Aaron ring and I'm delighted to introduce our next set of speakers. Our first speaker, especially for this particular symposium needs no introduction from delighted to do it anyway. And that’s my colleague doctor leaping chin, who’s the United Technologies Corporation Professor in Cancer Research and professor of Immunobiology Dermatology in Madison.

So leaping please.

Tell us what you.

See very soon.

OK thanks for the for the invitation.

So the

Today, actually this is my talk will be break 2. Two Part 1 is first I will tell you briefly what we learn from these anti PD one PD L1 study which?

We have have been going on in my lab for more than 20 years. So we urge you to learn quite a bit of stuff I will briefly summarize what we learn and what’s the key is key point we learn and then I will show you use this principle we learn?

Use that as a foundation and then to learn and to further progress and tie by that principle and into.
Develop the new therapies you therapy means this could be a next generation and could be a better better. One so the case for immunology. Traditionally, you view. This case immunology as the kind of car racing game that you have cancer growing in the body and you have immunity try to play catch up so immunity developed. Obviously, based on this morning. There were lots of lots of lectures. I think is a basic.

Principle we understand is the one tumor growing there's a lot of things available to you for immune system too.

To be stimulated and cancel the release of energies and.

Trigger the immune response so so this is a kind of traditional view. So then the based on that would be if the immunity can capture more powerful than the immunity name because.

Other way around in many cases, particularly in the tensor patient.

Well, we, we see what we see is the case of beat immunity is because immunity is not really pretty culture, so in this traditional view. Then this why I've mentioned that is because based on this then totally different idea to develop different type of email service.

So currently current view based on more basic immunology study, then we know there's not a simply these 2 is 2. Things out of raising raising the body is more like cancer actually be immunity also by developed immune evasion mechanism. This evasion mechanism. It should prayer very KIRO to shutdown immunity. You write a different way. So then in this case, the immunity never catch up.

OK, so the based on this 2 different view and in a lot of evidence of the research. Then the my mind is cancelled in new serapi can be clearly divided to 2 different type and based on 2 different ideas.
First type, which is being a very traditional as being used for many, many years, probably more than 50 years now
code enhancement.

I just summarizing hasten anyways. Where is based on the idea is a mission is the you have a two cars racing in the body and
then intrinsic community is not sufficient and that meaning they’re not cannot picture.

The approach there will be just two promoting stronger immunity to generate better immunity to enhance the normal immune
response. So then you basically promoting all entire process of the immune response just to raise the immune response and now we actually doing pretty well in the field of the cancer immunology. You can use particular way. Cytokines
vaccines, or write different way and then you can enhance normal immunity, too much higher level.

Now isolated adapter transfer of Diesels. For example, you can raise immunity 200 times or even 1000 times, then the normal
physiological level. So it’s so it’s already the colors are cheap.

Then the but based on the another idea, which is the immune response is often defect. It’s because of racial mechanism developer
cancer, then idea then is to repair the defective immune response rather than just promoting in general to raise the immune response. You specifically go. Find out what is wrong, there and then to correct that defect so this actually
call.

Normalization approach.

So you can see this is very different. The way to look the immunity so this cartoons and show the differences of these 2 types of
approaches the on the Top or is this a weakened escriba. Simi response as the water flows through the pipe.
Normally water just go through it cause it would rain and if tumor start growing which indicated here by there's a block in the middle of the type. Then there's a different way to do. One is to really increase the pressure increase the water pressure for example, to push through the.

The water so too.

Hopefully, 2.

To pursue this block.

So that is enhancement approaches and normalization would be to identify what’s the problem and where is it and then selectively move that particular block so you can see this is a quite different?

So this slide basically summarize what we learn from many years, many, many years of study on the.

With so-called more image any tumors and also the toxicity is much lower compared with enhancement so the differently, something quite different need to Relearn. So we summarize as the three essential the principles. One is the type of therapy has to identify what type of invasion mechanism is these type of evasion mechanism is associated with tumor progression.
Meaning is in normal tissue such mechanism mechanism is not present or minimally present.

So this is a zodia with skins or what they will induce by case, number, 2 is immune evasion mechanism appears to be frequently happened in the tumor microenvironment, meaning in the tumor site. Very few of those mechanisms develop systemically so that again is very different from enhancement enhancement as I mentioned to you.

Often is the novel generation of the new immune response so usually get systemic boost of the emirate’s bars #3 is the target master switch, which is reprogram or reset your response I think this is getting very critical now.

For this particular issue is the as we know also you can see, there’s a lot of data presented in this morning in the if you analyze the?

The nearest bars in the tumor. Michael environment, you can see, there’s a multiple mechanism can be Co present in the UG for example, say you have P. DL1 always press. But you also have a teacher beta. You have teams relax really whatever whatever there’s a series of of those, and the How do you know you just simply manipulate one single password and you can overcome immune response it seems impossible?

Because there’s a multiple possibly it’s all if all operating then you just manipulating one how you get you can reverse.

The suppression immune response seems impossible right so the key. However, this argument has been going on actually for more than 30 years, OK, even with before we started work. We started to isolated the molecule are like a PDA or one that argue is already there, OK, I can tell you the.
The way right now looks like it is there’s maybe multiple mechanism available, but always one will take a dominant seat OK. If this storm didn’t see fail. Then there’s another one click in very few we see very few cases will occasionally you could see you might see in the patient. Then you can see maybe both mechanisms are very strong, the inhibit immune response, but many cases is single dominant mechanism payroll.

The opportunity OK, you can manipulate you single pass away , you can actually read up lots of cancers.

So this is important is to identify what to target particular mask must switch so then the.

Can be any normal immune inhibitory mechanism typically is like for example, CTR 4 city 04 is required for the control of the auto immune autoimmunity autoimmunity, so reactivities, you get rid of the mouse. You knockout knockout molecules. You don’t even have to give them any enerji my style already so it’s required physiologically so this is one part of normal, inhibitory mechanism, which require for keep the peace of the response.

So it is a very different. We talk about this is tumor induced a mechanism, so this is not part of a normal the control.

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Put in the criminal there, too.

To test the efficacies these are all single agent, I listed and this every single agent fell in the clinical trial. A single agent. This is just a chore is a short list. There’s a more more than that it should probably double that so the I think we have enough the evidence. I think showing is not just simply checkpoint will work is not just any has to be very selective.

So how we approach it then.

How we approach this question is the?

As a summation early the PD one PD L1. It works in fraction notation, but we know is works about quarter patient late stage cancer about 25%.

So there’s a lot of other case, the patient. What is what happened happened in the immune response to those measures?

OK. This is one of the very simple classification of human cancer. These all advanced human solid tumors.

And we start with them in an oma and then later goes to all the different type of cases and I’m going to show you in a minute, so this is this is the classification. This is these are time time classification? Is is the tumor immunity in the micro environment.

And you can see on the left is the P. TL1 or a piece of expression. OK, based on that and then the array in the bottom is the.

It is Weasel is Artie sauce, so you can see this is clearly there’s on Top are left.
The couple level or or lower right. This is more single positive and in the lower part which is the label is type one which is double negative on the right upper upper corner is the double positive, which is do have posed he sells and the P. DL1 expression so by this way. Then you can see this very different profile. Clearly, there’s a hero. GDP of the human case is quite different. It’s just based on this very simple 22 parameters, you already can see this.

Quite that most so this is a summary of the variety different. The study from first from us. There’s a few study for us and then there’s a lot of others or pulled together from different type of cancer showing left when a normal. This is your how many cases 256. This is our only study published 2012 and then there’s a long cancer. Prater columns or these different type of cases and you can see the first type is double negative which means there’s no.

Piso infiltration OK and then obviously there’s an opium. One also so that’s double negative which is basically is.

It’s there’s no immune response in the UG so typically this double negative type of cases immunologist is walk away. They say well. There’s no email response so that’s not my business. But if his case an immunologist. Then you have to take it so that’s a different differences of immunologist versus cancer immunology so second type is double positive, which as I mentioned this type, which is the best as your response to.

Or benefit best.

From the

PD1PD at Alliance Arripis, there, which is about quarter quarter of the of the patient.

And it I’m sorry is have a teaser infiltration, but there’s no P. DL1 OK, so these pretty obvious. This is teaser still dysfunctional is immediate by some other mechanism then.
Then the PP want people don’t want that because pedia ones, not even there so there must be something else. So the Type 4 is the PD1 positive that there’s.

But there’s no real teaser infiltration like this is often due to the genetic mutation, which directly hit the password. RP DL1, so people. One is expressed automatically is not even needed to be induced.

And as we know pedia one is typically induced by interval Gamma, released by the link for Scio and K cells in a tumor UG right. But it’s Type 4 don’t fit. This is a genetic mutations, which theoretically ternal so, based on this you can see this is we see in the middle type of tool corner, which is about 2520 four 25% which is about quarter of can benefit from these therapies and I was 3 is the healthy cells. But other mechanism right so this is a.

Population we actually very interested so let me show you some.

Some data today and how we based on this. The classification with develop our next generation self. So this type 2 as I mentioned this is larger than my benefit from a seller. Please type of story is non PD one. PD L1 mechanism. Obviously type one and 4, which is today. We still working on that and I’m not going to talk about today. Hopefully soon in the future.

So Type 2 as I mentioned the problem is.

Diesel is clearly clearly infiltrating they recognize something like that.

But the PD into one is not expressed so this must be something else. So we have actually developed the quite a many years ago. About 10 years ago, where you develop try to address this question. And we’ve developed a couple system, literally to address this so 12 platform, basically right now is running. One is called Receptor, A, which is developed by a very talent poster showing y’all.
Share this in that time was control app and then he strained trained biochemist.

OK, Mister for Mount Sinai and then as from from Albert Einstein, sorry and then in that time, we talk about developer system, which basically including as much as we can all the membrane proteins in our system so basically is we try to display.

All possible membrane protein honor cell surface by that way, then if we want to identify the binding partner OK. They say this is reset the like an interaction so with this system, they have the very sensitive system to detect the protein interaction.

This actually is not it’s actually it is a big deal because we know in the in the field of the receptor likely interation majority or cell membrane protein interaction are very low affinity? How low the best of cell membrane natural protein reset. The Liger Interation, the best actually is probably 1, two to lower the lower than the worst. Monaco anybody meeting is worse tomorrow. Anybody the Infinity is still one or 2 log better than the best.

Our cell surface protein interaction so with that issue. Then you can see this majority of receptor lie again identification work is very difficult.

Right now actually is in probably 2 hours to re reset the light can be identified every year so that kind of slow speed. So we developed the first for the purpose, then #2, is when we have the system going we can. Display the molecule in the cell surface. This is thousands of jeans so that individually display in the cell service of the we choose to Nicely Cho cells.

Then we develop is functional, functional array, OK, so basically wanted to know who wanted to develop a high throughput system, which you can edit. Display this protein and then very quickly identify? What kind of function. They have so this is one is the poster fellow and graduate student change way.

Actually develop this system is the we have this label as 6500 membrane protein individually transfer into artificial entity imprisoning cells. These cells already have OK T sorry everybody.
Expresses a membrane form, which means they can stimulate his US right, they can buy some cities, Rhiannon stimulate his ass.

So then use that to mimic a teaser receptor signal, then this additional.

Membrane protein expression well, then star Marjorie that ease of activity right. So so that’s the idea. So modulation means either promoting or inhibited right. So then we do have a Reporter readout, which is in this case is another copy to show the TCR signal eventually can travel down down through the Passway and to have a sensitive reader or teaser, either get activated or inhibited.

So by this way, this is one of one of display of the table, 100 jeans, a couple 100. The cell membrane protein activities in the middle of Mark Mark means is this is only cells with PCR signals so in the middle, then use that as the background. Then whatever things whatever the molecule can trigger above the mock is considered stima. Tori and lower than that, then consider is the.

Inhibitors so that you can see this There’s a variety differently mirrors, which is already being reported stimulators so the idea then is.

We will have these 2 platforms and screen. Wholesale jeans usually thousands of teen now. Even the thousands of jeans. The looks the quite a lot of work, but now we already automated system and now remember the entire human genome. There’s only about 9000 teens so we’re very close to.

Will be able to run entire cell service member improving to detect to detect activities. So the idea is then with this Greening we will get a set up.
The molecule which either inhibit immune response or stimulate response so let’s focus on inhibitors if come over auntie so ATP array than if they inhibit immune response. Obviously this is one of the essays with multiple different ways, depending on what kind of question you’re asking this kind of essay you can set up for alcovy readout. TCR signal you can set up for other things like probably for Asian or settle kind release, you can say whatever you want.

So by that way, then we come out whole setup for Inhibitors, then we took that data and then to match what we found in the consultation OK. This is for example, as I mentioned a type III patience this type of sorry patience.

Time is revision have we don’t know what’s there right there must be hypothesis is they must have some powerful inhibitors, there and the shutdown in response, and this powerful vehicular is not the PD one. PD L1 because they’re not there, so then the.

We will go through that data and then to a microarray or protein analysis and showing in a Type 3 patients. What kind of molecule overexpressed there and use that to match what we find out in our array so by that bench, then we pick the target this target is which is.

Show activities in Alpha screening and then also showed right location, which is in a micro environment. Obviously, the express in minimal level in a normal tissue OK. This is as I mentioned that one hour. Criteria now goes to the numbers 3 criteria, which is this has to be a master switch. This has to be dominant. The emitters so we move to our visual in vivo logical essays to identify this molecule is.

A dominant or not there in bright different system this system, including mouse models and they also.

Lots of human studies that we also conduct so the one today. I’m going to show you one quickly. Show you one or molecules. We identified and this is now is already moved to clinic is called secret 15.
Camera screen screening cannot screening it can be any genius that can be anything. Family can be can be something on now so this is a member of sialic acid binding. The electing family molecules is a large pieces, IG IG Vid Si Domain and then there’s Indiana end of terminal this side.

NOTE Confidence: 0.732976317405701

00:25:23.360 --> 00:25:29.100 Yes, it binding motifs, which means they could interact with Sally acid.

NOTE Confidence: 0.826270282268524

00:25:29.940 --> 00:25:42.410 So now this is a type one protein OK and Y intercept domain. There’s I think domain OK, so potentially this molecule could deliver single through the cell to be receptive actually.

NOTE Confidence: 0.812541306018829

00:25:43.460 --> 00:26:01.370 Normally this molecule are expressed in low level in my garage. My alloy sell some of my lawyer so useful field injury cells and pieces. The piece of osteoclast also expressed but it’s very low level in general, very low level, even make cells.

NOTE Confidence: 0.950449347496033

00:26:01.910 --> 00:26:04.000 It’s about 1520% of.

NOTE Confidence: 0.863106250762939

00:26:04.750 --> 00:26:31.330 Cells normally expressed this molecule in low level, so it’s it is very low but in the case is much higher expression so this match. One of our criteria so this is the only data showing normal tissue is very minimal level on Top of the human data and there’s a positive control is Mako veg in the mouse. You can see this very low level also in most issues.

NOTE Confidence: 0.804127156734467

00:26:32.580 --> 00:27:04.230 Now there in human cancer is clearly upper regulation. You can see this variety different type of cancers place RNA data. This is you can see predicates. Colon rectal skinny long. They all have a fraction of the patient could have a clearly operating Messenger RNA or signif team and this is David rain in the pathology department’s work and you can see this is one example of many study, he had done is the long small cell lung cancer is.

NOTE Confidence: 0.863617756734467

00:27:04.230 --> 00:27:17.280 In the 159 cases, we see this 49 of them positive. You know based on these quantity email for license. The interesting Lee is the expression in the human cancer patient.

NOTE Confidence: 0.821678817272186

00:27:17.780 --> 00:27:31.920 Appears to be in either in the stroma because this is the cost remark, which is a red show is red, which is most likely the Mayo
sauce and then also in a tumor mask, which means this molecule are linked directly operated.

NOTE Confidence: 0.817180454730988

00:27:32.440 --> 00:27:54.220 On a cancer cell surface, so why then, we know most of these long small cell lung cancer. Cells are epithelial cells. So why or how this in theory, so can express this monitor which is quite surprised and buy anyway. This is this is the data the fact.

NOTE Confidence: 0.871721088886261

00:27:54.760 --> 00:28:09.610 And the another interesting thing is these signal 15 appears to be reversed inversely correlate with PPL why expression so that makes sense because we purposely looking at, I’m sorry monoculus.

NOTE Confidence: 0.839352428913116

00:28:10.130 --> 00:28:22.210 The molecule in the type III cancer, which supposed pedia. One is very low anyway, so which is actually match what we were hypothesis. So you can see this expression on the on the.

NOTE Confidence: 0.720941543579102


NOTE Confidence: 0.837509632110596

00:28:24.870 --> 00:28:33.020 On on the Y axis the pedia one on on X axis. You can see this correlation is very, very weak, you have.

NOTE Confidence: 0.78663033246994

00:28:33.660 --> 00:28:39.110 Puppy Ste, 4 cases coordinated in couple 100 samples.

NOTE Confidence: 0.819837987422943

00:28:40.430 --> 00:29:10.500 So the obviously will show series of data showing secretly thing can inhibit is alliteration. This is one of the data showing you can use signal team purify Fusion protein, either human or mouse? Can you give it diesel proliferation and we also the Valley? Which is specific for signal 15 can inhibit tumor grows this is the image is growing in the body in the mouse and then you give anybody anything inhibit.

NOTE Confidence: 0.826930522918701

00:29:10.780 --> 00:29:23.470 So we did a site of profiling, which is this is still preliminary and data is quite interesting is the implying the MCC into the mice, which is why type or a significant markup.

NOTE Confidence: 0.845041275024414

00:29:24.030 --> 00:29:31.840 So wait. I’m versus Doc I’m not always show is red and you can see this we did. This is swimming, particularly interested in.
What kind of change on my Roy sells right because my old cell is as I mentioned my loiselle is one of the major signals within powers and sells so on the left, you can see see VA in this dark. Amaze obviously tumor grow much slower then you can see the threat is not changing much here, XE D4.

But CV A is clearly much higher in the Nakama is unclear. Sales also increase appears but my OS else. This is a very complicated. Phone number 7 Channel Channel #7 to 19. You can see this is a 13 different subsets of my liver cells based on the marker showing the right. This is all my OS else but it’s different subset. Minor oysters and there’s clearly this is some of some subset of my Roy sells unchanged.

And some over change dramatically so this is the way still conducting further analysis to see as I mentioned Indiana early signal 15, only express in subset of Milo ourselves OK. This is the idea is not in order my or sell so that which is reasonable when we see this data, so the issue. Is there, which subset any unique feature can, we use that to predict the outcome so all these things is ongoing right now.

So the 2 again this is a couple of the concept 3 different concept. We will talk about and use that we can developed the based on this guy by these principles, then we can actually.

Come out the molecule like this so this as I mentioned this again. This is not the checkpoint OK check going pro. K means any inhibitors can be put on. I actually strongly against the ideas I think that’s really what we’re looking for because we have lots of experience only time from the so-called enhancement approaches. You can see when you push immune system to a certain level, then the price to pay is toxicities.

So by this way by this more focused normalization approach you can actually avoid larger toxicities. You basically try to.

You know to get fired on the micro environment rather than the whole body. This is a general ideas. So the now this entire SQL thing. Anybody is in criminal trial or their Phase 1, started last October.
And the Phase 1, two together and the in collaboration with this cure companies and the illegible illegible patients 2 type of patience. One is patient have this all is patient. Every advanced solid tumors.

Who either have a pedia one low OK typically pedia on low patients who sometime after screening they were not eligible for PD one treatment. So those are those are eligible for our treatment for our direct #2 is the patient is give anti PD or my PDR. One therapy and then they fail the therapy so you can see this type of the.

The trial is not really competing with current the.

Ongoing therapy or trials and biomarker. This this is above a study we take very seriously. We are going to do richer spectrum. We are doing each of introspective and perspective biomarker study try to identify the particular sub celebration as I mentioned the type strip Asian is.

From that, we can start wings and the hospital in the country, the year. Leslie’s Leaside demeans. The sample or close to us for analysis, so at least 1 result will be released. This is a place. One is basically is that the because from October. So the because this account for interest issues social with this and this skill center fountain this cool.

So the I will not be able to talk, too much. But it’s something I can tell you is number one in the freezer one result the truck is very safe, but we haven’t seen much severe too much severe toxicities unless drug use huge number so this is so it’s very safe #2. We already see some responded so which is a single agent so I think this is the way very happy with that and hopefully.

So the again this is a kind of summary what we target target full as I mentioned to you number type of two patient, which is now larger than or more than 50% anything from 51, PPL Center. Please by majority or other is not so then secretly team, which is target, very different subset of patients with a P 01.
Lower or not or connected and this type of Asian have a piece of information every single team might benefit from that, we think is a simple team I also actually.

Benefits summer patient in the PT1 PT01 resistant patient and which could be could be interesting. These are our plastics. So then you can see here. Obviously type one and there before which is more than 50% of patients what we’re going to do about. I can tell you where activity study that the idea is in our lab is in this type of patient.

Is not as simply absence of the piece of infiltration? Is teaser actually cater single now not to come not to migrate.

That, it is a reason is not simply because of the absence of of the Diesels. It’s because our active mechanism operating in a tumor site and then.

Cause these are not to come so this is from very basic science angle tool to approach this question. So this is very different from what right now is the mainstream idea, which is just can simply inject some of things, which can stimulate immune response directly into 2, there for example, taller receptors think or whatever into a tumor. Theoretically, which is most eventually right now already failing criminal trials and we think is if.

Clearly active process or inhibitory mechanism in this type of tumor. Then the viewer not figure out their first then will not work. Obviously, try to force the email system. It’s targeted work, so this is what we are working on so recap what I’m talking about. Here’s an image therapy. I think is the basically is end of the beginning. The beginning means we care, some promising result. PD one PD. L1 we learn something we learn something very different.

For all the traditional cancer immunotherapy, which is mostly based on idea or enhancement. So now I think we have different ideas is the obviously there’s I’m not saying enhancement quesadilla service will be stopped handsome. I initially actually give lots of aliens, we know how immune system worked, how you can operate the issue is more like you have to watch the toxicities for normalization right now is the.
Many targets still need to be discovered. OK. This is what I think it’s for the next many years. The efforts need to be put in here, so the obviously larger work as a major. Few people in the lab and the also there’s a large team of the translation now and the clinical team is you see lawyer helps set there, they will rim crush operas pathologists and the.

Caruso and their marriage know who is a clinical team, potentially involved in clinical trials. Thank you.