

throughout those times he's been extremely productive I think 26 publications so far but there are several that are in review or re review right now so that number may have increased and what's pretty amazing is throughout that voyage he's really focused on a very specific set of questions which is understanding neurodegeneration and cell death in a variety of neurodegenerative diseases most of which have really focused on Alzheimer's and he's attacked this question in a dish looking at compounds and drugs that can prevent cell death prevent excited toxicity he's looked at it from the perspective of a glial cell biologist trying to understand how microglia and the pack a beta fibrils and most recently he has turned to Mouse genetics and human samples to get at some cell specificity in regards to the disease pathology and so I'll just comment a little bit about that there's been quite a controversy in the field about how accumulation and the pathological accumulation of tau in a variety of cell types and has been thought over the last few years that many cell types can actually accumulate this pathological how and what Harry is found is that it's not actually true it's that a very specific subset of cells in the brain accumulate pal and it's a certain type of neuron excited for neurons and so he's really starting to build his career over the cell specific vulnerability of excitatory neurons and so that's culminated in a recent neuron paper and it's really going to be what pushes his board to his individual independent career and he's already gotten the k1 award from that from in Sudan aging to study this and also an Alzheimer's Association fellowship rewarding to study this so he's well on his way on this path forward to understand how individual cell types in the brain so we're very grateful that

you're here and so let's let's give our candidate a warm welcome here me everyone so first I won't stand Star Fox for very kind introduction and also thank the search committee member for inviting me here I'm very glad here to be here and then I have met few faculty members and then talked about science in the morning and then looking forward to collaboration in the future and then I'm looking also looking forward to meeting more people today and tomorrow and so today I'm going to share with you some of some of my family when I was associate research scientist in dr. Karen software and the second part is my independent project and then the last part I'll give you overview of my future plans and then I always interest in which self subtype of neurons are vulnerable in North ahmadies and then particularly to table pathology which is immense and pathological marks in Alzheimer disease because I'll give you an overview of a neurodegenerative disease in the audience several key I also do the some work for some areas work and we know there's a current unfortunately there is no neuro protective or disease altering treatment for these neurodegenerative disease for this chair a common feature we have protein aggregation for example in ultimate oops sorry so 13 hours how many days they have an extra server a beta from the scene I parks and the intra new neuronal tau from the neurofibrillary tangles and this is at our protein aggregates has also been found in a group of Tao related disease called topsis including the frontal temporal dementia and alpha-synuclein impacted in disease and fast and tdp-43 in a Ras and the fgd disease and a very recently the c9 open reading frame frame not 72 called the mutation caused a dipeptide repeat protein aggregates has also been found in ARS and FTD patients as well as SOG protein agrees in areas and honking King in the Huntington disease this is just give you what the protein aggregates look like in these neurodegenerative disease this is the extracellular signal

flux and this is an inter neuron or neurofibrillary tangles in Alzheimer disease this is a Lewis body in

Parkinson disease this is a honking 'don intranuclear inclusions as well as protein aggregation in ARS and extracellular prion amyloid plaques although they have a specific protein completion in different protein aggregate they share a common structure and a electron microscope they looks like this it's a feebler polymers and then this protein aggregation followed a nucleation process and then that it from the start from the monomer and from dimer or Qamar and finally you will they form the big protein aggregates seen in those disease although the exact form of the protein and cost neuro degeneration is not clear yet so in terms of the cell

type involved in the pathogenesis in these disease beside the common activation of astrocytes and macro clear and article dental size they have a specific neuronal population affected in this disease for example in autumn a DDD the many affect the cortical and hippocampal neurons especially the and Toronto cortex layer to analyse

three neurons and ca1 pyramidal neurons and in Packingtown disease the mini effector top urges neurons honking entities effective strategy Iran by Ras disease in many affects the motor neurons so one of the fundamental questions and common to all of the neurodegenerative disease is a why a particular disease target a specific neuronal population so let's look at the distribution distribution of the pathological hallmarks of Alzheimer

disease again as I mentioned before this is the scene I parks and this is the neurofibrillary tangles formed by tau and then the distribution of the Cineplex is prod is a pretty broad the car added even at the early stage they already covered the most a cortex region and then the middle state they spread into the cyber nuclei and the motor

cortex and the later two in the cerebellum and brain stem however the new fever tangos the distribution

followed up well-defined and follow the anatomic connection they originated in

the Lucas chorus and the internal cortex and then spread into the limbic system including hippocampus and then at later

stage to read into the neocortex and then at that late stage and they caused

the associated with the cognitive test so just to remember this region internal

cortex I will mention the many times in my following talks so to replicate or

mimic the tower distribution in human ad dr. Cameron Tufts they have a generator

mouth line we call ec2 line this is a human mutant owl with the p30 one L

predominantly is present in the EC the middle region I mentioned before is

early affecting Osama disease and a using the new rocking promoter and then

they can cut at the early stage most of tau staining are located at Exxon and

they are diffused accents tinny the in the MEAC the media under I know cortex and a letter and her

on a cortex as well as the XML terminal following the proper and pathway in the

middle molecular layer of Dan de Jerez and the cr1 and the fiercely superficial layers when you look at the middle-aged

to see those external staining is speared and then instead they have more

granular cell body and the so much summer sumito dendritic how staining

this is indicating the mature adult staining and also you see this spread

into a little bit deeper layer of the EC region and also the granular layer of

the dandy jurors and the parameter cells obviously a one-year-old so I took over

the project I further captured this line at the very aged mouse they are at a

thirty four month age and then I look at the particular newer cortex region because this region is a the latest

stage in Ultima disease they have a lot of buildup Travis ology and then indeed

I found they have a significant to say about it how staining in this region and

then instead of with cut many sections and into the staining of a bunch of

staining and then this is a kind of tedious laborious work and then you can and you visualize that out distribution

in 3d way at one time using a method at the you know in my study I Union I disco

class method this method is a similar is similar to the clarity you designed me

familiar with that if you make it a brain transparent so basically is a you isolate the brain fix them and then just

do the immunostaining either you did for regular - training but just the longer incubation time and then you're using

three disco clearing method to clear the brain make it transparent and then using

the light sheet microscope to scan it and then using our marriage software to do the 3d

reconstruction and then you will see looks tidy this is the snapshot of the

3d image then at early stage they both Exynos training at the ec and dangerous

mid-american alaya and then this white part indicating those aggregate granular

tau staining if we're using the super color to indicate those regions with tau

and then you can clearly see the distribution and from the m ec eg to the

latest New York cortex region and even to the anterior factor Barbra Jean and I

just give you two movies to show the early a stage standby humans perfect

house and also the late stage so this is

the early stage you see that you had axonal staining and we see a little bit in a big delay region indicated by the

blue color and then when you look at the

aged easy Thomas you see a lot of granular steering sit how staining and

has spread into the neocortex and interior factor bath and also those fluids amygdala region so

also you can

use this method to visualize the table pathology which giveth gliosis at the same time at the shown by this movie so

the green stand for the tau staining and then the red is a stand by the IBA Y and

which is specially for multiplying macrophage and then you see those macro

crea just surrounding those tau pathology of course you can use this method to do like Exeter

trance in a big

twisting study and then your client also look at the brain circuitry map map the

green secretary also for us for the neurodegenerative disease we are particularly including to see

how how

spreading or vicinity in fattening disease reading from one area to another

area so the second character of this Mouse

line is the closest so we look at the MVC region the medial temporal internal cortex is a early effector you know comedy and this is a house thinning just focus on the MEP region and using the IBA one

to stand tall the microglia and you see at 24 rounds the number of markiplier significant hands and then were using a more specific activity marker clear marker cd68 to see the how looks like at Mouse H and then we see marker clear start to activate at early as 14 months age at this age I should mention they have no neuronal loss at all yeah

the the pattern is a pretty similar in of in our line and then for this study are using an animal each group each age so it's not like 50 patter is a pretty consistent for the distribution you mean

a 3d movie yeah you can do that yeah

that you can yeah that'd be better but at that time we just did a few we and we rushed for publication program yeah but for this we do a lot of characterization for the quantitation data for this it's a pretty consistent in the meed region

and then the top Authority may be vary a little bit in the neocortex but you do see they spread into that region a lot compared with the young age so this line is a pretty stable edge rates at rising again so also we're using the gif a key

to stain the astrocyte we saw similar phenomenon they activity at early as a 14 months and then they

further activate at a later stage so this indicating that the progressive closest is associated with the top Authority in the MVC region in the EC

Tom house so this is a consider consistent with previous republication that indicating that cleo sees is not

just outcome of the neuronal loss they may play a role in the early stage the past genesis of Alzheimer disease so the

third model a third character of this line is the memory deficit first reunion

a traditional Morris water maze to test to the spatial memory at the beginning

you just let the mouse learn how to find to find the hidden platform and after several trial the

Mouser shooters the directory goes straight to the platform and then that means they are learning and then you can

compare different genotypes to see what looks they performed and then at the early stage 14 months we

didn't see a difference between EC and control mice however at age this is the control this is a easy Tomas you see they take much longer to find those hidden platform indicating that some problem with the learning process and then two hours or 24 hour after removed the hidden platform and then you let the mouse swim and then go straight go to the target quadrant with a hidden platform and then you record how many times it crossing the freedom platform that's indicating the the long-term

memory and then again at young age we didn't see big difference and then at late stage the EC Thomas do have significantly in memory tap days then we test a way want to confirm this special memory that's it using another test this is a t-test as a and then this is the basic setup this is a stem this is the left arm and the right arm and to test a spatial memory we personally perpetrate block this right arm and then foster my mice go to the left arm with black cubes and then the nest right you just to put the mask here but don't let them see the arm just feedback and then let them to

choose which side to go and then due to the nature of the mammals and then they should we have a spontaneous automation

and then they should go to the right side and then if they go to the right side that indicate the correct choice

but if they to go to the left arm that's the wrong choice so then we calculate

the how many correct choice they made and then again at 40 months no difference at HCC Thomas we performed worse compared with the open

Oh My yes yeah it's a we have a middle

yeah which we do have a middle age and then they have a trend and not reach significant yet so this isn't may it may

mimic the human is that you need the towel spread into the neocortex region

and then you have a memory cognitive adaptive so this is consistent with the denomination yeah
yeah you're correct by the dislike if you look at the towel you decide by
pressing s which is stand for the maturity and then they're not positive
for the New York howtechs region and then they only call positive for the MSE region and then
indicating that though
although they have a distribution of tau but they are not a total aggregate into
maybe Tosca from yet so that's one waiting maybe those are toxic the aggregate tau may be more
toxic although
they live the debate of argue more favorite Taoism orthotic but they this
may explain why we didn't see a at the middle age I mean do we only found in
the late stage although this is a at the end of the life span of the might but is still in terms of
pathologists the of
relative early is a comparable with a human that's not nice
sorry that yeah I should mention that mutation not found in human automata zis
lady found in the frontal temporal dementia in our field we use that as a
model mutation to cut to generate the marks to see how spreading all the
toxicity of tau but no mutation has been found in the of tau in human ad yet
although some locals close to that region maybe have some variant indicating that but no
confirmation yet
yes so the internal cortex and
hippocampus are two main regions involved in the spatial memory and it's
a grid cell in the adrenal cortex region discovered by dr. Moses group and the
place there in the hip hemorrhage region discovered by dr. O'Keefe and then they shared the
Nobel Prize in 2014 and these
two know types of exaggerator ons and a contributor in GPS system and then
involved in the spatial navigation during our study we clap release dr.
Hassan eye at our University to look at the retail activity this is the first
time I think it is a report the brezza activity in the cow mouse model and
basically they made those tetrode and then attached the micro drive and the
head stage gear and then connected to a pre amplifier to amplify the signal and

then reduce the signal noise advance through the amplification and a filter process and then they give in software

to distinguish the spike clustering and then can distinguish different cell types and then in our study we focused

on the m ec region especially at also a meaty region which had been suggested to

be still a significant effect by tau pathology and then this is the set up of

his recording system so big a scale you

have those that had rode attach the head and also this the light actually is a combined with optogenetics setup you can

regulate the activity at the same time but not in our study so I just keep

assure you a movie was a freestyle barring and looks like so this is a

single grid cell and then when the mouse is powering our box and then this cell

time firing at different places and when you connect this the center of the

firing map and then use the form a triangular grid pageant we called

greivoux and then when you do the autocorrelation you get this map and then you can calculate the grease or to

marry the spatial symmetry of the grid pattern so this is the data we got and

then when we compare the HDC Tom mouse with control and then you can appreciate

the grid pattern significant and messed up with compared with control and then

you look at the average grease score in

HEC Tom a second equally low then control but not at a young age and also

the distribution of the grid got mostly lower score at the HD feed her mouth how

about the firing rate and then we look at the peak Perry and the average firing

rate and we found a both technically reduced at the EC Tom out at aged at a

30 plus month then how about the inhibitory neurons and we found the

average firing rates tick enabling enhance we assume this is a due to the deficits of the attachment neurons cause

the feedback constraint of inhibitory neurons

we test with

thirty months is around eighty humor around here yeah we do tested this for

this particular enviable recording they do reduce the reduction of the freezer activity the same we tested around 24 it's a middle yeah this is that between that but we didn't put you in this yeah because the one review also asks for that question because that's easily you just see the earlier and later why I didn't test for the middle yeah yeah

that sure so this way we are first to identify the research activity second agreed introduced in the MVC in HCC Thomas so the in vivo single unit recording data together tau pathology caused the imbalance between excitatory and inhibitory neurons and then we are wondering what type of neurons are impacted by a pathological Tahoe so we look at the m ec again and then we do the sequential staining of neuronal marker map to and the tau human how specific antibody MC one and then we found the perfect correlation in agreement by those black arrows when they look at the marker clear and then we didn't find the correlation at all and then we look at the astrocyte there are very few colocalization and this is a very consistent with the previous publication indicating that the pathological colonized with neurons for north korea cells in the early stage of a VEC of HCC Thomas but is the local or lab no colocalization does not mean the markiplier is Crichton and play any role in the process of the Alzheimer disease may be those neurons those the clear cells can t greet those tau aggregation quickly so that we didn't found it these through secreting and I'm two-degree them extracellularly the we haven't tested it completely but we saw they do have distressed in the neurons and mockery I haven't test yet according to that group the Mayo Clinic they generate mice that they a thing is not just a neuronal yeah but I don't have the data for that yeah but I'd like to see you in my single efficacy later and

then we further dig into this question which is the estatua neuronal marker and TBR wine is things for the nuclei of

estatua neurons and then look at the co-localization and we found tau philip

writes very well with the it's a in girona markers and then we choose the

pub every mean and assumed as steady as in hip junior on markers and then we didn't found co-localization at all I

should mention I do the sequential staining and then not coasting if you do Co staining us the perfect

colocalization we assume as steady that's my original finding and then I realized why the looks perfect

I then I using sequential staining to test it again actually they obvious result that's a detail another story at

the beginning of its all is a heavy tree but now attending to inside tree so she'll be careful with the post inning

going to the housing particularly so

when you look at the number of TVR one you saw the and m ec layer two and the layers three on the layer four region is the number of key darwin second opinion reviews but

the inhibitor neuronal marker no difference between control and easy to our mind so this is not the number of

eSATA neurons but inhibited manat inhibitor neurons is reduced in the m ec

of HEC Thomas then we look further look at this the second spreading area like Perry rhino

cortex and neocortex region this time we include a one Maurice

artery neuronal markers because of we are worried this is a tree neuron can old cover most it's a trainer on this is

another marker it's also stained the nuclear open it's a tree in Iran and

then again we found perfect correlation with the it's a tree neurons but when

you're using the this time we're using three inhibitory neurons which according to previous publications should cover

over 95 percent of Egyptian neurons and then we found no of them polarize with a towel

that's extracellular recording they

based on the I'm not expert on that so but I think they based on that frequency

and the amplitude right and then to distinguish the exciting history but I'm

not exactly no down

yes yes we saw is the cause of feedback is because the inhibitory lower and then

relative that inhibitor in your own still number didn't change that's called the that I we think it just do the

balance change we don't know exactly but in the future we can do space create it

stressed out in the surgery and inhibitory neuron and to see whether they really affect affected those

different types of neurons yeah so apparently

yes we think that

yeah they were didn't found it yeah

but if you think about this if you have less in stature in your own right and

then you have the relative more inhibitor in your own now right the inhibitor in your own way inhibited is

actually in your right called feedback so that's maybe that's why you see the like a common Satori effect of

inhibitory but I don't know he's actually I can't

maybe ask him more about that with ami yeah your question later thank you so

when we look at the the ratio of a colocalization we found over 90% four

guys with the sorry neurons but the very few colocalization with the inhibitory

neurons is the less than 1% and then if you look at the number of researchers in

Iran again Emme Sea region and then at HCC Tom Mouse the number significant

reduced but not for the inhibitory neurons and also we screwed the aging effect and when by comparing the Y type

mice the 22 and a study last month and thence with we didn't found significant

difference between TDR one at SAT two numbers so this is reductions use of town not due to the aging effect so how

about in humans and then we get the humor bridge section from the brain banks and then we look at the this is

the this is a blue region is the hippocampus this is a temporal lobe and then including this internal cortex

region and then again we using the same exact tree in Iran America TDR one & SSAT d2

yeah that's a good question for most of my study I choose the MSE one let's generate about it dr. Peter Davis is a

confirmational and also recognized the phosphorus and tau but we also do a lot of a bunch of tau specific antibody Hospital anybody by Tamil eighty eight eighty one hundred and course for theory

in for to the to a data anybody we get a similar result

this is the human human town

you mean like in here between Iran they didn't his great stuff I will show the fish data later they do yeah so again we look at the

localization we found the perfect cook the perfect colic IV the asari neurons

but no not colic eyes with inhibitory neurons again these the quantitative data over

90% colic I've been heaped researcher in Iran but let's then want to thank a look

at behavior neurons as the tau expression level enhance at the middle

and a late stage and a USC the number of misogyny neurons technically reduced so

indicating that the exaggerator on and inhibiting neurons in humans also differentiate vulnerable to time for

ecology in the early affected region in AD brain so the summary for the first

part is that maturity pathologies are associated with the closest grid cell

dysfunction and the special memory deficits in the HD theta Mouse and then

exactly under inhibitory neurons are differentially vulnerable to accumulation of a pathological tahoe and

then he not in both human brains and also our mouse model and the exactly

neurons are vulnerable to pathological tau in both the early and the late affected regions in AD so

the next part

is my independent project

yeah that's good question I didn't show but I in my publication we using the immuno fish to double staining the town

Fremont our protein with messenger tall on a and then you will see the end of the spreading area they have a very few endogenous de mi level most today just crewmen town that's indicating they are spreading human town not due to the endogenous level if you interesting you

can look at that's why I'm theorizing here so we know that the protein homeostasis Network can maintain a functional program and then the newly done essent unfolded protein generates in the ribosome and a release and folded into functional protein to exert its function those are necessary or extra protein can be degraded in the protostomes or lysosome during aging or under stress condition or environmental factor caused stress and then those protein can be missed folded and the

further agric aggregate into the big protein aggregate and then luckily most time our body have a homeostasis network and regulate can unfolded I'm voting in those misfolded protein or sending to the lysosome or protozoan for decoration and then I'm particularly interesting in the upstream the miss folded protein and then whether they have a intrinsic difference between is surgery and inhibitory neurons and then this is the idea is the based on the funding from one group in the University Cambridge actually my parish collaborators and then they found they are they are group

of substrate protein they are much higher level compared high concentration compared Authority and then in the aging and the neurodegeneration this is much higher this group protein compared with the healthy brain and then they named this group protein as the metastable subah protium ms in short i will mention later in my data and then they further compare the different different cell types in terms of those the protease stasis signature and then they found in the neuron they have much less protectors that's the protein aggregation protectors but they have much higher promoters and a better and tom level so i clarin read them to look

at the further look at the subtype of the neuron it's actually an inhale neurons whether they have the same of

similar signature difference between the different cell types of neurons so we

took the advantage of two recently published single nuclear science six

dataset and then those datasets from the healthy donors they don't have any ad or

hudson disease and other diseases of protein aggregation it's a very early

stage and then the first stage said we

could be called SN and then they are say the nuclei from the early effector

region temporal cortex and also the frontal cortex and the very late stage

affected area is the primary visual cortex and then they stay in the nuclei with new end specially neuronal marker

and the tapi general nuclear staining and then they to the fact salty and then

the using the c1 and micro fluidics to separate into single nuclei and then

they do the highest secrecy and then they are able to identify eight different subtypes of exactly neurons

and eight different subtypes of research in neurons indicating that the neurons

are highly heterogeneous and another data set is from doctor of aviv regroup

in Broad Institute and then they combine the dropsy droplet technique with the

single nuclei and seek techniques basically they isolate the nuclei from

the early effector region this time it is a hippocampal region and then the relative late-stage effect area is the

prefrontal cortex and then they using the drop date techniques to separate the

single nuclei and then to the sequencing and then they are able to identify different cell type to so we can analyze

this tooth dataset first we look at the

just comparative satuary neurons and in Hibbs you know in general and then we

found that this tall aggregation promoters and the MS is stand for the

metastable Saba protium gene signatures secondary higher in the it's a in Iran

and then this is a transcriptome gene signature the hopefu scriptum used as a

reference control and then we found also found protectors significant lower in

it's actually in Iran and also this is as a control you see this a tree have much high it's actually neuronal markers

but much less in between your own markers we are also able to gravitate our data data funny in the another

independent dataset and you seek here promoters MSP convenient hands so this

is a dataset analysis the reviews spare speaker Tao homeostasis signature in the excitatory neurons in the human brain Italy they may contribute to the statuary neuron or vulnerability then we

further look at the deep in the region the early effect region and the late effects region and again we found the MS

and tangos is the Tao Co AG repeaters and then they see team they're higher in

the early affected regions compared with the late region and then we are able to

replicate the data similarly you see here enhance the tangos and MS and also

the from protective x-ray in this dataset the games were lower in the early

affected regions now you when you look at the Tao you appreciate they have a opposite direction right so this is a

due to the region we compared and I mentioned before this early region is a

temporal court and the pre-ground and frontal cortex and the latest affect every area is a

primary visual cortex and if here early is a hippocampal region and that this

related relative later is a prefrontal cortex that we cannot get identical regions before comparison we have to do

this so that's why in general the frontal cortex might have higher levels

of tau compared with the list relatively later of action regions that's why cause the different different trend here so

this can contribute to the regional vulnerability so I further using the

single molecule fluorescence in situ hybridization I see this is the method

called iron scope divided by this sed company basically you humanize your

cells on section and then you hover died with their customer customer eyes

portable V probe and then through a series of amplification process and then

you are able to visualize their single messenger RNA in particular cell and

then you can use in the software image a to quantify them so let's first look at the early effects region II C and then I choose the four genes from an edited analysis the first one is done ma PT is the microtubule associated protein like encoding at our itself and then map k1 is a cow cobra Gators and then fkbp5 which belong to the gene data set of a cow aggregation promoter and then this is the e NC one long to the metastable sour protein gene we designed the probes and then to the fish se and then we we do that close staining of these through three probes at same time this is target probe from this 400 G and this is satvinder on Oh proof as LC 1787 it is a inhibitory neuron a marker probe cat one and then you will found in terms of tau level the have big difference but we will look at the end okay map p1 the level is siglemic hai in stature in euros compared with inhibiting neurons and the same as same for the fkbp5 and also en z1 you look at the quantitative data you can quantify how many single messenger a in the ecstatic neurons and hit two neurons we found that significant high level in the satuary neurons so we also look at the late effects region in human prefrontal cortex we using the same strategy and then using the same four probes and then look at the colonizers localization and the messenger is crashing in estatua individual neurons and then again the tower itself no big difference and then when you look at the end where p1 fkbp5 and the en c1 they're significantly higher in sight ruin yours although the level is relatively lower compared with the early stage so for the take-home message for this part of story is that it's a three neurons are more vulnerable more susceptible to this regulate protein homeostasis that affects the tau aggregation we call this the tau homeostasis and in the human brain the regions affected by top the early in the disease were more likely to be successful to dysregulated tau homeostasis in regions the impact will aid in the disease and that this

regulation of a specific branch of the human protein homeostasis may play important role in the initiation and the spreading of the Tau pathogenesis in AD and a related at table T so in the last few minutes I want to talk about my future plans so the first project is based on my founding on the group of a subtype of neurons they stress in the top left one jeans and then they are vulnerable to type pathology and this is the actor my dear world and then a people some brief background of tablets Ron Jean it's team encoding or transmembrane glycoprotein at the ER and then it's mutation and caused the diabetes optic atrophy newer generation and some psychiatric illness at the window there the protein misfolding and aggregation and the inner er will trigger the GI unfolded protein response mainly consists of a three branched it's a perk ie one alpha and HTF six cleavage pathway and then regulator downstream a PRG and then can miss and solve those

mystery protein misfolding or senators protein to produce important relation and then if you over activate this at yahoo gr and or chronic activation and then you call you can cause the neuro degeneration so my prolimatch huh sorry this is a previous study have suggests that the SS one interaction with this particular 280 have a sixth pathway to regulate the ER stress my study has found this tau particularly co-located with this SS wines pressing neurons at a very early stage this is the 14 month no neuronal loss at all at the very few granular houston yet and then they also

characterized with tablets one expressing neurons in the human tissue when you look at this the the number of the expression level of the first one between 14 months and study marks you can appreciate the almost done and then although they are not totally tied some of them if you look at the type II and then some other ties some are just the expression level significantly reduce and then same in the human brain tissue which I D so my first aim we are look at the interaction between the SS 1 and tau and also he are stress pathway and the second aim I try to over

his pressions to boost the level of wine to see whether they can inhibit the ad pathology and how about the cognitive

deficit and also you can do it deletion the tablet one and then to see whether

they can accelerate the ad pathology or cognitive depth is so I already have those mouths ready and also have some

virus ready for my study Tao though

those interest questioning I don't think that people are very clearly answer for

that yet but people to found how in the ER and also some in the ER and their

mitochondrial contact region so you mean

though the top protein I don't know he's actually but this is a majority the

start of person protein right and then I

don't know exactly the answer yet god I don't have data to show

sorry yeah yeah they are better chief

structure yeah

but do they have a kind of process like under some can you know optic those how

and then get transport to me into the vascular and then get in the yard for their group date

segregation possibly

because yeah have a function relates right so that's made one possibility but

I don't have data on for that yeah

yeah they also have similar function they related to focus on Ryan degradation they may be same

in a

process yeah so the second project is a more broadly

er stress and neuronal variability in the neurodegenerative disease I still focus on the autumn

adidas fur

at first and then but the same approach can apply to different neurodegenerative disease and then

after the project one I

should figure out which pathway actually in the neuronal vulnerability especially

for Tibet when expressing neurons and then we we can reduce manipulate the special pathway

and then in the

spectacled neurons and to see how they affect the tau participate and this is

the neuronal cell autonomous a difference in the Yaya Jia and make how they contribute to the neurodegenerative disease and also we I want to look at the clear yourself non autonomous GI you

Chiara whether the especially the mock especially the dispatch of the macro clear to cause the inflammation and then they they directed for the neuro degeneration all they caused the neuronal desperate and then lead to neuro degeneration so also the extra

side either yeah stress directly a cause to the neurodegeneration all they interact with the macro player and on neurons and then cause the neuro degeneration the third part is that

previous study have suggest that you be block the one branch of the ER stress pathway particular for perk pathway and then they found significant improvements in the can reduce the ad pathology and

enhanced memory depth improve the memory and then so I want to know what's the Magnum and underline the neuroprotection of this intervention and then can kiss now to what pathways can colonize with the neuron availability pathway and to see what pathway overlap each other and then I can particularly targeted those pathways and then - in the future -

translational study developer drug us for small molecules and and manipulate the pathway to see whether they have a neuro protective effect that can avoid those side effects if you block the purpose way it's a very important pathway for us if you plot it you have a some candidate drugs have shown the kidney a side effect so you cannot do this totally blockade you need to find a very very specific pathways especially a

cell type specific pathway to appear this disease so with that I would like to thank my mentor dr. turned out for her bridge support and to help me to be independent get my own k1 and also her lab members for technical support as well as dr. ahead as I&I and his postdoc asked to the in beautiful in vivo imaging work and also thank the brain Bank for providing the fringe easy for me and especially thanks dr. Kelly went to school at the University of Cambridge

they do the one for single iron six dataset analysis and of course I should thank these two groups they generously shared the data itself to everyone although I got a little bit early before everyone and also Peter Davies for providing to anybody the rest of for buying collaborators for I disco and for the new method is the physical image to Mike and other pepara members is a new technique are trying to optimize now and also I get the ER stress indicator lines from javi and then called the tablets one not harder and conditional carbs from dr. verrano and dr. Park this is my funny stuff thanks for attention I would like take questions [Applause]

yeah that's a good question we haven't crossed yet but because the human Tao the white I'm tall used you really take a long time to gather the phenotype so but ideally we should using that so that's our next step also we get a human tanaka mice from the Japanese group will do the crossing with using that it's more very logical condition yeah though those data said analysis is from very healthy donors they are around 15 yes age they are not having any cow or a better technology yet so it's a very early stage those gene signature we identified it's the intrinsic is that early so that's why we think that may contribute to the pathogenesis of AD or aging but not like an eddy mouse model we that is the relative of late stage yeah proteus Daisy's changed yeah you can the mouse model the this one we particularly Rockstar are focused on the towel but you can using a PP mouse model right this is another hypothesis for ad view it's a most people believe that is like at the early event but now more people think is not that maybe not the true true things because think about how many clinical trial failed now most of them targets that a better hypothesis but none of them succeed so that's why I

make people try to switch the towel field and also try to have it like you

may be generally regulator focus homeostasis that have been indicating very protective in aging
and in other

neurodegenerative is so that's why we want I want to try to combine both

yeah thank you yeah