New Cancer Center grand rounds and actually we have a really interesting thematic presentations today, which is two of our faculty who are focused on imaging technologies in a way that I think is going to provide important insights into. Not only neuroscience but most specifically in brain tumors, and obviously for a disease like that novel imaging studies, I think are critical for true human in vivo research.
Soum without further ado,

let me introduce our first speaker,

Doctor Jason Kai is an assistant professor of radiology and biomedical imaging.

Jason did his postdoctoral work at University of Pittsburgh and then ultimately recruited.

TL to be an assistant professor.

Jason received the bursts in Yellow award for his original work in nuclear medicine,
and also the Arch of Foundation Research Award, which advances his novel research in neuroscience and Jason welcome and. Looking forward to your hearing about your work in brain tumor imaging. Thank you, thank you. Action so I'm gonna share my screen. OK. Here we go. Alright, are you looking at the right screen? Yes. OK, great. I’m very excited to be here to talk about our research in
the context of cancer imaging.

So our life, you know, spend a lot of time working on neuroimaging and tensor imaging. So neurology is a virtually crosstalk between these two fields.

So I’ll introduce pet imaging very quickly. A little bit of a brain tumor. I believe Rene is going to talk about that like in more details in the next talk.

And next I will talk about some of the radio pharmaceuticals or pet users that are commonly used in clinical research or clinical management of brain tumors using pads.
00:02:34.410 --> 00:02:35.112 And lastly, talk about some of the new targets.

00:02:37.570 --> 00:02:39.720 For Brent tumor imaging,

00:02:39.720 --> 00:02:41.748 which are not specifically interested in us for us,

00:02:41.748 --> 00:02:44.283 you know as research lab.

00:02:44.290 --> 00:02:46.530 So first blue bus stoma is fatal disease with less than 10% of patients surviving five years after initial diagnosis and treatment,

00:02:48.546 --> 00:02:50.424 and 15% of all parental merge and half of the uglyomas is glioblastoma,

00:02:50.424 --> 00:02:52.894 there’s still no early detection method available, so.

00:02:52.894 --> 00:02:54.870 No people in this world you are
calling for new and better imaging

So pat imaging. In a shell composed of 4 components.

So first we need to have a PET scanner to detect all the packs.

We call it patch razor because we read missed the turn of very small amount of radiopharmaceuticals.

The trace amounts and also because those molecules tend to be tracing the biological process or receptor protein and then.

So it’s patches are for for each.
And next we need to have a quantification managers mathematical models to generate physiological parameters on this path. Imaging studies and the last and most important component is in clinical impact. So this is up to nuclear physicians to how to use these tools. The combination of the scanner, patch tracer and quantification measures to make an impact in patient and disease management. So we just published a mini review on the current video pharmaceuticals or patterns in brain tumor. This year, so this talk is mainly around this.
Same from this review.

So first the most classic patches are used for brain.

Tumor is obviously a glucose and called effed floral deoxy

That’s back in 1982.

Parties several case reports actually.

As you can see from the image here,

the 1st and 2nd are contrasting Hung City images and you can

see the the brain tumor mass.

Indicated by enhanced mass.

By this contrast city.

And also from the patch
00:05:25.060 --> 00:05:26.740 you actually see a hypo.

00:05:30.300 --> 00:05:33.030 Because this happened to be a low grade brain tumors and later after

00:05:36.078 --> 00:05:38.890 after approved in 1997 and as

00:05:41.060 --> 00:05:42.735 the pass scanner has very low spatial resolution,

00:05:43.740 --> 00:05:46.820 is about 1.7 centimeter resolution

00:05:49.016 --> 00:05:53.927 two millimeters spatial resolution.

00:05:58.688 So after G as you see,

00:06:02.098 it has a high background in the brain

00:06:05.337 because the brain uses sugar as it’s

00:06:08.340 a major metabolism or energy source.
You can see from the green matter higher uptake.

Well I lower, but after you still useful for grading gliomas because for low grade or benign gliomas usea hypometabolism you have lower uptake in the brain region in the brain tumor region relative to the Gray matter, while at higher grade gliomas you have a higher optic for which is higher than Gray matter and white matter. With a global stoma, you can have even higher and also you can.

You can see there’s microsys car in the center of the tumor. So based on paper published in 1995,
there's a cut off level for differentiating low grade from high grade glioma which is 1.5 for tumor to white matter and one zero point 6 for tumor to cortex ratio. Nowadays, because of the fusion of PET with anatomical radiological imaging methods such as the city and actually you can use a contrast enhance and topical modalities to define the region of interest for the tumor to better quantify the FDG uptake. So because of the high background of sugar analogs, so people in this
field have been calling for a pet imaging agents with lower burn uptake.
So that turned out to be amino acids, so amino acid analogues tend to have lower uptick in healthy brain tissues, while higher uptake in tumors because tumor cells overexpress.
I mean, I'll type amino acid transporters. So the most advanced of C arguably is a missile in its carbon 11, labeled my selling, so this is essential amino acids that are taken by tumor cells while its uptake in healthy tissues or cells are limited. So it's useful in the clinic clinic to distinguish a tumor.
progression from radio necrosis. For example, in this case, from the anatomical images, it's pretty hard to distinguish these two cases, but from my selling is also called Matt from Matt Pat. You can easily tell the top cases a tumor progression while the bottom case is actually a radio. This. So besides, I mean the acid pat. There's also imaging agents derived from nuclear sites because nucleotides are used for DNA synthesis.
And it's up taken into the tumor and it's up taken into the tumor through, for example, this is a floral submitting I freaking labeled for submitting is a nuclear size up taken into cells by submitting kindness 1 and submitting kindness. One is over twice during the in the tumor because some of the DNA synthesis. Sides are involved in general in cellular proliferation, and they can correlate. Histological grade of brain tumors and its accumulation also correlates with the activity of summoning Chinese one. And it's a ideal tracer for imaging tumor proliferation.
But also, but also because I felt is not actually it’s not brain penetrant. It doesn’t cross blood brain barrier. So in order to have any signal up take the tumors, BBB needs to be compromised. So it’s not suitable for our lower create imaging. But nevertheless, it’s it’s. It’s has its role in the tumor imaging pad. It’s has its role in the tumor imaging pad. So from this case you can see the contrast getting contrast enhanced MRI images, which can clearly delineate the tumor regions, and you can see the hypermetabolism sugar metabolism in the center.
00:10:40.370 --> 00:10:44.036 of the tumor and also my selling
NOTE Confidence: 0.716899157142857
00:10:44.036 --> 00:10:47.457 uptake in a larger area while found
NOTE Confidence: 0.716899157142857
00:10:47.457 --> 00:10:50.007 felt pad you can actually.
NOTE Confidence: 0.716899157142857
00:10:50.010 --> 00:10:52.030 See not only the tumor,
NOTE Confidence: 0.716899157142857
00:10:52.030 --> 00:10:53.495 but also the infiltration of
NOTE Confidence: 0.716899157142857
00:10:53.495 --> 00:10:55.420 the tumor to the brain region.
NOTE Confidence: 0.568739178
00:10:59.100 --> 00:11:01.980 So besides my sounding match,
NOTE Confidence: 0.568739178
00:11:01.980 --> 00:11:04.980 there are other amino acid analogs
NOTE Confidence: 0.568739178
00:11:04.980 --> 00:11:08.406 being used in brain tumor pet.
NOTE Confidence: 0.568739178
00:11:08.410 --> 00:11:13.868 For example, tossing and floral floral
NOTE Confidence: 0.568739178
00:11:13.868 --> 00:11:17.940 dopa F dopa F dopa is actually approved
NOTE Confidence: 0.568739178
00:11:18.043 --> 00:11:21.283 by FDA to image Parkinsonian syndrome
NOTE Confidence: 0.568739178
00:11:21.283 --> 00:11:26.880 back in 2019 because after reflects its
NOTE Confidence: 0.568739178
00:11:26.880 --> 00:11:30.488 accumulated in dopaminergic neurons.
NOTE Confidence: 0.568739178
00:11:30.490 --> 00:11:34.246 Neurons are damaged in Parkinson’s disease,
NOTE Confidence: 0.568739178
00:11:34.250 --> 00:11:36.890 but but there are also a lot of
efforts in applying F DOP A in brain tumor imaging because F DOP A is also transported into brain tumor cells through all type of transporters and once it’s inside the cells, it’s metabolize into DOP A and it’s trapped in the cell. A recent relative recent Patricia for amino acids imaging is a floozy chlorine. This is this treasure is approved by FDA in 2016 for imaging recurrent prostate cancer, but they’re still great effort in applying this treasure in global imaging. And actually the tumor uptake of F18. In quality well with.
Bring to my images through night myself.

And it’s actually useful when the MRI contrast enhanced MRI is non diagnostic. But still, based on the preliminary data we have in the following clinical studies, we can’t tell whether the uptake of flu cycle is solely due to the recurrent tumor or perhaps some of the signals contributed from inflammation and other processes. So further studies is needed to establish the role of this treasure in the management of brain tumor in the clinic. So with that, I’d like to introduce some of the...
the emerging imaging targets for brain tumor.

So my interest in bringing my image and actually is originated from this part X Sigma 1 receptor imaging.

So we were initially interested in using Sigma 1 receptor PET to study in your degenerative disorders and in one summer there was a visiting student from Germany and he brought in a product to use Sigma 1 receptor developed in their lab to image burn tumor.

So to evaluate their imaging probe so we collaborate with John being slab. This is gone down from his lab, generated you 87 look,
which is a blue blastoma tumor

So we use valid methods to monitor the tumor growth over three weeks.

After the tumor reaches a certain size, we scan them by using PET small animal PET.

From the PET images, we can tell that tumor uptake is significantly higher than the rest of the brain, while the two updates decrease overtime, eventually getting lower than the healthy brain tissue. For each.

We can clearly visualize the tumor.
so we can analyze the region of interest for the tumor uptake.

So this tells us the Sigma 1 receptor expression in healthy brain is also significant, which may similarly to FG pad, complicates the PATH imaging data analysis. So this is also confirmed by doing nonhuman primate patting imaging.

So Sigma 1 receptor uptake in healthy brain regions significantly overtime. So the question now is to identify by marker for global stoma with low expression in healthy brain tissues. So that turned out to Park Park is

NOTE Confidence: 0.64455577

NOTE Confidence: 0.651361646266667

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NOTE Confidence: 0.651361646266667
the Poly ADP Ribosyl polymerase pop.

One is the DNA repair enzyme.

It’s always provides in blastoma

with overall lower expression

in healthy brain tissue.

So in that sense,

it might be an ideal image

engines for globalist tumor,

imaging and parks functions to

recognize DNA damage and recruit

proteins to repair single strand or

even double strength daily damage.

There are multiple active clinical trials

going on actually targeting part as a

therapeutic target in global storm,

so up at imaging agent targeting
Park could be also helpful in facilitating the drug development or stratify patients for park targeted images therapeutics. To evaluate any imaging agents before we do clinical imaging study, we need to evaluate those imaging probes using animal models. So this is work done by Carney and colleagues published in 2018. They actually surveyed part one expression over a panel of human PDX small cell lung cancer PDX, and together with healthy tissues, found rodents.
As you can see, the park is generally positive and highly expressed in these PDX tissues as well as in spleen of the animal, while its expression in brain tissue is relatively low.

So further, they injected a like rip derived TARP imaging pad agents into this PDX models. They were able to identify the tumor uptake overtime and compare it with the muscle as a reference region. Normally muscle has very low uptake of the tracer, indicating slow part expression in muscle.
And the park image agents showed quick uptake into the tumor, which is slowly decrease overtime. 

So by using pad imaging they were able to study. They found kinetics of the library derivatives. I did about the same time back in 2018. Another group at Upenn and Studies another park, Paddington agents, which is derived.
From a different scaffold, they name it F18 FT. So they did first in human study in.
They recruited 20 patients. And scan them at baseline and the patients underwent surgery so they were able to collect the tissues to correlate the packaging results with the immuno histo fluorescence results as well as autoradiography study. So in this study they actually showed. A panel of parks specific uptick in the tumor by PAT as well as a immunofluorescence. And there’s strong correlation between values and the fluorescence results, as well as between out radiography.
signal and fluorescence signal, but the part? Expression level doesn’t correlate with PAT, so FG cannot be used in place of park imaging. So about earlier this year, there’s they expanded their clinical trials of power pat into a breast cancer patients. However, all of the park imaging agents. We have currently do not penetrate intact blood brain barrier so that limits its application in brain tumor. And this is confirmed by their nonhuman primate, pet brain imaging study.
So we took a look at the pharmacokinetic information of the current park inhibitors and. Decided to pursue base scaffold for Patty medium, hopefully to identify a brain penetrant. Potting medium agents for park. So in that direction, so we have. I don’t know if I’d and synthesized lead park imaging agents derived from. And did a pilot study in collaboration with Hank for memory. Using their RG2 rank mode burn to more model, we were able to. Image CRD 2 tumor here the baseline scans using the power pad imaging.
agents and for this one we pre injected the animal with a code.

Well, if a rate which is also part specific molecule that can compete with Patrick to displace a tutor uptick in the tumor.

So after semiquantitative analysis.

We can tell from the average values from 30 to 60 minutes post tracer administration.

The tumor optic is about one after the blocking drug update.

was decreased to about 0.5, indicating the new park padding.

medium tracer actually really target Park in vivo as they ban to
the same target as a Liberator,
NOTE Confidence: 0.631713194315789
blocking drug at the same time we
NOTE Confidence: 0.631713194315789
look at the control later role,
NOTE Confidence: 0.631713194315789
which is presumably to be
NOTE Confidence: 0.631713194315789
the healthy brain tissue.
NOTE Confidence: 0.631713194315789
And it showed relatively lower uptake.
NOTE Confidence: 0.631713194315789
Send a tumor and the blocking doesn’t
NOTE Confidence: 0.631713194315789
have significant effect over there.
NOTE Confidence: 0.631713194315789
So here’s the tumor to contralateral
NOTE Confidence: 0.631713194315789
ratio and at baseline it’s about 2.5
NOTE Confidence: 0.631713194315789
after blocking drops to about 1.5,
NOTE Confidence: 0.631713194315789
indicating about 46% blockade from the.
NOTE Confidence: 0.522463101666667
To validate the path image data,
NOTE Confidence: 0.522463101666667
we perform pilot biodistribution study.
NOTE Confidence: 0.522463101666667
We look at the tracer distribution among
NOTE Confidence: 0.522463101666667
the different different tissues of animal.
Not surprising me that Rooster has high spleen uptake because spleen is another large organ and that’s positive. Also, it’s a blocked by the.

And consistent with the pattern medium data, we see high uptick in the tumor, and it’s blocked by the brick as well. Further analysis of this pilot data indicates very high spleen to blood ratio and also very high tumor to blood ratio. For the power quality of regions and it also shows some extent of the brain uptake, which is seem to be blocked by the cold drug. So further study confirmative study needs to be done to see if this traitor
00:23:29.572 --> 00:23:32.210 actually goes into the intact brain or not.
NOTE Confidence: 0.449307408
00:23:35.390 --> 00:23:36.526 OK, the next part,
NOTE Confidence: 0.449307408
00:23:36.526 --> 00:23:38.230 like the next image in target,
NOTE Confidence: 0.449307408
00:23:38.230 --> 00:23:40.288 I'd like to introduce is PDL one.
NOTE Confidence: 0.449307408
00:23:40.290 --> 00:23:42.495 I think for this target this is
NOTE Confidence: 0.449307408
00:23:42.495 --> 00:23:44.354 probably the targets that doesn’t
NOTE Confidence: 0.449307408
00:23:44.354 --> 00:23:46.896 need much introduction PDL 1 so
NOTE Confidence: 0.449307408
00:23:46.896 --> 00:23:49.850 we do have PDL 1 targeted PET
NOTE Confidence: 0.449307408
00:23:49.965 --> 00:23:53.300 imaging tracers in this field.
NOTE Confidence: 0.449307408
00:23:53.300 --> 00:23:56.441 Dave Donnelly published paper in 2017
NOTE Confidence: 0.449307408
00:23:56.441 --> 00:24:00.858 about their protein based PDL 1 Patricia.
NOTE Confidence: 0.53119207073
00:24:04.720 --> 00:24:09.940 Nine, six, 182 so the use a simple xenograft
NOTE Confidence: 0.53119207073
00:24:09.940 --> 00:24:13.184 with PD L1 positive tumor on one side and
NOTE Confidence: 0.53119207073
00:24:13.184 --> 00:24:16.426 PDL one negative tumor on the other side.
NOTE Confidence: 0.53119207073
00:24:16.430 --> 00:24:18.859 So they did the baseline scan without
NOTE Confidence: 0.53119207073
00:24:18.859 --> 00:24:21.392 blocking agents and they did a blocking scan

32
that you can see after blocking agents. The Twitter uptake was diminished to the same level of the unspecific. One negative tumor uptake. Well, the baseline scan showed higher uptake, so they also did autoradiography. This is in virtual autoradiography study. Not only look at this too, they don’t draft silence. They also look at some human tissues and they sell like higher PDL. One expression in those human tumor tissues. So with that data they translated their imaging probes to 1st in
human study they they chose non small cell lung cancer as there. Patient population in that study, published in 2018. They actually compared with PDL one pad and another at the only making nine labeled. If I look at the PD one pad so those three imaging modalities can all detect. Non small cell lung cancer, not you, but with the heterogeneous imaging patterns indicating those three modalities are actually complementary to each other. They provide different information on the tumor metabolism and PDL. One expression as well as PDL.
One expression.

Also they showed one case where there's a tumor metastasis, because the tumor metastasis, so it could be the low PDL expression or it could be the more intact blood brain barrier. So in order to apply PDL 1 packaging we initiated a project to develop brain punishment. PDL 1 patching million agents based on small molecules. So this project at early stage I don’t have animal data to share with you.
so do not just say very briefly the process for discovery and development of radiopharmaceuticals or patch research. So if you look at this project it's actually very similar to the R&D process of a therapeutic drug. You need to identify a target or clinically relevant biomarkers and you need to do met Cam to develop small molecules or. Micro molecules specific binding to the target after initial essay and in vivo essays using patent distribution. You can move on to the toxicity and dosimetry study and file and application after doing clinical trial,
NOTE Confidence: 0.673238764444444
00:27:10.140 --> 00:27:12.700 initial validations and clinical
NOTE Confidence: 0.673238764444444
00:27:12.700 --> 00:27:16.540 trials finally reached to FDA approval.
NOTE Confidence: 0.673238764444444
00:27:16.540 --> 00:27:19.268 So I’d like to use the last few
NOTE Confidence: 0.673238764444444
00:27:19.268 --> 00:27:21.981 minutes to update you the latest
NOTE Confidence: 0.673238764444444
00:27:21.981 --> 00:27:24.416 advancement in the past scanner,
NOTE Confidence: 0.673238764444444
00:27:24.420 --> 00:27:26.592 because pass scanner is a critical
NOTE Confidence: 0.673238764444444
00:27:26.592 --> 00:27:30.660 component in the pet imaging research.
NOTE Confidence: 0.673238764444444
00:27:30.660 --> 00:27:32.838 So very excitingly recently we saw
NOTE Confidence: 0.673238764444444
00:27:32.838 --> 00:27:34.940 a prototype for total body pad,
NOTE Confidence: 0.673238764444444
00:27:34.940 --> 00:27:37.830 so traditionally the path scanner needs
NOTE Confidence: 0.673238764444444
00:27:37.830 --> 00:27:40.620 to move the bed to get the whole body.
NOTE Confidence: 0.673238764444444
00:27:40.620 --> 00:27:42.212 PET imaging study done,
NOTE Confidence: 0.673238764444444
00:27:42.212 --> 00:27:44.600 but with a total body PAT
NOTE Confidence: 0.673238764444444
00:27:44.600 --> 00:27:46.290 we can collect all the.
NOTE Confidence: 0.673238764444444
00:27:46.290 --> 00:27:49.350 Emission signals from the patients,
so that means significantly. Increase some detection sensitivity and we which allows much lower dose for the patient. So supposedly we can reduce the dose by 40 fold. This means the whole body PET scan will cause 0.15 million safe dosimetry. Every year, 2.4 million safe and long Trip international round trip is about 1.1 million save this means the whole body PET can reduce the dosimetry to almost equivalent to a round trip international flight.
And also with the whole body pet scanner system, we can study the diseases at the systemic level. So looking at the cancer throughout the body.

So in summary. Pat’s imaging and potentially application in glioblastoma is to demonstrate the final type and disease severity correlations and hopefully you will be able to discover new therapeutic targets based on morgue imaging, clinical imaging studies and it’s also very helpful in the drug development process in demonstrating the
penetration and pharmacokinetics of the experimental drug in effect compartment.

It can be used to quantify commutate from Cortana, mix by doing receptor occupancy study to maximize the dose range to be used in efficacy clinical trials. And also how could be useful for patients stratification and to evaluate therapeutic effects? And in the clinic pet can be used for diagnosis or prognosis as well as tracking disease progression. I finally achieve precision medicine, so at last I’d like to acknowledge my group and staff.
NOTE Confidence: 0.85089961
00:30:03.076 --> 00:30:06.454 faculty and students at your pet
NOTE Confidence: 0.85089961
00:30:06.454 --> 00:30:09.000 center or internal and external
NOTE Confidence: 0.85089961
00:30:09.000 --> 00:30:10.980 collaborators and or finding
NOTE Confidence: 0.85089961
00:30:10.980 --> 00:30:13.584 agents for supporting our research,
NOTE Confidence: 0.85089961
00:30:13.584 --> 00:30:17.216 and this is picture we took last year
NOTE Confidence: 0.85089961
00:30:17.220 --> 00:30:19.506 and this is what we look at this year.
NOTE Confidence: 0.7139220458
00:30:22.390 --> 00:30:24.222 Well, Jason, thank you.
NOTE Confidence: 0.7139220458
00:30:24.222 --> 00:30:27.281 It was a really terrific review of,
NOTE Confidence: 0.7139220458
00:30:27.281 --> 00:30:29.147 you know, novel approaches to imaging
NOTE Confidence: 0.7139220458
00:30:29.147 --> 00:30:31.090 both for clinical care and research.
NOTE Confidence: 0.7139220458
00:30:31.090 --> 00:30:33.526 And yeah, thank you for changing
NOTE Confidence: 0.7139220458
00:30:33.526 --> 00:30:36.329 the context of your research group
NOTE Confidence: 0.7139220458
00:30:36.330 --> 00:30:39.389 photo in terms of the current world.
NOTE Confidence: 0.7139220458
00:30:39.390 --> 00:30:42.160 You know, Jason, we're at, why don't we?
NOTE Confidence: 0.7139220458
00:30:42.160 --> 00:30:43.900 Why don't I suggest that for
NOTE Confidence: 0.7139220458
fidos who have questions for you to direct them to you offline? Just 'cause we're at the we're a little late in the time and I want to make sure there's time for. For Zach but Jason thank you for us. Superb presentation again. I invite people to submit send questions to Jason to his email, but let me now turn to our second speaker. Did Doctor Zachary Corbin, as many of you know as an assistant professor of neurology, he. Received his medical degree at Yale and thereafter did his residency.
training at the University of California at San Francisco, ultimately being recruited back here to join the faculty in neurology and neurology. Zacks interest beyond CNS malignancies has been in research, most notably in understanding the biology of brain tumors through novel approaches to imaging, particularly the metabolic changes that occur in these tumors. So is Zach thank you for agreeing to present and really interested. Really excited to hear about
your work and Jason if you could

stop sharing your screen.

Perfect thank you very much. Let me start.

Sharing my screen.

OK. Doctor Fuchs thank you

so much for the introduction.

Can everyone hear me and see my screen?

Yes and thank you very much,

Jason and thank you for the introduction

or thank you for the invitation.

So I’m one of the neuro oncologist at Smilow

and it’s my privilege today to talk about.

In vivo metabolic imaging of primary

brain tumors and what a great

segue or transition to move on.

I’m going to start really by giving.
Some background clinical background on glioma, clinical treatments and limitations of glioma, and specifically glioblastoma as was introduced. I’m going to talk a little bit more specifically about pseudo progression. Which is something that Jason mentioned and also has been discussed in this venue by Doctor Chang with metastatic disease in the brain. I’m gonna talk about metabolism and cancer and the Warburg effect in particular as a prominent metabolic
change that we could potentially image.

The transition to methods results.

And our current investigations things

we can show you now and things we’re

very excited about showing you soon.

In particular,

I’m going to talk to you about something

that we call the Warburg index,

which we created here at Yale.

And then future directions and things.

We’re looking forward to sharing

with everyone in the future.

So to move forward and talk about

some background. I think that.

Glioma has a profound impact.

It’s a relatively rare disease.
But the public burden is substantial, right?

I like to think about important.

Public events that have happened recently,

So this is.

Ted Kennedy, President Kennedy’s brother.

Who died of glioblastoma as

Senator of Massachusetts in 2009?

And this is Beau Biden.

Vice President Joe Biden son.

So he was.

Previously, Attorney General Delaware, but.

He did die of what is known as an

aggressive primary brain tumor,
00:34:34.372 --> 00:34:35.758 of our country.
NOTE Confidence: 0.8933656
00:34:35.760 --> 00:34:37.780 And this is John McCain.
NOTE Confidence: 0.8933656
00:34:37.780 --> 00:34:41.585 Who died of glioblastoma as senator from Arizona?
NOTE Confidence: 0.8933656
00:34:41.585 --> 00:34:43.868 And so you know.
NOTE Confidence: 0.8933656
00:34:43.870 --> 00:34:45.818 That was a good introduction to what is a disease that has an annual incidence in the US of 20,000.
NOTE Confidence: 0.8933656
00:34:48.849 --> 00:35:00.576 Is glioma in general and glioblastoma in particular has an annual incidence of 11,000.
NOTE Confidence: 0.8933656
00:35:00.576 --> 00:35:04.310 Actually almost 12,000 / 11,000.
NOTE Confidence: 0.8933656
00:35:04.310 --> 00:35:06.495 It’s the most common primary malignant brain tumor.
NOTE Confidence: 0.8933656
00:35:06.495 --> 00:35:10.530 As Doctor Kai already mentioned, and its five year relative survival, it has increased recently.
I’m an optimist, so this is an improvement at 6.8% in five years. Only a few years ago we were discussing numbers in 5% and so. We’re moving forward, but we have a lot of movement to do. Glioblastoma is a profound disease, frequently at presentation. This is a case. That I cared for when I was a fellow at Stanford. This is a relatively common scan we see here you have. MRI, gadolinium enhanced T1 sequence.
where you can see boundaries of blood brain barrier,
breakdown of the primary tumor.
This is flare processed T2 sequence.
Axial projection of the MRI.
We can see some changes surrounding the tumor.
This is a substantial tumor with lots of Mass Effect.
You can see shifting of the normal brain.
This patient had relatively mild symptoms.
If I recall he had visual field changes and he had a neglect syndrome,
but actually really presented mostly because his.
Family brought him in and that is true.
This is a sudden and dramatic disease, but can actually be relatively subtle as well to some patients, which is remarkable.

And I like to show this slide for three reasons really. So despite what is really as it’s a privilege to talk here.

Research and clinical endeavor to improve care for this category of diseases. We still have a standard of care in glioblastoma from 2005. This is the Stroop paper, also called the Spook Protocol from 2005.
and it demonstrated that patients with glioblastoma have improved outcomes when they are treated with radiotherapy. It’s really chemo radiation radiotherapy plus temodar at the same time, followed by temozolomide after radiation. And they have improved outcomes compared to radiation alone. But as I said, I like to show a few things here. So we have a great deal of patients who have died and very quickly and this is relatively noisy out here, but we still have a number of patients to measure the effect so you can see that there’s a lot
00:37:35.982 --> 00:37:37.550 of room to grow as I mentioned.

But in addition,

00:37:37.550 --> 00:37:38.300 you can see something else that’s interesting, which is that.

There are a number of patients that survive and a long time years.

And it’s very difficult to predict as doctor time mentioned at the start.

Who is going to come from here and still live?

We don’t have prognostic or diagnostic ways of determining this.

So in order to discuss another related fact of care for.

Brain tumors currently is the delayed
results of other clinical trials in patients who have tumors that are less aggressive than glioblastoma. So these are the results of the RTOG 9402 Clinical trial. That really targeted a moderate severity brain tumor, and anaplastic oligodendroglioma OMA and oligoastrocytoma although oligo. Astrocytoma is a relatively antiquated term. Protocol enrolled patients, and similarly to the Stu Protocol patients received either chemotherapy, this time with PCV, chemotherapy with radiation,
00:38:47.590 --> 00:38:50.348 or radiation alone. And you can see.
00:38:50.350 --> 00:38:52.750 Approximately 10 years in 2006,
00:38:52.750 --> 00:38:54.190 approximately 10 years after
00:38:54.190 --> 00:38:55.630 the study was started,
00:38:55.630 --> 00:38:57.835 there was no indication as
00:38:57.835 --> 00:39:00.752 10 years later,
00:39:00.752 --> 00:39:03.440 almost 20 years after the study began,
00:39:03.440 --> 00:39:04.718 and by this analysis it demonstrated
00:39:04.720 --> 00:39:07.168 that patients do better with PCV
00:39:07.168 --> 00:39:09.666 to radiotherapy alone.
00:39:09.666 --> 00:39:11.258 So we have.
00:39:11.258 --> 00:39:13.830 Two processes going on where you
00:39:13.830 --> 00:39:15.558
have a substantial burden of a very aggressive disease and difficult to predict long term survivors in that disease. And then less aggressive tumors we have. Prolonged 20 years, potentially wait between when we institute a standard of care or when we are trying to define the same care when we have results that help us with that standard of care. So this is really good fodder for exactly what the context today is for other ways. Biomarkers of measuring this disease. So I want to switch gears for a second and also discuss pseudo progression.
00:39:51.350 --> 00:39:51.681 Specifically, this is another case that was brought up to me when I was a fellow at Stanford. This patient had a glioblastoma. He underwent treatment and then this is very similar pictures as I’ve shown you before, so gadolinium enhanced MRI and flare T2 MRI and you can see tumor here. So the patient actually had growth of the lesion. And it was raised whether this lesion wasn’t true tumor progression, or whether it was pseudo progression. Pseudo progression, largely in necrosis.
but really a response, probably by the tumor and also the brain to treatment that we give the patient. And so standard of care studies include FDG PET, which we’ve heard a lot about in this study, and you can see the background, as was mentioned, is quite bright. This is all normal brain. But in the area of this tumor, you can see that there is uptake, and so this is hypermetabolic. It was felt that favored tumor, and so this patient went to surgery. Unfortunately, surgery showed that this patient had
in crisis with his pseudo progression. So it’s very challenging to deal with pseudo progression in primary brain tumors, especially in the setting of the need to have a large surgery to confirm. One of the potential areas to expand our knowledge is imaging and really imaging has moved forward with the overall understanding of cancer, which has been maybe 100 years ago in anatomical disease, tumors, balls that are growing to physiologic disease, tumors that acquire blood vessels and other changes as they grow and.
become more aggressive to really, what is a metabolic disease where they are fundamental, likely metabolic? Changes that might be the night is of cancer and certainly are associated with aggressive disease. Imaging is really move forward with our understanding. Anatomical and 1st we were able to, just as we showed here. See the tumor ball. Then we learn much more about the tumor by things like perfusion imaging, which can tell us a great deal about the heterogeneity,
especially of aggressive primary brain tumors. And metabolic imaging now has become at the forefront where we might be able to do many things. Potentially, I'll show you. Do some prognosis and diagnosis, but in addition, potentially treatment effect measurements. So to understand a little bit more about how we could use metabolism in this way, I want to talk a little bit about the Warburg effect. In particular, this is probably the most famous
metabolic change that is known to occur in cancer and in primary brain tumors in particular.

So to take everyone back to biochemistry, here is a cell, and this is the cell membrane, and so there's glucose outside the cell, and as glucose comes into the cell, one of the large junctures is pyruvate, and pyruvate can get processed basically into oxidative phosphorylation.

And in that direction, is mediated largely through the mitochondria. You have evolution of CO2 in the aqueous cytosol.
It really transfers back and forth to bicarbonate. However, glycolysis is also a potential route for processing pyruvate, and the end result is lactate in glycolysis. And so the Warburg effect is in the absence of any other stressors, including normal blood flow, tumors are known to favor glycolysis. They shift to lactate, they produce more lactate, and they undergo less oxidative phosphorylation.
And in this diagram, as you move further to the right, you have more Warburg effect. This preference for glycolysis seems unusual initially, however, there’s really a lot of reasons why tumors may benefit hydrocarbon backbones and also redox species may be usable in biosynthesis, especially through the pentose phosphate pathway, to produce more tumor. In addition, energy production and also really more simpler apparatus is less vulnerable to
the oxidative damage that occurs in tumors and in normal tissue. The resulting acidic environment is important for many physiologic changes related to tumor, including tumor invasion. Excuse me and also immunosuppression so immune cells less able to attack the tumor in the acidic environment and also normal tissue that’s able to survive. It’s been linked to tumor aggressiveness already. And so really is a great target to image.
we have as well as current investigations.

00:44:30.030 --> 00:44:32.559 So first I'd like to talk about the deuterium metabolic imaging and then the Warburg index.

00:44:32.559 --> 00:44:34.686 Really the credit goes to my colleagues at Yale.

00:44:34.690 --> 00:44:36.058 So deuterium metabolic imaging.

00:44:36.058 --> 00:44:37.768 Dr Defeater, Hank debater as well as Doctor Robin de Graff who have really done an amazing job in developing this tool.

00:44:37.768 --> 00:44:39.250 We are able to give patients due rated glucose,

00:44:39.250 --> 00:44:42.197 an amazing job in developing this tool.

00:44:42.197 --> 00:44:45.282 Doctor Robin de Graff who have really done an amazing job in developing this tool.

00:44:45.282 --> 00:44:47.650 We are able to give patients due rated glucose,

00:44:47.650 --> 00:44:49.750 so this is heavy water or sorry, Basically protons with a neutron attached.

00:44:49.750 --> 00:44:51.150 Patients can drink them and it actually goes into their cells
over the course of about an hour. And we can see due to rated lactates evolving in tumor and we can see the evolution through oxidative phosphorylation of glutamate and technically it includes glutamate and glutamine signal. And as you can see, the shifting more towards glycolysis. You can actually image a really direct bound worker of the Warburg effect. So once again, so you have due to rated lactate over glutamate, really glutamate glutamine is related to glycolysis over oxidative phosphorylation, which is the Warburg effect.
So we were able to start with multiple different types of brain tumors, and I'm going to show you a few today to discuss the tumor I mentioned before. That medium grade tumor and anaplastic oligodendroglia. Here you have a patient. This is flare. This is post contrast. You can see residual chamber. The patient has two voxels that are shown here in the Mr spectroscopic spectrum, and so you can see the glucose is measurable in both Spectra, and you can see in the map that you can see lots of glutamate and glutamine evolving in the normal brain,
so this is really wonderful this tumor.

So the black, tumor is producing glutamate and glutamine through oxidative phosphorylation, similar to perhaps normal brain and really.

Lactate measurement would be out here.

We don’t see the lactate in either side.

One of the reasons why this tumor may actually have a more favorable character is the idea expectation, which is famous all over the world.

Many different cancers, including glioma, and we have one of the world experts.
and IDH mutant glioma at Yale.
NOTE Confidence: 0.905427083333333

which who is one of my mentors.
NOTE Confidence: 0.905427083333333

Dr Bendure Ranjit bindra.
NOTE Confidence: 0.905427083333333

Has really been able to help me understand this better isocitrate and ideates wild type pathology or sorry Physiology produces alphabetically rate and with the IDH mutation that occurs in tumors, there’s a hetero diamond and a heterodimer produces 2 hydroxy butyrate. This has been called a onco metabolite, which is a metabolite that may actually be involved in the production or the continuation of tumorigenesis.
00:47:23.390 --> 00:47:24.962 Downstream to two hydroxy glutarate in IDH mutant,
00:47:26.540 --> 00:47:28.988 pathophysiology is methylation changes.
00:47:28.988 --> 00:47:31.436 DNA hypermethylation in particularly MGMT methylation in gliomas,
00:47:31.436 --> 00:47:36.598 but also histone methylation.
00:47:39.072 --> 00:47:41.271 for what is a relatively rare patient
00:47:41.271 --> 00:47:43.577 who is an IDH mutant glioblastoma and we were able to actually image the recurrent tumor.
00:47:43.577 --> 00:47:46.196 we were able to actually image the tumor with deuterium metabolic imaging.
00:47:50.280 --> 00:47:53.276 so this is really a perfect case
00:47:55.120 --> 00:47:56.798 here is the recurrent tumor.
This is once again an idea, glioblastoma. You can see that post gadolinium scan is showing you tumor there. This is evidence of bleeding, which is common. And this is evidence of diffusion weighted changes, which is also common. I wanna call your attention to voxels one and three here, which are up here. These are within the tumor. And you can see the maps that are generated by deterring metabolic imaging are really marvelous. They show that glucose is going everywhere in the brain.
They show that glutamate and glutamine is being produced by oxidative phosphorylation, as is expected in the normal brain. And it's really a totally different picture over the brain tumor. Glutamine is a very large peak over the tumor and here you have the lactate visible on these spectrum and you can see. That there is a glutamate glutamine peak. It's a little easier to see with voxel one, so I'm going to call your attention in particular to voxel one,
and I’m going to show you an IDH wild type of much more common glioblastoma that we were able to image. Call your attention to two voxels in the spectroscopy so you can see there is 2 which is within the tumor and there’s one which is within normal brain. No lack tating the normal brain, lots of glutamate and glutamine in the normal brain, but lactate and glutamate, glutamine really within the tumor. Very little within the tumor, almost noise. But a very large Warburg effect. This is really an N of 1 experiment but it is very intriguing to see.
that there is more lactate and almost no glutamate and glutamine in the IDH wildtype yield estimate compared to much more even.

Presentation and ideates mutant. We have Western ma. So we’ve developed a theory that the Warburg effect may be blunted or muted in an IDH mutant pathophysiology such that it displays metabolism more like normal brain.

Where oxidative phosphorylation occurs. To a greater extent than in a idea 12 type tumor.
So you’ve heard a lot about today, FDG pets, just to go briefly, the way that we would use this to help us with a clinical tool that might show the Warburg effect right now. Really, the deuterium about imaging is wonderful, but really its preclinical technology. For my purposes, it kind of represents glucose demand.
the call of all energy into the tumor.

We are combining that it’s a multi-modality test so the patient also will receive magnetic resonance spectroscopy, this time without a stable isotope. We’ll be able to measure lactate which we can measure in the clinic.

Actually in brain tumors, in the research context, we can also measure 2-hydroxybutyrate, which will be very interesting in this study.

To correlate the IDH character of the tumor if you will, and the other measures
including the Warburg index.

So the Warburg effect being measured with a multi modality image where we have lactate by Mr spectroscopy over the standard uptake value with dog pet and we are saying that that should be relatively equal hopefully to glycolysis over oxidative phosphorylation. Which is the warburger connectbot.

We're labeling that the Warburg index, 'cause this can be a tool that we could use now in the clinic. we're looking forward to starting soon as we transform into a normal process of enrolling patients and observational clinical trials.
Will have cohorts of 17 and 1788 mutant gliomas and 98 well take llamas and will be performing marked prosperity imaging with protons, no label and measure lactate in two hydroxy glutarate and all of these patients and we will also perform FDG PET and and determine the sort of overall glucose demand energy demand from the tumor. Hopefully we’ll be able to enroll these patients in more technical studies where we’ll have really a research standard of the Warburg effect through things like the
deuterium metabolic imaging stable isotope methods at the same time we all work together in Doctor Defeaters, one of my closest collaborators. And we will then follow this cohort of patients to produce our own clinical outcome measures. Especially interested in progression free survival and overall survival, which will be diverse in this group of patients where some patients will have an IDH wild type tumor more similar to a glioblastoma as I’ve shown you here, and some will have an idea, it’s mutant chamber more similar
to these long term patients that have very slow growing tumors.

We will also through collaborations with Doctor Marat Daniels.

Laboratory be able to perform whole genome methylation studies in all of these patients.

So we’ll have. An extraordinarily diverse and deep data set where we’ll be able to potentially use preclinical Warburg effect measures to compare to Clinical Warburg index measures.

Compare both of these measures to clinical outcomes,
and then also in a vein of precision medicine implications. Be able to show exactly how much perhaps 2 hydroxy glutarate is being produced by the IDH mutant pathophysiology. And then what the implications to the methylome and the methylation of the genome is? So future directions we have actually recently been able to image a patient within their treatment. So I’ve shown you once again, IDH mutant glioblastoma and I’ve shown you idh, wildtype, Leo Lester, mother relatively similar appearing.
If you’re not looking at the spectrum per say, Looks like very large warburger effects. Classic aggressive tumor. We had a patient who had a glioblastoma shortly following chemoradiation and when we imaged this patient we were unable to detect the word with effect on. This is very exciting. We potentially have not only implications to diagnostic and prognostic implications, as I was mentioning before with the Warburg Index clinical study. But now we have the potential to follow the same patient during their course.
Where perhaps there are dynamic changes within the tumor. Perhaps this is just a time when we, when we caught this tumor and it was less, had less expression of the Warburg effect. But perhaps we’re able to modify the Warburg effect and perhaps the aggressiveness of the tumor. With treatment that we do, and really if we can find that this is what we’re really targeting and not the changes that can be so confusing. For example with pseudo progression. Then that’s a very exciting frontier, so we’re hopeful with the translational award moving forward,
that we’ll be able to scan some of these patients longitudinally both before and after chemo radiation. But in addition, along the way we scan patients in the clinic every two months. And so if we could potentially get metabolic imaging for all of these patients. Then it would potentially change our management fundamentally.

I want to thank lots of people for all of this effort. It’s definitely a village doing translational neuro oncology. This is really my laboratory size.
My current research assistant and alumni who are already at Duke and NYU and medical school. I’m extremely grateful for the support I’ve had here through the Y CCI Scholar award. Also, my collaborators are A1. I’m grateful to Doctor Fuchs and the Cancer Center. As well as just a multi institutional collaboration Dr Wrecked. one of my mentors from Stanford. All of these individuals. It’s not even a complete list at Yale. Really need no introduction,
but especially grateful for this talk for contributions from Doctor Defeater and Doctor Rothman, and I want to thank you very much for all of your attention, and I think this is time for questions. Derek, thank you. And yes, we do. Actually, it’s a great talk and we do have time for questions. If if individuals want to submit that on the chat, so is Zach. Let me ask you given the the thrust of your work, are there potentially? Developing on or ongoing targeted approaches.
That would sort of focus on metabolic pathways coming along that your technology. Your assessments would actually be informative for or and or does this potentially OfferUp new targets.

Well, I think it’s a great. It’s a great question and and I think. There’s a couple ways, so actually I VH mutation targeting has really gone both ways. In our field it has been proposed that IDH mutant pathophysiology should be blocked with an inhibitor. And there’s current clinical trials in that vein. And then there’s the exact opposite approach,
which is that IDH mutant pathophysiology conveys really a weakness that needs to be targeted and potentially promoted, which is really not just. To paraphrase simply Doctor Bender, thrust of work, and so this is actually. Pretty interested in potentially performing animal models where we can show them metabolic, correlate, Stew these interventions, but we have the potential also for doing so in the clinic, and that’s really why I find the Warburg index as opposed to the pre
clinical measures to be so exciting. This could be put in as an endpoint and potentially a phase two or phase three study very shortly, so hopefully over the next year I'll be able to recruit these cohorts and really have some exciting things to share.

Great, well I look forward to it Zack. So it is the top of the hour and I want to be sensitive to everyone's time so I wanna thank Zack and Jason for really 2 outstanding and informative talks about novel approaches to imaging for the CNS. And of course thank all of you for
00:58:20.744 --> 00:58:22.476 joining us today and enjoy the
rest of your day. Thank you.

00:58:25.930 --> 00:58:26.000 She.