> 00:29:07.850 ultimate goal with all of this.
00:29:09.930 --> 00:29:14.260 Another category is drugs and.
00:29:14.260 --> 00:29:16.852 Patients who are getting an allogeneic
00:29:16.852 --> 00:29:18.580 bone marrow transplantation at
00:29:18.648 --> 00:29:20.790 any given moment are probably on
00:29:20.790 --> 00:29:22.660 seven or eight different drugs.
00:29:22.660 --> 00:29:25.324 And it was a very nice study a couple
00:29:25.324 --> 00:29:28.219 of years back where it was demonstrated
00:29:28.219 --> 00:29:30.931 that many drugs that weren’t antibiotics
00:29:30.931 --> 00:29:33.769 that they actually could also impact
00:29:33.769 --> 00:29:36.700 on many of the bacteria that are
00:29:36.700 --> 00:29:39.559 part of the commensal flora and just
00:29:39.559 --> 00:29:41.959 to highlight some of these drugs.
These are all drugs that we frequently give to our patients, including things like slight cyclosporin. So a very talented, say, graduate student. She took all of the data that we have from all of the samples on 1100 patients. And she put them in a you map and therefore could see all these clusters. She came up with 10 different clusters and labeled them and then analyze. Since we had to kinetic data if the starting or stopping of a
certain drug would have impact on the flora in these patients, moving from one cluster to another cluster or staying put in that same a cluster. And when she did that kind of an analysis, what was very striking is that, 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 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. I'm still very cautious because I feel that we're in the early going, so we still need to know much, much more. But if you categorize the difference...
00:31:27.124 --> 00:31:28.330 in therapies in four,

00:31:28.330 --> 00:31:30.298 then you can think about the

00:31:30.298 --> 00:31:33.733 use of antibiotics,

00:31:33.733 --> 00:31:35.753 and that is probably the lowest hanging

00:31:35.753 --> 00:31:37.867 fruit because those are drugs that

00:31:37.870 --> 00:31:39.570 we given that we can easily monitor.

00:31:39.570 --> 00:31:41.454 The second category would be.

00:31:41.454 --> 00:31:43.523 Pre biotics were thinking of there

00:31:43.523 --> 00:31:45.773 is to maybe give specific nutrients

00:31:45.773 --> 00:31:47.577 that would help that would feed

00:31:47.577 --> 00:31:49.545 we think could be of benefit.

00:31:49.550 --> 00:31:51.482 The one that most people are

00:31:51.482 --> 00:31:53.330 focused on is Pro Biotic.

00:31:53.330 --> 00:31:55.790 So now we're talking bout fecal
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
00:33:10.679 --> 00:33:12.889 original flora from pre transplant?
NOTE Confidence: 0.8246579
00:33:12.890 --> 00:33:15.683 And since this was led by Eric
NOTE Confidence: 0.8246579
00:33:15.683 --> 00:33:18.354 Pamer Ann Young Tower our primary
NOTE Confidence: 0.8246579
00:33:18.354 --> 00:33:21.574 focus was the prevention of C diff.
NOTE Confidence: 0.8246579
00:33:21.580 --> 00:33:23.950 So we looked at that mostly,
NOTE Confidence: 0.8246579
00:33:23.950 --> 00:33:27.110 and as these things go in this series,
NOTE Confidence: 0.8246579
00:33:27.110 --> 00:33:29.480 the incidence of a C diff
NOTE Confidence: 0.8246579
00:33:29.480 --> 00:33:31.060 was actually relatively low,
NOTE Confidence: 0.8246579
00:33:31.060 --> 00:33:35.915 But what we did notice is first
NOTE Confidence: 0.8246579
00:33:35.915 --> 00:33:38.568 of all that’s the concept worked.
NOTE Confidence: 0.8246579
00:33:38.570 --> 00:33:41.762 You could indeed this is the pre transplant
NOTE Confidence: 0.8246579
00:33:41.762 --> 00:33:44.098 and diversity pattern of a patient,
NOTE Confidence: 0.8246579
00:33:44.100 --> 00:33:46.075 who then was transplant again
NOTE Confidence: 0.8246579
00:33:46.075 --> 00:33:48.050 with an auto fecal transplant,
NOTE Confidence: 0.8246579
00:33:48.050 --> 00:33:50.070 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 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

we have worked with at other centers.

So with that I would like to stop and

I should probably stop sharing also.

If I can do that? It seems to be.

But

thank you myself for this really,

really fascinating talk.

I have to say I coming up with

questions and was every next step

you answered my first question,
so maybe I can start with one so.

Right, so you are receiving these patients for transplant after they have gone through months and months of treatment.

And have you looked at how you know? For example,

you know whether patients receive, you know, is decided in or targeted therapy or chemotherapy before coming to transplant,

does that effect?

What you see, then, in terms of transplant outcomes,

yes. So this is of course, where we still don’t have very good data.
We do have some collection also of samples from patients before transplant, specifically with AML. We see a bit of the same patterns, but it hasn’t been analyzed that well yet that we see with allogeneic bone marrow transplantation that an AML patient getting in induction regiment will have the same pattern of the loss of a diversity dominance with certain tax are specifically with 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,

00:37:42.450 --> 00:37:45.410 so it’s very worthwhile to look at that.

00:37:46.260 --> 00:37:48.732 OK, awesome. So we have questions

00:37:48.732 --> 00:37:51.339 from the audience from Lucas Cauda,

00:37:51.340 --> 00:37:53.860 who says great talk in his first

00:37:53.860 --> 00:37:56.949 question is how well does this correlate

00:37:56.949 --> 00:37:59.364 with amino acid magic biomarkers?

00:37:59.370 --> 00:38:01.490 Rank 3 S, T2, etc.

00:38:04.640 --> 00:38:07.028 So as you know, since you

00:38:07.028 --> 00:38:08.620 then you know of course those are

00:38:08.620 --> 00:38:11.329 the markets that have been developed

00:38:11.329 --> 00:38:13.759 by Jamie Ferrara an he

00:38:13.759 --> 00:38:16.524 is doing these kind of studies

00:38:16.606 --> 00:38:18.976
with Ernst Holler at the moment,
NOTE Confidence: 0.8281397
within the context of the Magic Consortium,
NOTE Confidence: 0.8281397
and I haven’t seen direct connections
NOTE Confidence: 0.8281397
yet between, for instance,
NOTE Confidence: 0.8281397
which would be really interested rectally,
NOTE Confidence: 0.8281397
gamma and form.
NOTE Confidence: 0.8281397
So those are the studies that.
NOTE Confidence: 0.8281397
They are doing,
NOTE Confidence: 0.8281397
but I haven’t seen any data from them yet.
NOTE Confidence: 0.8281397
We have only very limited data
NOTE Confidence: 0.8281397
because we haven’t used that
NOTE Confidence: 0.8281397
panel that they are using so much.
NOTE Confidence: 0.8043221
OK, awesome and I’m gonna read you.
NOTE Confidence: 0.8043221
The second question from Lewis
NOTE Confidence: 0.8043221
is one of our transplanters.
NOTE Confidence: 0.8043221
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

00:39:09.446 --> 00:39:11.542 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 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 have been getting flora from.

00:39:20.194 --> 00:39:24.784 We at the moment are working with some companies also and I put didn’t put that into my slide 2.
Potentially do a sequel transplant for Graft versus host and you might have seen very small series from all over the world where people 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 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.

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, again starting immediately and
we see also links to outcomes. So for instance, for myeloma we could very nicely see that patients with less of a loss in their diversity would have better PFS and OS, so that 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 what I mean by that is that because so many patients heard about these stories? Oh, you can do something with microbiome, and my checkpoint therapy is going to go better. They went to their own pharmacy.
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
00:44:20.750 --> 00:44:23.110
mater 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?

I think it’s fascinating that cross centers you know in the world, whereas diet is probably quite different that you have such homogeneous centers you found very fascinating, right? I mean, you’re talking with patients from by iron versus the North patients from by iron versus the North.
00:45:00.840 --> 00:45:02.832 really think the diets
NOTE Confidence: 0.7930988
00:45:02.832 --> 00:45:04.326 are completely different.
NOTE Confidence: 0.7930988
00:45:04.330 --> 00:45:06.766 And they will go into these transplant
NOTE Confidence: 0.7930988
00:45:06.766 --> 00:45:08.200 with completely different flora.
NOTE Confidence: 0.7930988
00:45:08.200 --> 00:45:10.600 But as I mentioned during my talk,
NOTE Confidence: 0.7930988
00:45:10.600 --> 00:45:12.840 also, we really think that that is
NOTE Confidence: 0.7930988
00:45:12.840 --> 00:45:15.114 because most of these people have
NOTE Confidence: 0.7930988
00:45:15.114 --> 00:45:16.999 injured microbiomes to start with.
NOTE Confidence: 0.7930988
00:45:17.000 --> 00:45:19.406 They come, they come into transplant
NOTE Confidence: 0.7930988
00:45:19.406 --> 00:45:21.927 already having steam for a year or so.
NOTE Confidence: 0.7930988
00:45:21.930 --> 00:45:23.690 So many drugs and antibiotics.
NOTE Confidence: 0.7930988
00:45:23.690 --> 00:45:26.147 That is probably why it’s so simple.
NOTE Confidence: 0.783098002857143
00:45:28.180 --> 00:45:29.650 Something something so.
NOTE Confidence: 0.783098002857143
00:45:29.650 --> 00:45:32.994 Do you have a? Do you have a
NOTE Confidence: 0.783098002857143
00:45:32.994 --> 00:45:34.724 suggestion of a simple measure?
NOTE Confidence: 0.783098002857143
So we ask our hospital to change the diet.

What food is served in the cafeteria?

Well, I think first of all, when we started to look at the diet, I don’t know how it is at your center. But on our transplants floor we it’s almost like an ICU, right? We have such detailed data about everything finals every eight hours and and daily chemistries and blood counts and everything. But when it comes to what do patients actually eat? Most of what we saw is?

Eight half sandwich or something like that,
so we have no detail about what we're actually eating, so I think that is a moment where we need to operate. We need to take that a little bit more serious now that we know that it's a major factor that can have impacts on microbiome. 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 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. Well, I maybe maybe we close on the House and.
00:47:19.340 --> 00:47:20.452 Maybe a fantastic collaboration
NOTE Confidence: 0.842861

00:47:20.452 --> 00:47:22.410 that we would could then do with.
NOTE Confidence: 0.842861

00:47:22.410 --> 00:47:23.801 You have to do that.
NOTE Confidence: 0.842861

00:47:23.801 --> 00:47:25.172 Take that epic interface and
NOTE Confidence: 0.842861

00:47:25.172 --> 00:47:27.150 put it to use for patient care.
NOTE Confidence: 0.842861

00:47:27.150 --> 00:47:28.207 That’d be wonderful.
NOTE Confidence: 0.842861

00:47:28.207 --> 00:47:29.698 Thank you awesome.
NOTE Confidence: 0.842861

00:47:29.700 --> 00:47:31.686 So we’re not getting more questions
NOTE Confidence: 0.842861

00:47:31.686 --> 00:47:32.679 you have answered.
NOTE Confidence: 0.842861

00:47:32.680 --> 00:47:34.550 Everybody’s questions so thank you
NOTE Confidence: 0.842861

00:47:34.550 --> 00:47:37.196 so much again for giving a fantastic
NOTE Confidence: 0.842861

00:47:37.196 --> 00:47:39.326 talk and you certainly have my
NOTE Confidence: 0.842861

00:47:39.326 --> 00:47:41.620 mind spinning and I don’t know if I
NOTE Confidence: 0.842861

00:47:41.620 --> 00:47:44.191 should drink on my ginger tea now.
NOTE Confidence: 0.842861

00:47:44.191 --> 00:47:46.776 Let’s see how that goes.
NOTE Confidence: 0.842861
OK, thank you very much.

Much is great.

Thank you.