Noon it is clear that today’s speakers have drawn quite the crowd. And I appreciate all of you attending today. We are really very fortunate to have 2 of our leading faculty who both have taken science to innovate in a way that has impacted.

Missions across the Globe and I think these are really shiny examples of the many members of our faculty who really do move science into the clinic so I will start with our first speaker and I will say both really need no introduction, but our first speaker is doctor, Lee Ping Chen.

Lee is the United Technologies Corporation Professor in cancer research and a professor of Immunobiology Dermatology. Ann Medison and is also a Co director of our cancer immunology program at the Yale Cancer Center, leaping’s achievements in cancer menology.

Or Legion and and obviously his work in understanding PD one and PDL one was instrumental in actually changing the landscape of cancer care probably for generations to come and so it really is. My distinct privilege to introduce stuck sweeping Chen.

Thank you Charlie for introduction, so today, I’m going to briefly in beginning just briefly introduce what the concept of canceling you therapy is and I think this because of this anti PD one PD.

Now actually make us think the quite different directions for the casing. You certainly so this title. You can see the end of beginning is because we started new thinking now about this field later show. You some data will be very brief talk about what with what we are doing what we think is.

I can bring this kissing you therapy to next level, so this is a disclosure.

So the traditional thinking for the case if you therapy is like this is the car racing game that is, you have human growing in the body. Then you have immunity developed accordingly. Then this started raising tumor start growing the communities that developed then then if.

The kids that grow faster and the immunity. Can I catch up then kasapi immunity other way around then if it’s cancer immunity? Can catch up or even stronger than the cancer then we really will be case so this is this was thinking so, based on this thinking.

Because this influence the strategy of the how you develop casing yourself, so, so, so the now current view is very different.

Is the we know the case is not just keep growing curly faster and faster is kids are also trying to stop the immunity. We call immune evasion mechanism. The case that developer larger doesn’t mechanism tried to stop the ability of it. So it’s not really simple just racing game is the greedy cancer can start counter.

Immunity and then try to hold the immunity to fail so the because of these 2 tables thinking there. 2 type of thinking will lead to very different approach for kissing so for this type, which is based on this enhancement ideas basically you have since the.

Now we have 2 ideas, which is called normalization, which is based on this so which is based on believe is intrinsic immunity.

Is might be sufficient already OK so which means host immunity are capable of control tumors but the problem? Is this because of
this counterattack mechanism humor will develop developed and then they can
hold the immunity. So then all you need is to then strategy we quite different.

NOTE Confidence: 0.846921801567078

00:05:01.230 --> 00:05:21.240 He need to identify the problem and then to re-
store the defect particular mechanism. Then let immunity go back to the normal
level. Then it’s sufficient so you can see these are 2 different ideas, so the so
when I last year was screen, sometimes, and try to some.

NOTE Confidence: 0.77181613445282

00:05:22.030 --> 00:05:42.040 To reach through larger history of the casing
therapy as we lost you probably know is the first typical considers classical
in Yosemite is interfering pipeline different is developing 84 prove FDA.

NOTE Confidence: 0.829068660736084

00:05:42.830 --> 00:06:02.840 The Harry Leukemias and kidney cancer
melanoma, so that consider is the first actually FDA approved in you. Sarah P
and since then, there’s a few others developed based on this enhancement ideas,
which is IO 2 and then there’s a later is the CTO for you can see vaccine or.

NOTE Confidence: 0.81473833322525

00:06:03.630 --> 00:06:23.640 Recently, his that he hasn’t been as I majorly
mission is not based on Prefect of immune response. It’s based on how to
improve my immune response even this is normal mechanism OK, so that’s idea
now. You can see on the right side which is the entire PD one PD everyone,
said, which is.

NOTE Confidence: 0.823428988456726

00:06:24.430 --> 00:06:44.440 Cause of what he now you see how many indication
the morning 10 indication in the Kansas be improved and the including all the
major larger major solid tumors, especially Andy. But this is very limited
improvement by enhancement ideas that you can see this huge count contrast
this take.

NOTE Confidence: 0.809453308582306

00:06:45.230 --> 00:07:05.240 Is took 2 now and to develop few indications again
sincerity. But in my PD one PD or they should move much faster so the I think
from here. I think the key is we need to learn something for why is certainly is
much more effective and much of probably indication and also.

NOTE Confidence: 0.827685952186584

00:07:06.030 --> 00:07:26.040 Toxicities so this is something we wanted to know
so to this cartoon TV show showing the kind of major differences of these 2
type of 70s is let’s consider immune response as the water? What flow through
the pipe then the human start growing then.
Block the paper so there’s 2 strategy. One is enhancement, which is then literally increase the pressure of the water for the water to get so, so by that way. Consider this is the enhancement, but normalization is different normalization is trying to find where the blocks and.

The block this soup, so you can see the differences, then is with the enhancement. You might see some side effect. You might have lots of problems because you try to force the pressure obviously increase, and then you do have some some trouble, but block.

Issue then is you have to find a block so it’s not always easy to find it. So the enhancement email setup is based on the general idea is you have. We know this is a fundamental immunity. How these gains immunity could generate when you have a tumor growing in the body.

We will have lost anything they will make large anything available to the immune system. This anything could be mutated proteins could be the end always surprised proteins. They are available to some subset of cells cells.

Either then drizzles make a batch or peace as they can process. The editing and then bring this engaging 2, dealing for local Internet Vaughan. They will meet the lymphocyte these inputs. I then will activate input site.

We think that will come out become effector cells. We call you fit the cells. The various he’ll finally will come back to the tumor and recognize that particular entity license so that this is a general process now enhanced Minnesota P is basically designed based on this finding based on this basic process.

Cancel 18 would you base, though identify energy and then make anything percent excel present it make it unlikely better, so then the other strategy is the wimpy cells in the info. Logan try to increase the simplification.
Simulation or anti city, 04, which is deeply T regulatory cells. Then it will make these hours politically better settle kinds can promote survival improvement. Particulation, it that is so Sarah tied as a data strategy, which is very straightforward isolate this effect cell in the pool at or from that.

An individual educated M provider may engineer to make it a lot better cells and they infuse bad directory back to the to the pool at so hopefully, they will go back to the tool so all these strategies.

In fact, if you look at the Kobe to look at the history. All this strategy is immune logically successful that meaning every strange. It will lead to the appearance of better T cells in the plot, either by vaccine or the Co simulation setup kind city or or the.

Meaning is immunology immunologically successful, meaning is when you give a vaccine for example, you can get right. T cells, which you recognize the vaccine recognize that particular entity adaptive server. T all this lead to good piece else unfortunate this.

Amplified or enhance the diesel immunity is not always lead to clinical regression of 2. This is one of the dilemma has been in case city. Missouri feel for very long time.

Meeting is better immune response not always lead to the clinical response. So then the field in the 2000 hyper major crisis is the people believe the about 50% of people or maybe even more believes a case.

Nology or immunity is not going to work because you do show clearly there is case immunity look. A lot, but humans not regress so idea is there is a very clearly says immunity is not going to control so those people. Most of them walk away leave the field, but then it’s still have some people still.

Which believe there were different things like our lab actually believe there is some problems in the tumor micro environment here
even you have all these process successful. Eventually, you get good infected T
cells. But those things. Oh, and come to the tumor site try to get a tumor.

NOTE Confidence: 0.825616359710693

00:12:30.220 --> 00:12:50.230 That is because humans develop is all these in-
vansion mechanism which selectivity reader effector cells so final final step killer
step of the cells will not be able to execute so this is the general idea. We have
actually test this idea, so we allow that.

NOTE Confidence: 0.805647015571594

00:12:51.600 --> 00:13:11.610 To work on that and so this is the summary of
the incident casing. You said, so this is now this is actually huge effort. You
can see cytokines. The selective trials is a positive trial examination. Lots of
little trials. It’s not like we didn’t try hard trying very hard.

NOTE Confidence: 0.79430228471756

00:13:12.420 --> 00:13:32.430 You know kids a vaccine, which is a couple thou-
sand files, which is all failed. Negative trials in the majority of solid tumors
didn’t work, and ICT overall is not not trying not high enough more than 250
trials being tested largely because of costs we know sales.

NOTE Confidence: 0.787302017211914

00:13:33.220 --> 00:13:53.230 Now there’s a successful in the hemopoietic
Kansas, but not in the solid waste so all these in fact has been trying pretty
hard, but limited success. So the why is the majority of trial fail one is because
of toxicities?

NOTE Confidence: 0.770207524299622

00:13:54.020 --> 00:14:14.030 Agents before you see the effect toxicity will not
let you continue or low efficacy. We know there’s a vaccine in many cases is not
sufficient if you could see or copy car keys, so skip this one.

NOTE Confidence: 0.857398688793182

00:14:14.820 --> 00:14:34.830 You know there’s a concept called immune check-
point, which is pretty misleading. I should say based on that concept actually
is the literally any inhibitors you can make against and then try to remove it
and then the we see the frequently those trials.

NOTE Confidence: 0.843527674674988

00:14:35.620 --> 00:14:55.630 We still we continue hearing all these trial so this
is not just simple checkpoint is can do the job so this is what want to listen.
So, just tell you briefly what we have done in the past, so we have in 99, we
actually.

NOTE Confidence: 0.814347863197327
00:14:56.420 --> 00:15:16.430 Discover one molecule in a team will likely web we specifically looking at something highly express in AT one micro environment, but not in the other part because we believe there's a micro environment have a problem, so the first story was 99 Crown Esteem piece of each one later this month.

NOTE Confidence: 0.767342388629913

00:15:17.220 --> 00:15:37.230 PD Illinois and the because the the did you clone these PD one long time ago and then they don’t know this tool actually molecule is go with by pero they don’t really know the function is so the 2.

NOTE Confidence: 0.809140741825104

00:15:38.020 --> 00:15:58.030 After the Crony and the found this molecule binds each other so before so this in this stage is basic size OK. We just identify possibly which is potentially but that’s not enough. If you don’t move to the cancer therapies. That’s right now, so we actually work.

NOTE Confidence: 0.845889389514923

00:15:58.820 --> 00:16:18.830 They found this molecule is highly induced in the tumor micro environment only minimal in other tissues, but do have other tissues because other tissue. If there’s a sub clinical patient. Sometimes they do have a particular PDL one which might be responsible for the right now with.

NOTE Confidence: 0.822353541851044

00:16:19.620 --> 00:16:39.630 URE activities and we found this molecule, hitting immunity and then we, we actually make anybody in that I’m showing the animal study. They can block this interaction and can lead to increase in response in the table. Michael environment, so this is one of the early experiment prove principles.

NOTE Confidence: 0.809453725814819

00:16:40.420 --> 00:17:00.430 This study, we actually then convince the company called Matrix and then move this humanized anybody 2 clinical trial. So the first clinical trial. When I was Johns Hopkins started 2006 and and then the 2 finally D 2.

NOTE Confidence: 0.780623376369476

00:17:01.220 --> 00:17:21.230 So the this allows a different mechanism described we actually describe couple of potential mechanism of how PD one and PDL one iteration? How they inhibit is Mars like to say, These are released 10 it will induce up ptosis Energi.

NOTE Confidence: 0.755568563938141

00:17:22.020 --> 00:17:23.130 We published.

NOTE Confidence: 0.885266721248627
So then the next after the discovery of this interaction and pick us. Literally, 10 years to figure out how it works is the now. I just summarize what we describe now is what we know about how it works is we describe this.

Doing hippie new response by when you have this effect T cells as I mentioned come to finally when they already fully activate when it comes to tumor site, they will recognize human editing thereafter recognized humanity. And they will start a pack. Those tumor cells. Now there’s a couple things happened one is this piece of.

These salad kind called Interpro Gramma. We know interval. Gamma is very crazy. They can helping me see cause one articulation. Feasel survivals by unfortunate internal grammar deal very bad thing, which is the major cell accounting right now is the one on.

OK and literally in any to myself any cells actually interfere with my car so this then. This video and binds to PD one which is majority of effector cells already have and then lead to the death of T cells so.

This mechanism works in the final stage of the immune response to tumor when when everything is really make all the effector cells finally come to my side and could shut out there paralyzed in the end, so this is how it works, so as you all know it is now 6 drive could be.

How how this anti PD one PD one worked?

Number 2 is this immunization happen in the 2 of micro environment, but not systemically because now we only go back to study patient. You can see the immune response internal is pretty healthy. Actually, the other part of body but not in a few months, so this is a major problem side and the obvious also and uh.
The things which is we need to identify a master switch, which could restore or reprogram entire immunity in a few micro environment. This is a become a critical because a lot of those so called checkpoint. They’re capable of block particular defect or particular.

But they would not be able to reprogram entire language grammar, they can hit that particular pass away. But the password is not big enough or not must enough or there is maybe there’s a multi possibly did this one passwords might not sufficient to reverse entire chain.

So that is become a issue so we basically use this 3 criteria to identify our new the 30 agents. So I will show you a little bit later. So we then the how we approach this there. We know this when we?

Abdicate this all these ideas. We then just based on these 2 things. One is the piece of infiltration. We know that’s provided PD and is very critical for the killing of tumor cells and then there’s expression. RPDL one that based on these 2 simple markers when you look at the patient patient.

The these young kids that age and then you can clearly see, there’s a 4 types of tumors. The so we classify this very simple classification. There, based on this type of missing. RP sauce and video type 2 will be double positive opposes there right and these 3 is 3 and 4 is only have 13 have teaser only, but not video.

Ways only her pedia one, but not pieces. So now look look at this, then you almost no immediate that he says. PP one or PTOM per case therapy would be only benefit for this type of patient Type 2 because the mechanism is there PD? Why is there PTL one? Is there?

They’re interacting hippie new response now you give anybody you. Pull up there. So Type 2 patients will work, which is actually not turn out to be true in the clinic. Another all tables 3 or other type not work. Why? Because they simply missing target. So we actually call target missing resistant you can say.
Because I know clinician like to say if target on work. You say is resisted so all other is resistant going to be resisted but they call we call target missing resistance because there’s no target. So cattle will be show like this that. You have T cells here, you will sell here.

With those and then this is Type 1234, so when we put large data together. This is a collecting of all these multi study, including hours and you put all different type of cancer here, but I know how to save 256 cases.

You know a couple 100 if you put them into these 4 different categories. Quite interesting the number come back on interesting so this is total 2000.

And we see type one which is double negative, which is 37% double +24 percent. This is actually match what we see in clinic right now, responding patient patient response to the therapy. This is the average responding rate. Obviously tip goes to different type is different.

She was only T cells where pedia ones out there. That means these features not functional because they do not releasing term comma, which is another quarter. Then this type voice about 15% so all this is our strategy is we believe right now, this therapy is only.

Which is now large data is coming to support it? Which is about quarter of the patient in general that may be different type of type of patient even different type of diseases over different overall is about 25%.

Then there is type one in 4 that one in 4, which is the no T cells. So the problem. This is about 50% at a large portion and this type of patient for this problem is diesel is never come to the tool ignore these 2 so little.

Know any response against you so the problem is different. We are actually active work work on this and first try to figure out why diesel is ignoring tools that why is that right so that’s the first fundamental question?
And now Type 3, which is about quarter patient which is you have tumor. You have T cells. Coming they do. They actually identify the problems they know there’s a tumor there, but there’s no internal camera really snow pedia one so there’s either this other path.

Most likely is other pass away is their operating the independence of the PPYPDL. One so this is we actively also work on that, so we took the.

Comprehensive approach this is a very big approaches and obviously very expensive to is the we so we have spend more than 10 years to establish 2 big platform is 2 platform is one is called Tino scale reset array, which is basically.

Or the cell surface molecules, which is could be target by anybody so we have all the 8000 jeans basically in our play individually. We can express them and there’s screen them for binding to which so it’s like PD one binds to PDF that kind of screening system second.

Who is T selectivity array? Which is we then his suppressed each of these 8000 molecule in a cell in artificial cells. Tumor cells or antigen presenting cells and to show they can inhibit these always pass. So we can do large scale screen to show those inhibitors so to identify the inhibitor it is.

That sequence step then is we want we need to put this in the County of which type of tool as I mentioned is 4 different type. So then we spot them to the individual title of cases there. After that, then we study the function to see they really play a role in the anyway.

And in a human and also the expression profiles as I mentioned there has to be specifically operating during the tumor progression in the tumor site. We don’t want the Express. We don’t want to work on those molecules a surprise all over the place because that will lead to trouble with toxicity.
So by that way I'll just summarize here. I don't think I would have time to show the data as you can see the Type 2, which is double positive. We have PD one. PD already that this type of humans recently. We also found another molecule called FT one.

Molecule binds to Leg 3, they can express on either Type 2 or type 3 curious and he also another one is called Sickle 15, which is exclusively expressing that I'm sorry, meaning is they don't express in here. We still work on others, but other is unlikely because.

So the mechanism of this molecule is Pine-sol Receptor on T cells and inhibit immune response independence of the PD. One video one and also as you know Type 3, there's no PD or expression, but expressing so this is kind of interesting is signal team and whatever you have a tumor.

They're mostly unlikely express video one. So so this kind of market. So we now we know why is because they have different mechanism like for example, interference will shut down in turn will operate Europe either one but will shut down this molecule expression so this is one reason so we already put.

OK, the phase one clinical trial. This Tyler so the we have now so we talk about is the we have ideally we have large tools can deal with Type 2 Type 3 patient and now we go back to work on type one and Type 4, hopefully next time I will report it what we find it well.

So to summarize what I talk is there's a 2 type of ideas in the new therapy 2 approaches and we just started to understand that and then put him in practice. One is enhancement, which it has tradition has been along time is basically amplified human immunity.

So above the physiological level, so that's why you can start to see you start to see rather toxicities. There's an invitation there and the.

Very popular in the field by normalization is the newer one which is based understanding of the what is the in the tumor Michael environment? What's wrong? Is there and how can bring them to the normal
level that happen. So obviously disadvantages. Many Target still need to be discovered.

NOTE Confidence: 0.785630345344543

00:30:09.250 --> 00:30:29.260 Ellie needs to be evaluated individually in the clinic so that will take data. So the year. We actually work very closely with the group of ization scientist Lloyd herbs. We work on lots of lung cancer.

NOTE Confidence: 0.712357401847839

00:30:29.300 --> 00:30:49.310 Sports skins of war, which is the Mario snow and technologists. Obviously is very critical for us rims and very close collaborators and any Kim is selected surgeon, we work with with him for quite a bit used.

NOTE Confidence: 0.748540699481964

00:30:50.100 --> 00:31:10.110 Sample object study so my lap, yeah, Yale Ching Wong. The something with grad student. You want is a fellow and we are getting is a pathologist. Tina is the greatest illness and then as I mentioned a clinical trial. We secretly team where they bring to create I'll work with.

NOTE Confidence: 0.798539638519287

00:31:10.900 --> 00:31:24.430 Risk Europe and 2 now is already ongoing face one we have also lots of collaborative. I spend spend this ongoing trials. So we can get out of sample for analysis. Thank you.