WEBVTT

NOTE duration:"00:15:24"

NOTE recognizability:0.798

NOTE language:en-us

NOTE Confidence: 0.882362392857143

00:00:15.760 --> 00:00:17.785 Welcome back, this session is

NOTE Confidence: 0.882362392857143

00:00:17.785 --> 00:00:19.230 being recorded. Thank you.

NOTE Confidence: 0.88690593

00:00:22.590 --> 00:00:25.005 Good afternoon, my name is Cliff bug.

NOTE Confidence: 0.88690593

00:00:25.010 --> 00:00:26.870 I'm professor and chair of Pediatrics

NOTE Confidence: 0.88690593

00:00:26.870 --> 00:00:28.819 here at Yale School of Medicine.

NOTE Confidence: 0.88690593

00:00:28.820 --> 00:00:31.548 I'm proud to welcome you to this session

NOTE Confidence: 0.88690593

00:00:31.548 --> 00:00:34.312 entitled The Path ahead and I'll be Co

NOTE Confidence: 0.88690593

00:00:34.312 --> 00:00:36.300 chairing this session with Chen Liu,

NOTE Confidence: 0.88690593

00:00:36.300 --> 00:00:39.366 who's a professor and chair of

NOTE Confidence: 0.88690593

00:00:39.366 --> 00:00:41.410 the Department of Pathology.

NOTE Confidence: 0.88690593

00:00:41.410 --> 00:00:43.665 For our first speaker we

NOTE Confidence: 0.88690593

00:00:43.665 --> 00:00:45.469 I'm proud to welcome.

NOTE Confidence: 0.88690593

00:00:45.470 --> 00:00:46.814 Welcome Noah palm.

NOTE Confidence: 0.88690593

00:00:46.814 --> 00:00:49.502 Noah is an associate professor of

NOTE Confidence: 0.88690593

00:00:49.502 --> 00:00:51.337 Immunobiology at the Yale School

NOTE Confidence: 0.88690593

00:00:51.337 --> 00:00:53.050 of Medicine and he's going to

NOTE Confidence: 0.88690593

00:00:53.050 --> 00:00:55.186 be speaking on the gut liver,

NOTE Confidence: 0.88690593

00:00:55.186 --> 00:00:57.500 axis and liver disease,

NOTE Confidence: 0.88690593

00:00:57.500 --> 00:00:59.070 macrobiotics and more.

NOTE Confidence: 0.878469907222222

00:01:04.360 --> 00:01:06.694 Alright, thanks very much for that

NOTE Confidence: 0.878469907222222

00:01:06.694 --> 00:01:08.572 introduction for the invitation to

NOTE Confidence: 0.878469907222222

00:01:08.572 --> 00:01:10.378 share some of our our work here,

NOTE Confidence: 0.878469907222222

00:01:10.380 --> 00:01:12.420 so I'm going to go ahead and share my screen.

NOTE Confidence: 0.878469907222222

00:01:12.420 --> 00:01:14.844 Let me know if there are any problems.

NOTE Confidence: 0.7415815125

00:01:18.530 --> 00:01:21.170 This look OK Cliff. Looks great.

NOTE Confidence: 0.7415815125

00:01:21.170 --> 00:01:23.880 OK, so I'm going to.

NOTE Confidence: 0.7415815125

00:01:23.880 --> 00:01:25.651 Apologize in advance that I'm not going

NOTE Confidence: 0.7415815125

00:01:25.651 --> 00:01:27.656 to talk too much about things very,

NOTE Confidence: 0.7415815125

00:01:27.656 --> 00:01:29.744 very specific to the liver today,

NOTE Confidence: 0.7415815125

00:01:29.750 --> 00:01:31.631 but I want to share some work with you

NOTE Confidence: 0.7415815125

00:01:31.631 --> 00:01:33.689 that I think it will be hopefully obvious,

NOTE Confidence: 0.7415815125

00:01:33.690 --> 00:01:36.030 and I'll try to note along the way how

NOTE Confidence: 0.7415815125

00:01:36.030 --> 00:01:38.142 this can be applied to understanding

NOTE Confidence: 0.7415815125

00:01:38.142 --> 00:01:40.259 the effect of the trillions of

NOTE Confidence: 0.7415815125

00:01:40.259 --> 00:01:42.121 microbes that that live in our guts

NOTE Confidence: 0.7415815125

00:01:42.121 --> 00:01:44.492 on on liver pathology in particular,

NOTE Confidence: 0.7415815125

00:01:44.492 --> 00:01:48.100 but really kind of the focus of my lab.

NOTE Confidence: 0.7415815125

00:01:48.100 --> 00:01:50.335 More broadly is just understanding

NOTE Confidence: 0.7415815125

00:01:50.335 --> 00:01:52.570 the impacts of these microbes

NOTE Confidence: 0.7415815125

00:01:52.643 --> 00:01:54.245 that live in and on us.

NOTE Confidence: 0.7415815125

00:01:54.250 --> 00:01:56.134 On diverse aspects of of human

NOTE Confidence: 0.7415815125

00:01:56.134 --> 00:01:58.589 biology and so I'm going to try to

NOTE Confidence: 0.7415815125

00:01:58.589 --> 00:02:00.960 kind of give you an overview of the

NOTE Confidence: 0.7415815125

00:02:00.960 --> 00:02:03.136 problems we like to think about some

NOTE Confidence: 0.7415815125

00:02:03.136 --> 00:02:05.212 of the kind of unique approaches

NOTE Confidence: 0.7415815125

00:02:05.212 --> 00:02:08.267 that that we take and then tell you

NOTE Confidence: 0.7415815125

00:02:08.267 --> 00:02:10.207 very briefly some recent findings

NOTE Confidence: 0.7415815125

00:02:10.281 --> 00:02:12.605 that are coming out of a project

NOTE Confidence: 0.7415815125

00:02:12.605 --> 00:02:14.288 that started as a collaboration with

NOTE Confidence: 0.7415815125

00:02:14.288 --> 00:02:15.870 a colleague of mine here at Yale.

NOTE Confidence: 0.7415815125

00:02:15.870 --> 00:02:16.412 Aaron ring.

NOTE Confidence: 0.7415815125

00:02:16.412 --> 00:02:18.309 I guess almost seven years ago now

NOTE Confidence: 0.7415815125

00:02:18.309 --> 00:02:19.738 that we're really excited about

NOTE Confidence: 0.7415815125

00:02:19.738 --> 00:02:21.770 and so excited to kind of share.

NOTE Confidence: 0.7415815125

00:02:21.770 --> 00:02:24.250 Kind of this very hot off the press.

NOTE Confidence: 0.7415815125

00:02:24.250 --> 00:02:26.530 This is kind of work with you today

NOTE Confidence: 0.7415815125

00:02:26.530 --> 00:02:29.008 and so the the the title slightly

NOTE Confidence: 0.7415815125

00:02:29.008 --> 00:02:31.659 different from the title on the on the.

NOTE Confidence: 0.7415815125

00:02:31.660 --> 00:02:33.668 Schedule is mapping uncharted

NOTE Confidence: 0.7415815125

00:02:33.668 --> 00:02:35.676 landscapes of host microbiotic

NOTE Confidence: 0.7415815125

00:02:35.676 --> 00:02:37.350 communication and so by now I think

NOTE Confidence: 0.7415815125

00:02:37.350 --> 00:02:39.308 all of you are aware that we're

NOTE Confidence: 0.7415815125

00:02:39.308 --> 00:02:40.804 constitutively colonized by trillions

NOTE Confidence: 0.7415815125

00:02:40.804 --> 00:02:43.118 of microbes at all barrier surfaces,

NOTE Confidence: 0.7415815125

00:02:43.120 --> 00:02:44.760 maybe most notably in our

NOTE Confidence: 0.7415815125

00:02:44.760 --> 00:02:45.416 gastrointestinal tract,

NOTE Confidence: 0.7415815125

00:02:45.420 --> 00:02:47.592 where each of us contain a

NOTE Confidence: 0.7415815125

00:02:47.592 --> 00:02:49.040 unique consortium or harbor.

NOTE Confidence: 0.7415815125

00:02:49.040 --> 00:02:51.385 A unique consortium of hundreds

NOTE Confidence: 0.7415815125

00:02:51.385 --> 00:02:53.730 of species that encode millions

NOTE Confidence: 0.7415815125

00:02:53.810 --> 00:02:56.120 of genes and produce thousands,

NOTE Confidence: 0.7415815125

00:02:56.120 --> 00:02:58.283 or maybe even 10s of thousands or

NOTE Confidence: 0.7415815125

00:02:58.283 --> 00:03:00.109 hundreds of thousands of unique

NOTE Confidence: 0.7415815125

00:03:00.109 --> 00:03:01.360 small molecule metabolites.

NOTE Confidence: 0.7415815125

00:03:01.360 --> 00:03:03.495 And you're probably also all aware that.

NOTE Confidence: 0.7415815125

00:03:03.500 --> 00:03:05.560 Alterations in these microbial communities,

NOTE Confidence: 0.7415815125

00:03:05.560 --> 00:03:07.240 particularly gut microbial communities,

NOTE Confidence: 0.7415815125

00:03:07.240 --> 00:03:09.760 have been associated with basically every

NOTE Confidence: 0.7415815125

00:03:09.812 --> 00:03:11.726 disease and disorder you can imagine.

NOTE Confidence: 0.7415815125

00:03:11.730 --> 00:03:13.359 Particularly diseases involving

NOTE Confidence: 0.7415815125

00:03:13.359 --> 00:03:14.988 a chronic inflammation,

NOTE Confidence: 0.7415815125

00:03:14.990 --> 00:03:16.770 including diseases of the liver,

NOTE Confidence: 0.7415815125

00:03:16.770 --> 00:03:20.253 as as many of you will be interested in.

NOTE Confidence: 0.7415815125

00:03:20.260 --> 00:03:20.806 However,

NOTE Confidence: 0.7415815125

00:03:20.806 --> 00:03:24.082 despite kind of a revolution in

NOTE Confidence: 0.7415815125

00:03:24.082 --> 00:03:27.867 understanding of and our ability to catalog,

NOTE Confidence: 0.7415815125

00:03:27.870 --> 00:03:30.930 the microbes and their genes and

NOTE Confidence: 0.7415815125

00:03:30.930 --> 00:03:33.924 their products that exist in in

NOTE Confidence: 0.7415815125

00:03:33.924 --> 00:03:36.498 across a diverse array of humans,

NOTE Confidence: 0.7415815125

00:03:36.500 --> 00:03:38.528 using new omics technologies

NOTE Confidence: 0.7415815125

00:03:38.528 --> 00:03:40.556 like next generation sequencing

NOTE Confidence: 0.7415815125

00:03:40.556 --> 00:03:42.540 or untargeted metabolomics,

NOTE Confidence: 0.7415815125

00:03:42.540 --> 00:03:46.076 it actually remains quite hard and quite

NOTE Confidence: 0.7415815125

00:03:46.076 --> 00:03:48.566 challenging to draw causal connections

NOTE Confidence: 0.7415815125

00:03:48.566 --> 00:03:51.020 between specific changes in microbial.

NOTE Confidence: 0.7415815125

00:03:51.020 --> 00:03:53.500 Communities or individual microbes.

NOTE Confidence: 0.7415815125

00:03:53.500 --> 00:03:57.142 Are there products and and specific

NOTE Confidence: 0.7415815125

00:03:57.142 --> 00:03:59.518 physiological outcomes or pathophysiological

NOTE Confidence: 0.7415815125

00:03:59.518 --> 00:04:02.511 outcomes in humans and there really

NOTE Confidence: 0.7415815125

00:04:02.511 --> 00:04:05.245 are two main reasons for that that

NOTE Confidence: 0.7415815125

00:04:05.245 --> 00:04:07.975 my lab really tries to tackle.

NOTE Confidence: 0.7415815125

00:04:07.980 --> 00:04:09.710 One is that correlation does

NOTE Confidence: 0.7415815125

00:04:09.710 --> 00:04:10.748 not equal causation,

NOTE Confidence: 0.7415815125

00:04:10.750 --> 00:04:12.883 so there are lots of reasons that you can

NOTE Confidence: 0.7415815125

00:04:12.883 --> 00:04:14.905 see alterations in microbial communities

NOTE Confidence: 0.7415815125

00:04:14.905 --> 00:04:17.070 that are for epidemiological reasons,

NOTE Confidence: 0.7415815125

00:04:17.070 --> 00:04:19.518 or in fact where the change in the microbial

NOTE Confidence: 0.7415815125

00:04:19.518 --> 00:04:21.250 community is in effect of the disease.

NOTE Confidence: 0.7415815125

00:04:21.250 --> 00:04:23.084 Rather than the cause of the disease,

NOTE Confidence: 0.7415815125

00:04:23.090 --> 00:04:24.932 and the 2nd is that although

NOTE Confidence: 0.7415815125

00:04:24.932 --> 00:04:26.160 we're now getting better

NOTE Confidence: 0.831489862857143

00:04:26.219 --> 00:04:27.984 and better at again generating

NOTE Confidence: 0.831489862857143

00:04:27.984 --> 00:04:30.447 catalogs say of these millions of genes

NOTE Confidence: 0.831489862857143

00:04:30.447 --> 00:04:32.355 that are encoded by these microbes,

NOTE Confidence: 0.831489862857143

00:04:32.360 --> 00:04:34.082 we're still not very good at

NOTE Confidence: 0.831489862857143

00:04:34.082 --> 00:04:35.230 actually understanding what these

NOTE Confidence: 0.831489862857143

00:04:35.282 --> 00:04:36.577 genes and their products do.

NOTE Confidence: 0.831489862857143

00:04:36.580 --> 00:04:39.180 And therefore most of the genes and products,

NOTE Confidence: 0.831489862857143

00:04:39.180 --> 00:04:42.190 and of these microbes remain

NOTE Confidence: 0.831489862857143

00:04:42.190 --> 00:04:43.394 completely unannotated,

NOTE Confidence: 0.831489862857143

00:04:43.400 --> 00:04:45.930 and so that kind of brings me to the major

NOTE Confidence: 0.831489862857143

00:04:45.992 --> 00:04:48.080 question that drives really, you know,

NOTE Confidence: 0.831489862857143

00:04:48.080 --> 00:04:49.971 at least half of the work that we do

NOTE Confidence: 0.831489862857143

00:04:49.971 --> 00:04:51.679 in my lab that's focused on technology.

NOTE Confidence: 0.831489862857143

00:04:51.680 --> 00:04:53.648 Development, which I'll focus on today.

NOTE Confidence: 0.831489862857143

00:04:53.650 --> 00:04:54.850 Which is, you know,

NOTE Confidence: 0.831489862857143

00:04:54.850 --> 00:04:56.650 given this enormous amount of complexity,

NOTE Confidence: 0.831489862857143

00:04:56.650 --> 00:05:00.766 and this this real annotation challenge,

NOTE Confidence: 0.831489862857143

00:05:00.770 --> 00:05:02.630 how can we go about actually

NOTE Confidence: 0.831489862857143

00:05:02.630 --> 00:05:04.669 sifting through all of these genes,

NOTE Confidence: 0.831489862857143

00:05:04.670 --> 00:05:06.154 metabolites and microbes and

NOTE Confidence: 0.831489862857143

00:05:06.154 --> 00:05:08.380 potentially being able to pick out

NOTE Confidence: 0.831489862857143

00:05:08.443 --> 00:05:10.267 those microbes and metabolites?

NOTE Confidence: 0.831489862857143

00:05:10.270 --> 00:05:11.098 For example,

NOTE Confidence: 0.831489862857143

00:05:11.098 --> 00:05:13.582 that are actually playing causal roles

NOTE Confidence: 0.831489862857143

00:05:13.582 --> 00:05:16.031 in in human disease when they're

NOTE Confidence: 0.831489862857143

00:05:16.031 --> 00:05:18.990 hidden in this vast sea of mostly

NOTE Confidence: 0.831489862857143

00:05:18.990 --> 00:05:21.840 irrelevant and mostly unannotated noise.

NOTE Confidence: 0.831489862857143

00:05:21.840 --> 00:05:23.485 And are somewhat unique solution

NOTE Confidence: 0.831489862857143

00:05:23.485 --> 00:05:25.939 to this problem is to develop new

NOTE Confidence: 0.831489862857143

00:05:25.939 --> 00:05:28.171 technologies that we refer to often

NOTE Confidence: 0.831489862857143

00:05:28.171 --> 00:05:30.379 as functional profiling technologies,

NOTE Confidence: 0.831489862857143

00:05:30.380 --> 00:05:32.135 which we conceptualize as using

NOTE Confidence: 0.831489862857143

00:05:32.135 --> 00:05:33.890 the host as a lens.

NOTE Confidence: 0.831489862857143

00:05:33.890 --> 00:05:36.044 To achieve this kind of complexity

NOTE Confidence: 0.831489862857143

00:05:36.044 --> 00:05:38.340 reduction exercise that I alluded to

NOTE Confidence: 0.831489862857143

00:05:38.340 --> 00:05:40.340 to really illuminate the microbes

NOTE Confidence: 0.831489862857143

00:05:40.340 --> 00:05:42.505 and microbial products that are most

NOTE Confidence: 0.831489862857143

00:05:42.505 --> 00:05:44.598 likely to be shaping our own biology

NOTE Confidence: 0.831489862857143

00:05:44.600 --> 00:05:46.819 as well as their mechanisms of action.

NOTE Confidence: 0.831489862857143

00:05:46.820 --> 00:05:48.260 And all of these technologies.

NOTE Confidence: 0.831489862857143

00:05:48.260 --> 00:05:49.870 I won't go through the details of

NOTE Confidence: 0.831489862857143

00:05:49.870 --> 00:05:51.846 of all of the specifics of how

NOTE Confidence: 0.831489862857143

00:05:51.846 --> 00:05:52.764 we accomplish this.

NOTE Confidence: 0.831489862857143

00:05:52.770 --> 00:05:53.736 I'll just tell you about it.

NOTE Confidence: 0.831489862857143

00:05:53.740 --> 00:05:54.716 At a high level,

NOTE Confidence: 0.831489862857143

00:05:54.716 --> 00:05:56.180 but kind of the concept behind

NOTE Confidence: 0.831489862857143

00:05:56.238 --> 00:05:57.798 this is is really very simple,

NOTE Confidence: 0.831489862857143

00:05:57.800 --> 00:06:00.104 which is that those microbes or

NOTE Confidence: 0.831489862857143

00:06:00.104 --> 00:06:02.064 microbial metabolites that are most

NOTE Confidence: 0.831489862857143

00:06:02.064 --> 00:06:04.577 likely to impact us are those microbes

NOTE Confidence: 0.831489862857143

00:06:04.577 --> 00:06:06.721 or metabolites that can interact with

NOTE Confidence: 0.831489862857143

00:06:06.721 --> 00:06:09.171 our own biology in some specific way.

NOTE Confidence: 0.831489862857143

00:06:09.171 --> 00:06:11.978 And so we've developed a number of

NOTE Confidence: 0.831489862857143

00:06:11.978 --> 00:06:15.072 technologies to to kind of fish out these

NOTE Confidence: 0.831489862857143

00:06:15.072 --> 00:06:17.340 kinds of specific specific microbes,

NOTE Confidence: 0.831489862857143

00:06:17.340 --> 00:06:19.134 including a technology that uses the

NOTE Confidence: 0.831489862857143

00:06:19.134 --> 00:06:21.020 antibody response to the microbiology,

NOTE Confidence: 0.831489862857143

00:06:21.020 --> 00:06:22.396 to fish out immunomodulatory.

NOTE Confidence: 0.831489862857143

00:06:22.396 --> 00:06:24.116 Microbes which we've shown that

NOTE Confidence: 0.831489862857143

00:06:24.116 --> 00:06:25.787 these this can actually highlight

NOTE Confidence: 0.831489862857143

00:06:25.787 --> 00:06:27.377 microbes that play causal roles

NOTE Confidence: 0.831489862857143

00:06:27.377 --> 00:06:29.138 in inflammatory bowel disease.

NOTE Confidence: 0.831489862857143

00:06:29.140 --> 00:06:29.978 More recently,

NOTE Confidence: 0.831489862857143

00:06:29.978 --> 00:06:31.654 we've developed technologies that

NOTE Confidence: 0.831489862857143

00:06:31.654 --> 00:06:34.168 allow us to identify microbes that

NOTE Confidence: 0.831489862857143

00:06:34.168 --> 00:06:36.496 create and produce small molecules that

NOTE Confidence: 0.831489862857143

00:06:36.496 --> 00:06:38.919 activate G protein coupled receptors.

NOTE Confidence: 0.831489862857143

00:06:38.920 --> 00:06:40.348 Many of you may be familiar with

NOTE Confidence: 0.831489862857143

00:06:40.348 --> 00:06:40.960 this receptor family,

NOTE Confidence: 0.831489862857143

00:06:40.960 --> 00:06:43.384 that's the largest family of of

NOTE Confidence: 0.831489862857143

00:06:43.384 --> 00:06:46.020 receptors encoded in the human genome.

NOTE Confidence: 0.831489862857143

00:06:46.020 --> 00:06:47.676 But today I'm going to focus

NOTE Confidence: 0.831489862857143

00:06:47.676 --> 00:06:49.500 on on this middle group here,

NOTE Confidence: 0.831489862857143

00:06:49.500 --> 00:06:52.350 which is all unpublished work.

NOTE Confidence: 0.831489862857143

00:06:52.350 --> 00:06:55.026 Which is actually a technology we've

NOTE Confidence: 0.831489862857143

00:06:55.026 --> 00:06:56.810 developed to simultaneously assess

NOTE Confidence: 0.831489862857143

00:06:56.882 --> 00:06:59.147 all in potential interactions between

NOTE Confidence: 0.831489862857143

00:06:59.147 --> 00:07:01.412 individual microbes and nearly all

NOTE Confidence: 0.831489862857143

00:07:01.476 --> 00:07:04.116 human extracellular and secreted proteins.

NOTE Confidence: 0.831489862857143

00:07:04.120 --> 00:07:06.118 So all receptors expressed on the

NOTE Confidence: 0.831489862857143

00:07:06.118 --> 00:07:08.182 surface of cells or proteins secreted

NOTE Confidence: 0.831489862857143

00:07:08.182 --> 00:07:11.290 into the outside of the of the host cells,

NOTE Confidence: 0.831489862857143

00:07:11.290 --> 00:07:13.593 and so these would be nearly all

NOTE Confidence: 0.831489862857143

00:07:13.593 --> 00:07:15.449 proteins with which an extracellular

NOTE Confidence: 0.831489862857143

00:07:15.449 --> 00:07:17.867 microbe would be able to interact.

NOTE Confidence: 0.831489862857143

00:07:17.870 --> 00:07:20.350 And this, as I mentioned at the beginning,

NOTE Confidence: 0.831489862857143

00:07:20.350 --> 00:07:21.628 really is a.

NOTE Confidence: 0.831489862857143

00:07:21.628 --> 00:07:23.332 And incredibly close collaboration

NOTE Confidence: 0.831489862857143

00:07:23.332 --> 00:07:25.399 with my colleague Aaron Ring,

NOTE Confidence: 0.831489862857143

00:07:25.400 --> 00:07:26.924 who actually started his lab here

NOTE Confidence: 0.831489862857143

00:07:26.924 --> 00:07:27.940 at about the same

NOTE Confidence: 0.768497892631579

00:07:27.995 --> 00:07:30.207 time and was spearheaded by a commenter

NOTE Confidence: 0.768497892631579

00:07:30.207 --> 00:07:32.790 graduate student, Connor Rosen.

NOTE Confidence: 0.768497892631579

00:07:32.790 --> 00:07:34.813 And so hopefully it's obvious to many

NOTE Confidence: 0.768497892631579

00:07:34.813 --> 00:07:37.944 of you why it would be interesting to

NOTE Confidence: 0.768497892631579

00:07:37.944 --> 00:07:39.704 understand these specific interactions

NOTE Confidence: 0.768497892631579

00:07:39.704 --> 00:07:41.528 between microbes and the host,

NOTE Confidence: 0.768497892631579

00:07:41.530 --> 00:07:42.840 both because microbes that interact

NOTE Confidence: 0.768497892631579

00:07:42.840 --> 00:07:44.480 with the host in this specific

NOTE Confidence: 0.768497892631579

00:07:44.480 --> 00:07:46.136 way are likely to be interesting,

NOTE Confidence: 0.768497892631579

00:07:46.140 --> 00:07:48.135 and also because by understanding

NOTE Confidence: 0.768497892631579

00:07:48.135 --> 00:07:50.130 which receptors they engage and

NOTE Confidence: 0.768497892631579

00:07:50.199 --> 00:07:52.279 leveraging our our core knowledge

NOTE Confidence: 0.768497892631579

00:07:52.279 --> 00:07:53.943 about those host receptors,

NOTE Confidence: 0.768497892631579

00:07:53.950 --> 00:07:56.032 we can potentially make some very

NOTE Confidence: 0.768497892631579

00:07:56.032 --> 00:07:57.772 sophisticated predictions about what the

NOTE Confidence: 0.768497892631579

00:07:57.772 --> 00:07:59.554 outcomes of these interactions may be.

NOTE Confidence: 0.768497892631579

00:07:59.560 --> 00:08:01.037 And I'll give I'll show you one

NOTE Confidence: 0.768497892631579

00:08:01.037 --> 00:08:02.749 example of that at the end of the talk.

NOTE Confidence: 0.768497892631579

00:08:02.750 --> 00:08:04.010 Also, for this crowd,

NOTE Confidence: 0.768497892631579

00:08:04.010 --> 00:08:05.900 I think it's notable that we're

NOTE Confidence: 0.768497892631579

00:08:05.968 --> 00:08:08.110 accumulating more and more evidence that

NOTE Confidence: 0.768497892631579

00:08:08.110 --> 00:08:10.318 even though we used to conceptualize

NOTE Confidence: 0.768497892631579

00:08:10.318 --> 00:08:13.174 tissues such as the liver as being sterile,

NOTE Confidence: 0.768497892631579

00:08:13.180 --> 00:08:14.293 that in fact,

NOTE Confidence: 0.768497892631579

00:08:14.293 --> 00:08:16.519 in in many pathophysiological states as

NOTE Confidence: 0.768497892631579

00:08:16.519 --> 00:08:19.398 well as possibly even physiological states,

NOTE Confidence: 0.768497892631579

00:08:19.400 --> 00:08:21.032 that we do have microbes making

NOTE Confidence: 0.768497892631579

00:08:21.032 --> 00:08:22.739 it to places like the liver,

NOTE Confidence: 0.768497892631579

00:08:22.740 --> 00:08:24.220 and there's accumulating evidence

NOTE Confidence: 0.768497892631579

00:08:24.220 --> 00:08:26.827 that the the microbes that make it

NOTE Confidence: 0.768497892631579

00:08:26.827 --> 00:08:28.477 to those environments can actually

NOTE Confidence: 0.768497892631579

00:08:28.477 --> 00:08:30.684 play causal roles in initiating or

NOTE Confidence: 0.768497892631579

00:08:30.684 --> 00:08:32.754 exacerbating a diversity of diseases.

NOTE Confidence: 0.768497892631579

00:08:32.760 --> 00:08:34.260 Including diseases like primary

NOTE Confidence: 0.768497892631579

00:08:34.260 --> 00:08:35.010 sclerosing cholangitis,

NOTE Confidence: 0.768497892631579

00:08:35.010 --> 00:08:36.870 which we're all very familiar with,

NOTE Confidence: 0.768497892631579

00:08:36.870 --> 00:08:39.558 as well as even a seeding,

NOTE Confidence: 0.768497892631579

00:08:39.560 --> 00:08:42.056 a systemic autoimmunity from

NOTE Confidence: 0.768497892631579

00:08:42.056 --> 00:08:43.928 those liver sites.

NOTE Confidence: 0.768497892631579

00:08:43.930 --> 00:08:45.680 So we basically set out a few

NOTE Confidence: 0.768497892631579

00:08:45.680 --> 00:08:47.946 years ago to think about whether

NOTE Confidence: 0.768497892631579

00:08:47.946 --> 00:08:49.878 we could actually systematically

NOTE Confidence: 0.768497892631579

00:08:49.878 --> 00:08:51.750 interrogate this interaction space,

NOTE Confidence: 0.768497892631579

00:08:51.750 --> 00:08:54.108 the dream being to actually understand

NOTE Confidence: 0.768497892631579

00:08:54.108 --> 00:08:57.004 and math all of the potential

NOTE Confidence: 0.768497892631579

00:08:57.004 --> 00:08:58.873 interactions between individual

NOTE Confidence: 0.768497892631579

00:08:58.873 --> 00:09:01.930 hundreds of individual microbes cultured

NOTE Confidence: 0.768497892631579

00:09:01.930 --> 00:09:05.850 from human gut samples and all human

NOTE Confidence: 0.768497892631579

00:09:05.850 --> 00:09:08.660 extracellular and secreted proteins.

NOTE Confidence: 0.768497892631579

00:09:08.660 --> 00:09:10.460 And so this is kind of was the goal

NOTE Confidence: 0.768497892631579

00:09:10.460 --> 00:09:12.445 was to create this kind of molecular

NOTE Confidence: 0.768497892631579

00:09:12.445 --> 00:09:14.219 search engine where the input would

NOTE Confidence: 0.768497892631579

00:09:14.219 --> 00:09:16.214 be a microbe plus the human explodium,

NOTE Confidence: 0.768497892631579

00:09:16.220 --> 00:09:17.630 all extracellular and secreted proteins,

NOTE Confidence: 0.768497892631579

00:09:17.630 --> 00:09:19.120 which is about 5000 proteins.

NOTE Confidence: 0.768497892631579

00:09:19.120 --> 00:09:20.464 The output would be this interactome

NOTE Confidence: 0.768497892631579

00:09:20.464 --> 00:09:22.113 and that we would undercover these

NOTE Confidence: 0.768497892631579

00:09:22.113 --> 00:09:22.819 new interactions.

NOTE Confidence: 0.768497892631579

00:09:22.820 --> 00:09:24.818 That may explain the role of

NOTE Confidence: 0.768497892631579

00:09:24.818 --> 00:09:26.150 these microbes and disease.

NOTE Confidence: 0.768497892631579

00:09:26.150 --> 00:09:27.530 And I'm gonna go very quickly

NOTE Confidence: 0.768497892631579

00:09:27.530 --> 00:09:28.450 over this complex slide,

NOTE Confidence: 0.768497892631579

00:09:28.450 --> 00:09:30.760 but suffice it to say that using

NOTE Confidence: 0.768497892631579

00:09:30.760 --> 00:09:33.062 yeast display and the really hard

NOTE Confidence: 0.768497892631579

00:09:33.062 --> 00:09:35.127 work of remarkable student Connor,

NOTE Confidence: 0.768497892631579

00:09:35.130 --> 00:09:37.890 who painstakingly curated and cloned

NOTE Confidence: 0.768497892631579

00:09:37.890 --> 00:09:40.650 4000 proteins during his PhD,

NOTE Confidence: 0.768497892631579

00:09:40.650 --> 00:09:42.658 that we were able to set up this

NOTE Confidence: 0.768497892631579

00:09:42.658 --> 00:09:44.287 technology where we could basically mix

NOTE Confidence: 0.768497892631579

00:09:44.287 --> 00:09:46.250 a bacterium with a library of yeast,

NOTE Confidence: 0.768497892631579

00:09:46.250 --> 00:09:48.248 pull out the yeast that bind.

NOTE Confidence: 0.768497892631579

00:09:48.250 --> 00:09:49.810 And because we had genetically

NOTE Confidence: 0.768497892631579

00:09:49.810 --> 00:09:50.746 barcoded these yeast,

NOTE Confidence: 0.768497892631579

00:09:50.750 --> 00:09:53.361 we were able to use next generation

NOTE Confidence: 0.768497892631579

00:09:53.361 --> 00:09:55.075 sequencing to determine which

NOTE Confidence: 0.768497892631579

00:09:55.075 --> 00:09:56.129 host extracellular.

NOTE Confidence: 0.768497892631579

00:09:56.130 --> 00:09:58.094 Looking actually in dowed

NOTE Confidence: 0.768497892631579

00:09:58.094 --> 00:09:59.567 that binding capacity.

NOTE Confidence: 0.768497892631579

00:09:59.570 --> 00:10:02.270 And we've done this now across

NOTE Confidence: 0.768497892631579

00:10:02.270 --> 00:10:04.070 actually hundreds of microbes,

NOTE Confidence: 0.768497892631579

00:10:04.070 --> 00:10:05.906 not just within the gut microbiome,

NOTE Confidence: 0.768497892631579

00:10:05.910 --> 00:10:09.150 but actually across multiple different

NOTE Confidence: 0.768497892631579

00:10:09.150 --> 00:10:12.390 tissues from skin oral cavity.

NOTE Confidence: 0.768497892631579

00:10:12.390 --> 00:10:12.951 Long,

NOTE Confidence: 0.768497892631579

00:10:12.951 --> 00:10:15.756 and also including the female

NOTE Confidence: 0.768497892631579

00:10:15.756 --> 00:10:16.878 reproductive tract.

NOTE Confidence: 0.768497892631579

00:10:16.880 --> 00:10:19.260 And in going through this

NOTE Confidence: 0.768497892631579

00:10:19.260 --> 00:10:20.562 exercise and kind of,

NOTE Confidence: 0.768497892631579

00:10:20.562 --> 00:10:21.110 I think,

NOTE Confidence: 0.768497892631579

00:10:21.110 --> 00:10:23.085 really illustrating the power of

NOTE Confidence: 0.768497892631579

00:10:23.085 --> 00:10:25.060 these kinds of combinatorial technologies,

NOTE Confidence: 0.768497892631579

00:10:25.060 --> 00:10:27.610 we were able to explore almost

NOTE Confidence: 0.768497892631579

00:10:27.610 --> 00:10:28.885 2,000,000 potential binary

NOTE Confidence: 0.768497892631579

00:10:28.885 --> 00:10:30.365 interactions between individual

NOTE Confidence: 0.768497892631579

00:10:30.365 --> 00:10:32.840 microbes and individual host proteins,

NOTE Confidence: 0.768497892631579

00:10:32.840 --> 00:10:34.520 and have and we've actually

NOTE Confidence: 0.768497892631579

00:10:34.520 --> 00:10:36.200 uncovered a really extensive network

NOTE Confidence: 0.80794160025

00:10:36.254 --> 00:10:38.606 of what you could think of as Trans

NOTE Confidence: 0.80794160025

00:10:38.606 --> 00:10:39.825 Kingdom connectivity that we're

NOTE Confidence: 0.80794160025

00:10:39.825 --> 00:10:41.553 just starting to dig through now.

NOTE Confidence: 0.80794160025

00:10:41.560 --> 00:10:43.975 I should mention that we've validated now

NOTE Confidence: 0.80794160025

00:10:43.975 --> 00:10:46.780 many of these interactions we identified.

NOTE Confidence: 0.80794160025

00:10:46.780 --> 00:10:48.450 Thousands of interactions involving hundreds

NOTE Confidence: 0.80794160025

00:10:48.450 --> 00:10:50.590 of strains and hundreds of proteins.

NOTE Confidence: 0.80794160025

00:10:50.590 --> 00:10:51.628 Of course, as you would expect.

NOTE Confidence: 0.80794160025

00:10:51.630 --> 00:10:53.122 Still, most proteins don't

NOTE Confidence: 0.80794160025

00:10:53.122 --> 00:10:54.987 interact with bacteria at all,

NOTE Confidence: 0.80794160025

00:10:54.990 --> 00:10:56.815 and most bacteria interact with

NOTE Confidence: 0.80794160025

00:10:56.815 --> 00:10:59.069 very few or sometimes even don't

NOTE Confidence: 0.80794160025

00:10:59.069 --> 00:11:01.229 interact with any proteins at all.

NOTE Confidence: 0.80794160025

00:11:01.230 --> 00:11:04.482 But we do see really fascinating

NOTE Confidence: 0.80794160025

00:11:04.482 --> 00:11:06.452 examples of specific interactions

NOTE Confidence: 0.80794160025

00:11:06.452 --> 00:11:08.822 among these hundreds of interactions

NOTE Confidence: 0.80794160025

00:11:08.822 --> 00:11:10.840 we've uncovered that imply that

NOTE Confidence: 0.80794160025

00:11:10.840 --> 00:11:12.838 there really is this rich landscape

NOTE Confidence: 0.80794160025

00:11:12.838 --> 00:11:15.018 of interactions that may play really

NOTE Confidence: 0.80794160025

00:11:15.018 --> 00:11:17.484 diverse roles in in both microbial.

NOTE Confidence: 0.80794160025

00:11:17.484 --> 00:11:20.660 Colonization of specific niches in

NOTE Confidence: 0.80794160025

00:11:20.660 --> 00:11:23.060 microbial manipulation of those niches,

NOTE Confidence: 0.80794160025

00:11:23.060 --> 00:11:24.870 potentially to for the benefit

NOTE Confidence: 0.80794160025

00:11:24.870 --> 00:11:25.956 of that bacterium.

NOTE Confidence: 0.80794160025

00:11:25.960 --> 00:11:27.016 For example,

NOTE Confidence: 0.80794160025

00:11:27.016 --> 00:11:29.970 the initiation of tissue remodeling which

NOTE Confidence: 0.80794160025

00:11:29.970 --> 00:11:31.520 may have really interesting implications

NOTE Confidence: 0.80794160025

00:11:31.520 --> 00:11:33.379 in in the multitude of diseases.

NOTE Confidence: 0.80794160025

00:11:33.380 --> 00:11:35.460 And finally as an immunologist,

NOTE Confidence: 0.80794160025

00:11:35.460 --> 00:11:36.604 it was particularly exciting

NOTE Confidence: 0.80794160025

00:11:36.604 --> 00:11:39.292 to me to see that that we see a

NOTE Confidence: 0.80794160025

00:11:39.292 --> 00:11:40.807 number of examples of interactions

NOTE Confidence: 0.80794160025

00:11:40.807 --> 00:11:42.598 that imply that these microbes,

NOTE Confidence: 0.80794160025

00:11:42.600 --> 00:11:43.604 even though these are

NOTE Confidence: 0.80794160025

00:11:43.604 --> 00:11:44.357 quote commensal microbes,

NOTE Confidence: 0.80794160025

00:11:44.360 --> 00:11:46.485 are not pathogens that similar

NOTE Confidence: 0.80794160025

00:11:46.485 --> 00:11:47.760 to pathogens that.

NOTE Confidence: 0.80794160025

00:11:47.760 --> 00:11:50.776 That some or even many of these commensal

NOTE Confidence: 0.80794160025

00:11:50.776 --> 00:11:53.336 microbes may interact with the immune

NOTE Confidence: 0.80794160025

00:11:53.336 --> 00:11:56.206 system in ways that lead to immunomodulation,

NOTE Confidence: 0.80794160025

00:11:56.210 --> 00:11:56.834 and so.

NOTE Confidence: 0.80794160025

00:11:56.834 --> 00:11:59.018 One example of that that we've found

NOTE Confidence: 0.80794160025

00:11:59.018 --> 00:12:00.861 really interesting is this example

NOTE Confidence: 0.80794160025

00:12:00.861 --> 00:12:03.500 of Ruminococcus Navis strain that has

NOTE Confidence: 0.80794160025

00:12:03.500 --> 00:12:05.770 been associated with Crohn's disease,

NOTE Confidence: 0.80794160025

00:12:05.770 --> 00:12:09.234 which actually binds to this Co receptor

NOTE Confidence: 0.80794160025

00:12:09.234 --> 00:12:11.838 expressed on T cells called CD 7,

NOTE Confidence: 0.80794160025

00:12:11.840 --> 00:12:14.312 and we validated this with an

NOTE Confidence: 0.80794160025

00:12:14.312 --> 00:12:15.939 orthogonal fact standing here

NOTE Confidence: 0.80794160025

00:12:15.939 --> 00:12:17.954 and this was really intriguing.

NOTE Confidence: 0.80794160025

00:12:17.960 --> 00:12:18.670 For us,

NOTE Confidence: 0.80794160025

00:12:18.670 --> 00:12:20.800 because actually CD 7 is really

NOTE Confidence: 0.80794160025

00:12:20.800 --> 00:12:22.837 highly expressed on these specialized

NOTE Confidence: 0.80794160025

00:12:22.837 --> 00:12:24.932 subset of lymphocytes that don't

NOTE Confidence: 0.80794160025

00:12:24.932 --> 00:12:27.207 circulate in our blood but actually

NOTE Confidence: 0.80794160025

00:12:27.207 --> 00:12:28.711 live within the epithelium.

NOTE Confidence: 0.80794160025

00:12:28.711 --> 00:12:30.259 These so called intraepithelial

NOTE Confidence: 0.80794160025

00:12:30.259 --> 00:12:32.421 lymphocytes and so it raises this

NOTE Confidence: 0.80794160025

00:12:32.421 --> 00:12:33.360 interesting possibility that

NOTE Confidence: 0.80794160025

00:12:33.360 --> 00:12:35.786 this bug may be able to actually

NOTE Confidence: 0.80794160025

00:12:35.786 --> 00:12:37.274 directly activate these special

NOTE Confidence: 0.80794160025

00:12:37.274 --> 00:12:39.398 this specialized cell type leading

NOTE Confidence: 0.80794160025

00:12:39.398 --> 00:12:41.414 to potentially outcomes consistent

NOTE Confidence: 0.80794160025

00:12:41.414 --> 00:12:44.207 with the inflammation that we see

NOTE Confidence: 0.80794160025

00:12:44.207 --> 00:12:46.054 in chronic disease. OK, so.

NOTE Confidence: 0.80794160025

00:12:46.054 --> 00:12:48.798 Just to finish up in the last

NOTE Confidence: 0.80794160025

00:12:48.800 --> 00:12:50.336 3030 or 60 seconds,

NOTE Confidence: 0.80794160025

00:12:50.336 --> 00:12:52.640 we've used this new technology to

NOTE Confidence: 0.80794160025

00:12:52.721 --> 00:12:55.157 really build what we think is the

NOTE Confidence: 0.80794160025

00:12:55.157 --> 00:12:57.440 first Atlas of host microbiota.

NOTE Confidence: 0.80794160025

00:12:57.440 --> 00:13:00.488 Interactions across nearly whole

NOTE Confidence: 0.80794160025

00:13:00.488 --> 00:13:02.774 EXO proteome scale.

NOTE Confidence: 0.80794160025

00:13:02.780 --> 00:13:04.747 This really is the first glimpse that

NOTE Confidence: 0.80794160025

00:13:04.747 --> 00:13:07.580 we have of this potential interaction space,

NOTE Confidence: 0.80794160025

00:13:07.580 --> 00:13:09.911 but it implies a lot of interesting

NOTE Confidence: 0.80794160025

00:13:09.911 --> 00:13:11.360 things about how micro,

NOTE Confidence: 0.80794160025

00:13:11.360 --> 00:13:12.724 which microbes are interesting,

NOTE Confidence: 0.80794160025

00:13:12.724 --> 00:13:15.236 how those microbes may be doing those

NOTE Confidence: 0.80794160025

00:13:15.236 --> 00:13:17.266 interesting things and what particular.

NOTE Confidence: 0.80794160025

00:13:17.270 --> 00:13:17.937 Phenotypes,

NOTE Confidence: 0.80794160025

00:13:17.937 --> 00:13:20.605 those those host phenotypes

NOTE Confidence: 0.80794160025

00:13:20.605 --> 00:13:23.273 those microbes may elicit,

NOTE Confidence: 0.80794160025

00:13:23.280 --> 00:13:25.338 and so kind of going forward.

NOTE Confidence: 0.80794160025

00:13:25.340 --> 00:13:26.850 We're really excited about the

NOTE Confidence: 0.80794160025

00:13:26.850 --> 00:13:28.360 possibility that we can continue

NOTE Confidence: 0.80794160025

00:13:28.413 --> 00:13:30.043 to leverage these technologies to

NOTE Confidence: 0.80794160025

00:13:30.043 --> 00:13:31.673 identify causal microbes and their

NOTE Confidence: 0.80794160025

00:13:31.727 --> 00:13:33.142 mechanisms of action that eventually

NOTE Confidence: 0.80794160025

00:13:33.142 --> 00:13:35.415 this is going to allow us to actually

NOTE Confidence: 0.80794160025

00:13:35.415 --> 00:13:37.125 start to solve that annotation problem.

NOTE Confidence: 0.80794160025

00:13:37.130 --> 00:13:38.845 I alluded to that will start to

NOTE Confidence: 0.80794160025

00:13:38.845 --> 00:13:40.893 be able to actually combine these

NOTE Confidence: 0.80794160025

00:13:40.893 --> 00:13:42.553 technologies with other omics

NOTE Confidence: 0.80794160025

00:13:42.553 --> 00:13:44.862 technologies to be able to assign

NOTE Confidence: 0.80794160025

00:13:44.862 --> 00:13:46.527 functions to dozens or maybe

NOTE Confidence: 0.80794160025

00:13:46.527 --> 00:13:47.193 even hundreds

NOTE Confidence: 0.86082466

00:13:47.200 --> 00:13:48.676 of bacterial genes.

NOTE Confidence: 0.86082466

00:13:48.676 --> 00:13:50.644 Previously were completely unstudied,

NOTE Confidence: 0.86082466

00:13:50.650 --> 00:13:53.572 and finally that by understanding these

NOTE Confidence: 0.86082466

00:13:53.572 --> 00:13:56.868 specific interactions we may be able to

NOTE Confidence: 0.86082466

00:13:56.868 --> 00:13:58.983 actually identify subsets of patients

NOTE Confidence: 0.86082466

00:13:58.983 --> 00:14:01.446 that share core disease etiologies.

NOTE Confidence: 0.86082466

00:14:01.446 --> 00:14:04.586 Microbially driven etiologies of disease,

NOTE Confidence: 0.86082466

00:14:04.590 --> 00:14:06.745 and this has obvious also

NOTE Confidence: 0.86082466

00:14:06.745 --> 00:14:07.607 therapeutic implications,

NOTE Confidence: 0.86082466

00:14:07.610 --> 00:14:09.262 and so with that I'll just say

NOTE Confidence: 0.86082466

00:14:09.262 --> 00:14:11.029 thank you guys for your attention.

NOTE Confidence: 0.86082466

00:14:11.030 --> 00:14:13.922 Hopefully I finished close to on

NOTE Confidence: 0.86082466

00:14:13.922 --> 00:14:16.950 time and really just acknowledge

NOTE Confidence: 0.86082466

00:14:16.950 --> 00:14:18.130 Aaron's Ring and Connor.

NOTE Confidence: 0.86082466

00:14:18.130 --> 00:14:20.224 We started the project and that since

NOTE Confidence: 0.86082466

00:14:20.224 --> 00:14:22.336 been taken over by over by a really

NOTE Confidence: 0.86082466

00:14:22.336 --> 00:14:24.079 talented graduate student in my lab,

NOTE Confidence: 0.86082466

00:14:24.080 --> 00:14:25.935 the full sonnet and also

NOTE Confidence: 0.86082466

00:14:25.935 --> 00:14:27.419 Chris Buttonholer at Harvard,

NOTE Confidence: 0.86082466

00:14:27.420 --> 00:14:30.380 who is a really brilliant.

NOTE Confidence: 0.86082466

00:14:30.380 --> 00:14:31.136 Computational biologist who's

NOTE Confidence: 0.86082466

00:14:31.136 --> 00:14:33.218 been helping us with a lot of the

NOTE Confidence: 0.86082466

00:14:33.218 --> 00:14:34.294 more sophisticated analysis that

NOTE Confidence: 0.86082466

00:14:34.294 --> 00:14:35.990 we've had to start working on now.

NOTE Confidence: 0.86082466

00:14:35.990 --> 00:14:38.328 And of course, the funders as well.

NOTE Confidence: 0.86082466

00:14:38.330 --> 00:14:40.154 So thank you guys for your time and

NOTE Confidence: 0.86082466

00:14:40.154 --> 00:14:41.900 and thanks again for the invitation.