It's my pleasure to introduce Doctor Yang, who is received this MD from Shanghai Medical College of Punan University and his PhD at Baylor College of Medicine. And he completed his pediatric residency and Clinical Genetics Fellowship at Texas Children’s Hospital at Baylor, at Baylor and then joined the Yale Department of Genetics in 2019. His research focuses are the discovery of rare diseases and modeling neurogenetics and neuro epigenetic disorders using.
human derived ipscs and mutant mice.

Thank you. All right.

Well, thank you for organize this event.
Also for the invitation,

I shoot the clothes.

I'm not stem cell biologist,
I'm not biomedical engineer either.

So while I'm here,

sorry, how do I convince?

So how do we get interesting for the

bring organize IPSC and 2DS3 neuron?

So I'm kind of called genetics. I see.

The patient in the clinical. Sorry

for real genetic disorder
and then back to the lab.
Wow, that didn’t work. Sorry.

Go one more time.

Oh, OK. Thank you. That means we need every step together, right? So.

Next lab, we can try modeling the genetic new epigenetic primary aspect of brain development in the lab, primarily using the Moss model or other animal model, understanding the function of gene, understanding the disease mechanism, passive Physiology as a physician, definitely interesting develop a treatment back to the family.

However, as probably I would say
almost all the success we learn primary from the brain from the mice. Did not translate well come to the human we fail miserably for many, many of the successful exciting So that’s what we’re asking could kind of study for the IPSC, we kind of study for the IPSC, So I’m going to give you two example in in my lab, probably focus on the first one the time I say. So I hope you feel these two disorder are very interesting in general.
So this is Engram syndrome which is oftentimes many syndrome named by physician, the first recognized name endrum, it’s a very classical severe end of the new developmental disorder IQ, it’s very low IQ like 20, they don’t speech at all, don’t have any speech. More challenges and they have very severe epilepsy and almost 1/3 is medically intractable. It’s very devastating to the family. It’s very interesting molecular basis, a primary genetic defect IS15Q11Q13 and matured patient have a 15Q11Q13
00:03:31.238 --> 00:03:33.510 deletion cross this region,
NOTE Confidence: 0.817245815454545
00:03:33.510 --> 00:03:35.085 but interestingly because
NOTE Confidence: 0.817245815454545
00:03:35.085 --> 00:03:36.660 it’s imprinting related.
NOTE Confidence: 0.817245815454545
00:03:36.660 --> 00:03:38.995 So the paternal delition delition
NOTE Confidence: 0.817245815454545
00:03:38.995 --> 00:03:40.863 come from paternal chromosome
NOTE Confidence: 0.817245815454545
00:03:40.863 --> 00:03:43.069 caused a complete separate syndrome
NOTE Confidence: 0.817245815454545
00:03:43.069 --> 00:03:45.494 called the pero alloy and with
NOTE Confidence: 0.817245815454545
00:03:45.494 --> 00:03:47.379 the delition come from mother
NOTE Confidence: 0.817245815454545
00:03:47.379 --> 00:03:49.540 maternal alloy cause the end German.
NOTE Confidence: 0.817245815454545
00:03:49.540 --> 00:03:52.540 So over the time we know the gene
NOTE Confidence: 0.817245815454545
00:03:52.540 --> 00:03:54.995 response for this larger delition
NOTE Confidence: 0.817245815454545
00:03:54.995 --> 00:03:58.088 it’s ubiquitin protein like this 3A.
NOTE Confidence: 0.817245815454545
00:03:58.088 --> 00:04:00.416 As more interesting this region is,
NOTE Confidence: 0.817245815454545
00:04:00.420 --> 00:04:03.285 we also know maternal duplication
NOTE Confidence: 0.817245815454545
00:04:03.285 --> 00:04:06.150 only maternal duplication from mother.
NOTE Confidence: 0.817245815454545
00:04:06.150 --> 00:04:08.982 Costs about 1 to 2% in the Ed Pass
00:04:08.982 --> 00:04:11.007 autism but not paternal so you can
00:04:11.007 --> 00:04:12.747 see it’s very very interesting.
00:04:12.750 --> 00:04:14.750 If a duplication for father
00:04:14.750 --> 00:04:15.550 relatively normal
00:04:18.350 --> 00:04:21.871 so. So with with over the time we
00:04:21.871 --> 00:04:24.047 learned this is more complex sort of
00:04:24.047 --> 00:04:25.737 a genetic epigenetic defect majority
00:04:25.737 --> 00:04:28.068 of the logic deletion we have a poor
00:04:28.068 --> 00:04:30.160 mutation in the maternal chromosome you
00:04:30.160 --> 00:04:32.845 put in like H3A we have another two
00:04:32.845 --> 00:04:35.037 class of a where kind of uniprantal
00:04:35.037 --> 00:04:37.480 dysomy 2 comes come from same parents
00:04:37.480 --> 00:04:39.793 and of imprinting defect that’s also
00:04:39.793 --> 00:04:43.070 small number for case color you B3
00:04:43.070 --> 00:04:46.495 gainer function contributor for autism.

So now you put in like a G is an open. H3A some of you very familiarly percolation pathway and the most interesting to us is this is epigenetic phenomenon kind of imprinting the expression for the gene in the next generation. It’s depend where this come from. So for the ENDROOM gene actually it’s very interesting which is first kind of new specific imprinting gene in non neuro both Gene Express both earlier express. In the neuron in the brain only maternal allele expressed. So that’s the how interesting this phenomenon is and over the time we and many other understanding for the
00:05:25.592 --> 00:05:27.866 mechanism how could this they cell
00:05:27.866 --> 00:05:30.520 type specific as a less specific
00:05:30.520 --> 00:05:31.966 infinite phenomena happen.
00:05:31.970 --> 00:05:33.810 It’s actually due to a very very long,
00:05:33.810 --> 00:05:37.674 almost mega based long non coding a RNA.
00:05:37.680 --> 00:05:40.416 Are part of what we called also antisense
00:05:40.416 --> 00:05:43.443 for the UB3 gene only expressed from
00:05:43.443 --> 00:05:45.713 paternal chromosome then silence for
00:05:45.785 --> 00:05:48.155 the sense on the paternal console.
00:05:48.160 --> 00:05:50.617 So that’s the mechanism and we also
00:05:50.617 --> 00:05:52.868 generate a many Moss model over
00:05:52.868 --> 00:05:55.118 the time to study this mechanism.
00:05:55.120 --> 00:05:58.330 Overall Moss model provide many many
00:05:58.330 --> 00:06:01.690 valuable insight however that’s.
00:06:01.690 --> 00:06:05.162 Also the capitulate a lot of the human
00:06:05.162 --> 00:06:07.098 phenotype reasonable well especially
NOTE Confidence: 0.9201268
00:06:07.098 --> 00:06:09.563 we're interesting for the epilepsy
NOTE Confidence: 0.9201268
00:06:09.563 --> 00:06:11.042 or abnormal EEG.
NOTE Confidence: 0.9201268
00:06:11.050 --> 00:06:13.650 However then we take this one on try
NOTE Confidence: 0.9201268
00:06:13.650 --> 00:06:15.497 understanding it because as you know
NOTE Confidence: 0.9201268
00:06:15.497 --> 00:06:17.939 one set of patient have no control for
NOTE Confidence: 0.9201268
00:06:17.939 --> 00:06:20.326 the seizure or lifetime which is very,
NOTE Confidence: 0.9201268
00:06:20.330 --> 00:06:20.916 very challenging.
NOTE Confidence: 0.9201268
00:06:20.916 --> 00:06:22.088 So we try understanding,
NOTE Confidence: 0.9201268
00:06:22.090 --> 00:06:24.345 use the muscle model industry
NOTE Confidence: 0.9201268
00:06:24.345 --> 00:06:26.600 understanding why this epilepsy so
NOTE Confidence: 0.9201268
00:06:26.675 --> 00:06:28.650 common just highlight one phenomenon
NOTE Confidence: 0.9201268
00:06:28.650 --> 00:06:31.330 we use this is very specific.
NOTE Confidence: 0.9201268
00:06:31.330 --> 00:06:33.940 To Physiology phenomena measure the
NOTE Confidence: 0.9201268
00:06:33.940 --> 00:06:36.028 action potential with particular
NOTE Confidence: 0.9201268
00:06:36.028 --> 00:06:38.879 folks on fast component after
hyperpolar polarization.

We realized in this particular engine mouse model in the brain and neuron this FHP is increased and we have done a lot of work using the biochemical molecular and linked it to the Ek channel. It’s enhanced function for BK channel contribute this phenomena. Then we also show this link to indeed in link to the epilepsy in the mice, which is you can use the antagonist Hassel and can reduce the amplitude and the frequency eventually suppress the seizure in the mice.

So that’s all good.
The question came to whether this is translated between the human so that came to what we got into the IPSC 2D and three you are. That’s one time I moved to the Yale and then I realized the world class of the stem cell center. So I talked to Hifi and India and the child home and say hey why we just do this create a repository for the Andrew IPIC. So luckily we got a very generous support for the fast foundation for Andrew and therapeutic they give very general support and right before the COVID. So over the last three years even during the COVID,
we were able to generate.

One day cell line IPS IPSC cell line from different genotype including the control.

This is free to everyone here.

If you’re interested you can just e-mail me

are free to distribute it to each of you.

So that allow us to really ask the

question whether phenomenon we study from mice is the translator from the mice.

So I’ll just give you a few slide and

the summers are published already.

And then to shows the phenomena,

same phenomena we observed from

the mice which you can see the FHHP

which indeed in IPSC the wife the
2D new one in the cortical new one

in this is enhanced the two.

So that’s increased the frequency

Suggestion the hyperexcitable new

one and then we all can can use

shows that deficiency UPC is a

responsibly electrophysiology.

Now we got to choose also biochemical assay.

Indeed it’s correlated for the BK

channel function in the 2D neuron.

Now you can show also the

paxilance same as in vivo,

in the mice can suppress

this hyperexcitability,
but in the 2D neuron, now we move on together. That’s we cannot advance. So that’s right. Maybe I did something which I should not do. So then when you organize 3D neurons, it shows very similar discovery of funding to. Yeah, same thing, the increase the. Frequency then the pass and suppress the hyperexcitability. Of course the question will come to whether you can recapitulate epileptic form in the brain organelle. That’s question we still have not get into that very very very detail.
So that’s all looks good because we can study the mice to translate the human allow us to the confidence maybe indeed we can allow these two system to testing additional. Particular for treatment strategy. So one of the thing we are working on right now is to try to using this strategy. As I told you, I could not get into the very detail. So the mechanism regulate this imprinting is due to the antisense Bay long megabase continuous antisense long line coding RNA. So the one strategy is if we can disrupt this long line coding RNA
and then you can reactivate the gene.

On matpat and chromosome is supposed as like a gene therapy can approach.

So the ASO has proved it’s effective and it's also in the phase one trial right now.

So we think about it with whether we should do a more permanent fix.

The ASO we need every month sort of the eye spinal injection and now we work on this with CRISPR additive.

So working with collaborative with the.

People from the biomedical engineer as deliver crisp to brain is a challenge.

We actually got this piece of very exciting data by our AIS in the lab.
shall now shows you we use this chemical modified MP conjugated CAS 9 protein and Gala and they together deliver IT intracego injection which you can see. Amazingly this deliver the editing in the cortical neuro and cerebellum. Which you can see this a new M cell, then this green cell, it’s a reactivation after editing the anti sense. It’s almost like 70% efficiency for this coach similar to the cortico. That is pretty amazing. So we feel like this will be the next step. We are watching actually active working
00:11:44.954 --> 00:11:47.297 on the 2D and the 3D neuron right now, see if for the same delivery it’s effective if entry before we go to FDI&D and to the human.

00:11:49.932 --> 00:11:51.677 So I’m gonna switch the GAIL for second disorder, which I hope that you will find also very interesting.

00:11:51.677 --> 00:11:55.370 So this is a patient I saw about four or five years ago in the clinic.

00:11:55.370 --> 00:11:58.490 In the same scene I could genetically related disorder.

00:11:58.490 --> 00:12:01.370 which I hope that you will find also very interesting.

00:12:01.370 --> 00:12:02.970 In the same scene I could genetically related disorder.

00:12:02.970 --> 00:12:04.806 In the same scene I could genetically related disorder.

00:12:04.806 --> 00:12:05.724 So this is a patient I saw about four

00:12:07.872 --> 00:12:09.906 or five years ago in the clinic.

00:12:07.872 --> 00:12:09.906 or five years ago in the clinic.

00:12:09.910 --> 00:12:12.344 It’s a very similar to engerman but that’s definitely severity it’s 11

00:12:13.859 --> 00:12:15.279 mile and moderated compare engerman
and to me it's a severe and this
is a moderate and with autism as
a predominant feature intellectual
disability interesting they have
macrosuppony which the big brain is
the bigger they have a low percentage
of low frequent preference of epilepsy
too and so so this is the the boy
and what he was nine years old and then.
Later on was to find interesting
another end of a phenotype.
This is the
sort of a longitudinal sort of picture
of a longitudinal sort of picture
from the infant to when he was thirty.
I hope you probably say okay,
it’s probably more old than that.

So that’s a premature Asian phenotype that’s we think it’s also the other end.

It’s very interesting.

That’s a delay early new development somehow later on.

Is actually accelerated aging process so that’s clear a puzzle and and then

we’re looking for the genetic we we

did a whole accident in the clinic we

identified the first mutation is patient

other colleague from UK also similar

time 2017 2018 report a few other

case and eventually last five years

will accumulate almost 100 case now.
So what you notice quickly matured for mutation in the C terminal domain. And majority for them it’s A-frame shift mutation. What’s more interesting when you do the computational prediction, the open reading frame, actually it’s quite interesting, you can see here if you do the open reading from open reading prediction, regardless where the mutation location near all and very very same tail about for the amino acid at N. So that’s to me is a little unusual. I’m a geneticist, I see a lot of patient database.
I have not seen this kind of phenomenon very often. If it happen one of you, you have some case like this talking to me and we kind of working together to figure out this puzzle. Interestingly we also generate and antibody specifically against this tail. The antibody actually very easy to generate because this tail if you against the genome or podium you against the genome or podium actually pretty unique. So allow you to very quickly generate this antibody. Now you’re testing the patient IP.
At the same time we generate about a
IPSC cell line from this patient too.
So you can see this IPSC cell line and this abnormal tail,
It’s indeed it’s stable.
So that raised the question whether this abnormal tail.
It’s actually gain of function or dominant net function because when
you now call this gene in the mice, they have no significant phenotype.
But in the habazygs in the human, it’s very definitely a very severe phenotype.
So that we interesting also this is same mutation or same mutation
in the mouse gene or mouse gene,
you won’t be able to create the same tail.
So it’s only to the human coating.
So that create a little challenge
to manipulate in the mice but
of course we can’t do it.
We made in the humanized mouse model
by engineering the entire human gene
in the marketing of the car knocking
and replace the anti mouse genome.
So that’s ongoing.
We’re just talking to people outside
like it’s a mouse have azyg have
mild phenol type homozygic actually
end the post Natal early so.
So,
but in any way so we will say OK

that would be good to kind of look a

little more this is a very definitely

because my title is a new epigenetic.

So it’s a, it’s a H1 link protein

as you know probably have about

11 H one link some of the somatic

form is one of five somatic form.

So this H1 link and the function

for H1 link in largely we still

don’t know because over the last

25 years lot of people study cold.

For histone, very, very detailed,

but this is almost like a forgotten

histone for over the last decade.

But now you can come to interesting for
many people because the human disease link. So again it’s a link histone with the link DNA and it’s core histone. Presumably function is making the chromity more compact but it’s a very basic component of the histone, but the link to very selectively human neuro behaviour and neuro developmental phenotype. So, so that’s what we would generate a panel of an IPSL again, again a child home and in you. And for this effort, sometimes people ask and say why you didn’t do it at Duke.
And I would say, well, yeah, we want to do at Duke, but we don’t have a facility like here. I find I left two years ago before I joined the Duke. But that’s what we lost high final deal and now we don’t have the stem cell facility there. So that’s what’s asking you should have taken advantage of for we have indeed excellent facility environment here. So again remind you this phenotype patient have a macrocell, a big cell, a big brain. So you look at the cell proliferation
indeed somehow suggesting that maybe correlate the human phenotype they are proliferated faster. Then both in IPSA and MPSC new one early precursor and we also did it for the I, and they seek and looking for. Whether it’s a chromatin structure affect the downstream transcription indeed is when you have this mutation chromatin sounds like more relaxing. So more gene up regulated and surprising to us it’s you actually see the set of a gene regulated, it’s actually still in the chromatin related gene.
Many ask actually chromatin related gene.

So we are very intriguing by this founding.

We also look because this is a chromatin structural later protein,

we asking whether that’s actually indeed affect the chromatin nuclear morphology or chromatin structure.

So indeed because the unique this protein alteration which are not mimicking in the mice. 

So we did a EM for this IPIC and

and the neuron we look in the morphology of the nucleolo and

the nucleus indeed that’s alter

the morphology from the nucleus.

So indeed because the unique this protein alteration which are not mimicking in the mice.
So that I PRC derived 2D and 3D new one actually indeed it's the one way to do more sort of investigation. I do have time to show you the organized other data on different time and almost close perfect time there. So I hope that by using the two example illustrated 21 is that you don’t have to be the stem cell biologist to study stem cell work. Second is I hope you also. Data from if you study mice actually indeed it would be good to translate what your mouse discovery of funding from mutant mice to one.
more step between the human device, this neuron before moving to the we call it FDI&D study because we are fail many many occasion, many example everything is beautiful in the mice, it’s a fail in the human stage. So large of the people in the lab primarily I think the people Kung Yun is the primary thing is now here working on the andrewman IPSC and IPSC organelle and then so nice data from the mouse for the IP and then a few other kind of also work in the similar sort of standing project. And then of course without your stem
cell center support this kind of large scale production will not be the feasible. And all the support I’ve received and also the collaboration with Duke and the EOS for the engine work together. Thank you.