And I welcome Dr. Peni Tan to talk on T-cell receptor therapy.
She is virtually going to connect with us.
So I would request the organizers to allow her to share the screen
and start the lecture.
This is Dr. Mhaviz.
Hi, Dr. Vijay.
Yeah, hi, hi, Peni.
Good afternoon, everyone.
Good.
Good.
Good.
Thanks for inviting me.
And I also thank the brassine for sharing the section.
So because actually TCL is also very related to the same topic,
like what Dr. Bache has just now presented.
So today I'm just sharing about TCL.
Yeah, TCL receptor.
And I move on from that.
I just a little bit of declaration
that today the topic may be talking more on about the TCL.
So not much about any other company,
either or whatever.
So it will relate more on personal perspective itself.
Yeah, so talking about the TCL receptor,
we know that actually TCL receptor is actually a protein complex
that you can find and present it in the surface of the TCL.
So the major one is a J-comp 2-time.
Well, in our human, 95% of the TCL receptor,
we found it is alpha and beta TCL.
And there is only 5% actually is gamma and beta TCL.
So you can see actually from here, the laser pointer.
Yeah, so this is how it looked like, the way it differentiate
by variable and also the constant and also the transmembrane
and cytoplasmic teal.
When you move on to the role, why TCL role?
What is TCL role?
So the TCL, we know that actually when TCL,
it will have this alpha and beta.
At the same time, it will work up together with the CD3.
So the CDT will have zer, epsilon, gamma, and epsilon delta.
At the same time, what is the cine ring or bicoye endo domain?
For the endo domain, actually, you can see that it is a TCL zeta zeta.
Slightly different with the car T cell.
What is different if the car T cell is?
Car T cell actually presented here with a heavy change and light change.
Whereas in the TCL, what you will see actually is a T cell gamma and T cell beta.
Talking about the cine ring, for car T cell, you will have CD3 zeta.
But this one is actually considered CD3, double zeta, zeta, zeta.
So it's slightly different in terms of the structure, why?
But it still has a little bit of similar because both also have this kind of way of
structure.
So when antigen presenting it so that it will be triggered out and stimulated out,
the T cell becomes a helper CD4 plus or either a cytotoxic CD8 plus.
So the role actually, the function is slightly different.
Can see that the helper CD4 plus actually has on perforation.
And cytotoxic CD8 plus more on killing effect.
So whereby you can see that how it works out different.
And also when it comes actually to because actually TCL is slightly different,
it's compared the other because it's very MHC dependent.

So the MHC dependent is like, for example, now if you present it at the surface, like MHC class presented at the APC.
So it will come with helper CD4 A plus, the one who actually work out on that.
So that it will bind up to that so that it will respond.
Same to CD toxicity CD8 plus, it will actually bind with MHC class 1, which is different kind of the cell.
So how it works is that you can see that the flow from here, when it comes to here actually either it stimulates it up or either it in AP.
In the bit then of course stimulates the bit then it will come with a different kind of the signaling 1 and signaling 2, because it's a signaling cascade.
So whereby CD TCL the way work is actually to be honest to say that TCL is naturally available in our body.
But when you come in the engineering or you calculate in the adaptive cell, then it will change the form.
But however, the action will be still the same, which is you've got helper CD4 and also the cytotoxic CD8 plus to work up on the both function to recognize the antigen and then to destroy the cancer cell.
So the role of the TCL-A-G immunity is why we choose the TCL-A-G is because it's got precision targeting.
You can able to distinguish even the very minor differences in bad type sequencing and able specific immunotherapy immune response.
You can assess the intra another different point I would like to highlight for the TCL versus the other like for example the CAR T cell because CAR T cell actually targeted on the very surface of the antigen.
Whereas the TCL-A-G on intracellular antigen so that it can able to assess the intracellular antigen and process and present it via the MHC complex.
So it's slightly different with the CAR T cell and the core function is it can able to identify and eliminate cancerous effectors or the disfunction cell and drives the adaptive immune response with the very high specific and minimum of target effect.
So that is the different that versus CAR T cell versus the TCL.
You can see that the major point that we want to know is the target recognition.
Can see that CAR T cell actually work mainly on a lot of surface antigen such as CD for CD 19 or either CD 20 BCMA or either CS 1 BCMA or either we can look at CD 123 CD 137 with a different count the DCC cell.
But mainly more focus actually on the HEMATO MCL.
Of course it will still have the solid tumor cancer like for example like what Dr. Bresher had presented like Crota 18.2 or either HODO either GBC3, mesotylene or what else I certainly can remember or interleukin 13 R alpha 2 or this one mainly you can you can see that it actually presented at the surface of the cell.
Where else the TCR they actually targeted on intracellular and the surface intracellular and surface antigen virus the MHC that ties complex.
So the mechanism slightly different because CAR T cell do not depends actually on MHC but where else TCR actually really much depends on MHC.

It needs to virus that so that it can work on that so that you can see that both structures
slightly different and also of course I wouldn't say very limited actually to the surface antigen for CAR T cell.
However majority will work on the surface no doubt some like for example like just not one
question having post-op asking about CD 19 but see then you do we know that CD 22 actually is
intracellular or intracellular antigen but where else most of the time it will go in buying
dual CAR T which is CD 19 plus combined two in one of the vector in order for it to sit in at the
surface first that only will trigger up and go in up to the intracellular antigen.
So it's still limited because you need the surface of the intracellular
antigen actually to carry it in order actually to enter into the surface intracellular
intracellular antigen.
When else the TCR what is the benefit is it's very broad it can actually in terms of the intracellular
antigen it also can be including the target not just that even though mutated gene also as well
because it's actually targeted a lot on the back side.
So it's very broad in terms of the coverage on the antigen and talking about the ease of the
engineering of course is what is different is like relatively for CAR T cell we would say it's
more simple use because it only use the antibody to drive a small change fragment domain for target
binding. When I put the TCR it got a lot of the process it unique dual isolation affinity
optimization and also extensive of specific testing because for TCR it depends on what you
want to work up you want to work up TAA or either you want to work up a new antigen TSA
all this will be to drive very different you need to and also the HEIA typing as well.
So that's why it got a lot of sequencing you need to do very specific a lot of testing
to pull out and then you need to synthesize it and then only you can do the engineering for the TCR.
So that's why in terms of the merit fracturing site it's slightly different and talking about
on target and off tumor toxicity I would say that both side CAR T cell is moderate in terms of the
on target of tumor toxicity because it will have it will raise the risk actually will arise if the
target and agent are expressed on normal tissue for example like a certain like for example there
is some people have been questioned like AGFR because it's the AGFR of CAR T cell because we know the
EGFR also it can be expressed actually on the normal tissue so whereby it will have that issue of
on target of tumor toxicity but of course it depends on how the way you assess it I just would like
to highlight that if let's say you go for intratumum or local delivery for the specific we know that
it will appear one like for example VEGFR CAR T cell if you do a local delivery of course you
will minimize all the issue of on target of tumor toxicity unless you go for IV

then of course the
story were different but else for TCR I would say that if you go with new and decent specific TCR then
the chances of on target of tumor toxicity it was slightly lower it's compared to CAR T cell but
however it will be higher if let's say you are using different kind of like TTAA specific TCR
yeah and talking about the generation of the TCR actually it has a lot of very different
kind of the version you probably will listen to the first generation what they have is just a
normal TCR without any engineering type without any of the cold domain coming in the picture
so it's just a normal TCR okay normally when TCR you can come with a two different kind of the source
either you use the PBMC or either you use the TLTIL TL which is you extract out the T cell
already infiltrated from the tumor so we call it TLTIL cell two way to do it but the second
generation was slightly different because we will do the engineering with the cold domain coming in
the picture either you use a CD28 or either use 401 BB come in the picture so that's why you can
see the green color here yeah that is the changes and also what is the slightly different is you come
to the third generation a lot of people actually combining both CD28 cold domain and also 401 BB cold
domain but move on to the fourth generation what which the difference is they believe that if
let's say you just drive it out with the cold domain in it is not enough because you're still
very depending actually on the MHC so they believe that if let's say you're able to engineer a TCR
which is MHC independent and agent specific with the signaling so that it will actually
have a broader targeted and effect and cancer destroying effect so whereby you can see that here
the structure is it will come in with the TA small change fragment with two double healing with the CD
CD3 then after that it will actually pull it up together with another side so that's why we call
T-R-U-C it's one U-F which is called T cell receptor fusion complex a trap we call it a trap
so for the trap actually you also can change different way there is many methods that you can
go on either you go with alpha trap or beta trap or gamma trap or delta trap or either another
one we call epsilon which is you have a two tier on that there is also another new evolution of TCR
as well right now already ongoing many people actually have been run and also started the clinical
trial so you can see that one type is genomic editing the TCR alpha beta either you knock out
or you knock in depends on what you want to like for example the first one you can see that when
you go with the endogenous of TCR alpha beta knock out so you knock out the alpha and beta
so you no longer having the alpha and beta so that you will appear only in beta gamma and delta

cell only and also in that and the blue color point you can see the zeta which is the signoring site
or another way that you can go with you knock in first you knock in the alpha beta then after that
you knock in it for a three round so that you make it out very differently so that the structure
is completely different you want to make it very strong three times which is like you amplify
actually the effect of the TCR but of course it really depends because this is still at very
preliminary result at this point of time for genomic editing for the TCR alpha beta not in and not out
now we come in another four type which is ongoing the first one is you still have to go through
we call it APC antigen presenting cell which is TCR like CAR TCR they are combining using the
TCR antibody PCR utilize the TCR like antibody for recognizing so you add on one more
antigen here and also the antibody and also the codomain here on the red color one which is either
you go with CE28 or a 4-1 BB codomain and of course you remaining the CD3 zeta but you are not a double
zeta you just change a one zeta it's slightly like the CAR T cell but it changed a little bit different
which is at one another segment side so that you can see that actually it works
those side you present things slightly halfway similar like a CAR T cell at the same time it's
still got the TCR so this is at this point of time this is still under a preliminary data
another one way is TACT which is TACT you combining the TCR with specific TAA by using the two small
change fragment still remember in the CAR T cell there is a one small change fragment
so they are combining both consides using the TAA here yeah TAA which is two more associated
antigen you pull out for example like let's say you go for uh you go for uh
uh WT1 or you go for N1 SO1 so this is the TAA so from the TAA you pull out you sequence it out
then after that from the CD3 zeta small change fragment you have one and two so you pull
out combine and then you link it back with the TCR so this is called TACT another type is called
ABTCRT ABTCRT incorporate the fat which is using the the fat ligand and also using the alpha
gamma delta sorry no alpha gamma delta TCR still remember just now I mentioned there is a 5%
that in our body it's commonly what consists of gamma delta TCR so you pull out that very red
because they believe that this will be less dependent on the MHC so when you incorporate
both then become AB AB actually presenting of anti-body so ABTCRT another last one is called
starte the starte is the changes is you can see that they pull out the the heavy change and also
the light change like a CAR T cell side on the top and then you're still remaining but you
remaining like what the TCR normal have but you removed out this the top you move it out as a
heavy change and also the light change like an anti-body put on and then so you

combine the VH
and the VL with the TCR alpha and beta in that the changes is there so a lot of way that actually
is a lot of evolution of the TCR how to go or that but the moment that you design of course for us
is as a scientist what what is our objective and what we want to target on and how we want to go
in and also to penetrate and also actually to tackle the target the target and vision that
what we want to do so that is a a lot of work that we need to think of that why we need to design
in that way so a lot of classification of target and vision in transgenic which is we call it
engineering TCR it has a two major type either you go with TAA too much associated and vision or
either you go with the TSA new and vision type so you can see that there is a very different
if you go with the tissue differentiation and vision you will have the Mc1, Mc1, Gb100,
TYRP1, Mesotylene and like cancer another type for TAA also you can go with the cancer germline
and vision like N1, SO1, MACA and also yes okay I'm going to finish very fast okay
okay and also I think I will make it very quick so there is a two major way is TAA and TSA so
of course everything also will have is all pro pros and also accounts so events are actually
what you want to target on so like I believe today I will just cut it short so I will just share
more on new and vision specific engineering TCR because we believe it is a game changer in
personalised immunotherapy because new and vision energy is very unique tumor specific and vision
and the more important is it's not present actually in a normal tissue but we'll make it a more ideal
target for personalised immunotherapy and the source is actually for example like for example
KRA, TB, TB 50 all this is we know that it's commonly being found in majority of the cancer patient
so whereby we will go for new and vision specific TCR due to the high specificity and also broad
application and in immune, invasion, overcome so manufacturing side actually we have two way to go
majority people using PBMC but I would suggest that actually the best way actually to use is the
tumor sample which is using a biosis plus the PBL the blood tube when you use the tumor the
biosis sample you can actually take out the T, like Dr. Brashan that just not mentioned
T because of it already being I would say that he actually able to overcome the TME to tumor
microenvironment so whereby it is a better idea a source of for the cell that we should use
the T cell that we should use to manufacturing the TCR so that is the major one way first thing
is we have to sort out first the T the TIL so we need to do the TIL isolation that after that
you need to select a very specific one that after that we will need to go through the
whole genome sequencing to identify the type that what we want to you call it TMG

what kind of
the peptides you need to go through one by one you're sheenering after that you synthesize
after you synthesize it then only you engineering it of course you still need to run and I want
HLA typing after run HLA typing so that you have one two two thing that only you can engineering
on the T cell which is isolated the TIL then you select the TCR out so that after you isolate
out and then you engineering it then only you do the screening and then you you formulate it and
also infuse back to the patient so what is the quality control is needed if first thing is you
need to check the purity, potency, identity identity and safety and of course what kind of the test
that you can run is flow cytometry cytotoxicity assay and sequencing actually to check the genetic
integration so of course the other are not changing but that is how when you're running a flow you
can see all the item like CD137 CD156 and also CD69 CD69 and CD137 and all that yeah
I think my time is quite okay I'm going to finish this like then it will be almost an end
of course there is still a some limitation of new antigen specific TCR I will like to highlight
few things is like because of the sample biosis sometimes is very limited so that is very insufficient
of production of new antigen specific T cell we can do even you need to do the sequencing
because the sequencing is shown we need at least one million to two million of the cell so that's why
it will have a lot of lots of new antigen and also down regulation of HLA issue so all this is
few of that actually will be happened but of course we are trying to minimize it and
yeah the key takeaway on the TCR is we believe that TCR actually is a game changer in the immunotherapy
and a lot of way to do it you can do TCR combining with other to improve it and we always believe that
TCR immunotherapy holds a must promise for teaching the cancer and TARI is a challenging a lot of
challenging force actually to address so thank you yeah