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 force 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 be introduce in 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.
And lastly, talk about some of the new targets. For Brent tumor imaging, which are not specifically interested in us for us, you know as research lab. So first blue bus stoma is fatal disease with less than 10% of patients surviving five years after initial diagnosis and treatment, and 15% of all parental merge and half of the ugly omas is glioblastoma, there’s still no early detection method available, so. No people in this world you are
calling for new and better imaging

So pat imaging. In a shell composed

So first we need to have a pet

We call it patch razor because we

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 brain tumor mass.

Indicated by enhanced mass.

By this contrast city.

And also from the patch
you actually see a hypo.

Because this happened to be a low grade brain tumors and later after approved in 1997 and as you can see at the earliest time, the pass scanner has very low spatial resolution, is about 1.7 centimeter resolution.

And now we have dedicated brain PET scanners up with up to one or two millimeters spatial resolution.

So after G as you see, it has a high background in the brain because the brain uses sugar as it’s 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 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
00:08:31.546 --> 00:08:34.198 progression from radio necrosis.

00:08:34.200 --> 00:08:36.615 For example, in this case, from the anatomical images,

00:08:36.620 --> 00:08:38.428 it’s pretty hard to distinguish these two cases,

00:08:40.688 --> 00:08:42.338 but from my selling is also called Matt from Matt Pat.

00:08:42.340 --> 00:08:45.352 You can easily tell the top cases a tumor progression while the bottom case is actually a radio.

00:08:45.352 --> 00:08:47.880 You can easily tell the top cases a tumor progression while the bottom case is actually a radio.

00:08:47.880 --> 00:08:50.659 You can easily tell the top cases a tumor progression while the bottom case is actually a radio.

00:08:50.659 --> 00:08:55.270 There’s also imaging agents derived from nuclear sites because nucleotides are used for DNA synthesis.
And it's up taken into the tumor cells 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 cell 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 from this case you can see the contrast getting contrast enhanced MRI images, which can clearly delineate the tumor regions,
of the tumor and also my selling

uptake in a larger area while found

felt pad you can actually.

See not only the tumor,

but also the infiltration of

the tumor to the brain region.

So besides my sounding match,

there are other amino acid analogs

being used in brain tumor PET.

For example, tossing and floral floral
dopa F dopa F dopa is actually approved

by FDA to image Parkinsonian syndrome

back in 2019 because after reflects its

accumulated in dopaminergic neurons.

Neurons are damaged in Parkinson’s disease,

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.
the emerging imaging targets for brain tumor.

So my interest in bringing my imaging 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 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. So this is gone down from his lab, generated you 87 look,
which is a blue blastoma tumor

So we use valid methods to monitor

After the tumor reaches a certain size,

From the pet images, we can tell

that rumor update 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.

Natural nurse and found the T2 MRI.

We can clearly visualize the tumor
00:14:55.488 --> 00:14:58.779 so we can analyze the region of interest for the tumor uptake.

00:15:04.140 --> 00:15:06.450 So this tells us the Sigma 1 receptor expression in healthy brain is also significant,

00:15:09.720 --> 00:15:12.276 which may similarly to FG pad, complicates the PATH imaging data analysis.

00:15:17.387 --> 00:15:18.930 nonhuman primate patting imaging.

00:15:25.120 --> 00:15:28.920 Sigma 1 receptor uptake in healthy brain regions significantly overtime.

00:15:28.920 --> 00:15:31.860 So the question now is to identify by marker for global stoma with low expression in healthy brain tissues.

00:15:38.290 --> 00:15:42.826 So that turned out to Park Park is
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 T ARP 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 and mass tumor to muscle region reaches the highest level at 2 hours post Twitter injection. 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 immuno fluorescence. 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, 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,
blocking drug at the same time we
look at the control later role,
which is presumably to be
the healthy brain tissue.
And it showed relatively lower uptake.
Send a tumor and the blocking doesn’t
have significant effect over there.
So here’s the tumor to contralateral
ratio and at baseline it’s about 2.5
after blocking drops to about 1.5,
indicating about 46% blockade from the.
To validate the path image data,
we perform pilot biodistribution study.
We look at the tracer distribution among
the different different tissues of animal.
00:22:37.590 --> 00:22:40.650 Not surprising me that Rooster has
00:22:40.650 --> 00:22:43.829 high spleen uptake because spleen is
00:22:43.829 --> 00:22:46.967 another large organ and that’s positive.
00:22:46.970 --> 00:22:48.920 Also, it’s a blocked by the.
00:22:51.230 --> 00:22:53.505 And consistent with the pattern medium data,
00:22:53.510 --> 00:22:56.807 we see high uptick in the tumor,
00:22:56.810 --> 00:23:00.098 and it’s blocked by the brick as well.
00:23:03.230 --> 00:23:06.056 Further analysis of this pilot data
00:23:06.060 --> 00:23:11.060 indicates very high spleen to blood ratio
00:23:11.060 --> 00:23:14.657 and also very high tumor to blood ratio.
00:23:14.660 --> 00:23:17.636 For the power quality of regions and it
00:23:17.636 --> 00:23:20.845 also shows some extent of the brain uptake,
00:23:20.850 --> 00:23:24.560 which is seem to be blocked by the cold drug.
00:23:24.560 --> 00:23:26.325 So further study confirmative study
00:23:26.325 --> 00:23:29.572 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
that you can see after blocking agents.

The Twitter uptake was diminished to the same level of the unspecific update to the same level of Cpl.

One negative tumor uptake.

Well, the baseline scan showed higher uptake, so they also did autoradiography.

This is in virtual autoradiography study.

Not not only look at this too, they don’t draft silence.

They also look at some 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 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.
Also they showed one case where there's a tumor metastasis because the tumor metastasis, so it could be the low PDL expression over there, or it could be the more intact blood brain barrier. So in order to apply PDL 1 packaging in tumor imaging or glioma patch, we initiated a project to develop brain punishment. PDL 1 patting 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,
00:27:10.140 --> 00:27:12.700 initial validations and clinical trials finally reached to FDA approval.
00:27:16.540 --> 00:27:19.268 So I’d like to use the last few minutes to update you the latest advancement in the past scanner, because pass scanner is a critical component in the pet imaging research.
00:27:19.268 --> 00:27:21.981 minutes to update you the latest advancement in the past scanner,
00:27:21.981 --> 00:27:24.416 So very excitingly recently we saw a prototype for total body pad, so traditionally the path scanner needs to move the bed to get the whole body.
00:27:24.420 --> 00:27:26.592 because pass scanner is a critical component in the pet imaging research.
00:27:26.592 --> 00:27:30.660 So very excitingly recently we saw a prototype for total body pad,
00:27:30.660 --> 00:27:32.838 a prototype for total body pad,
00:27:32.838 --> 00:27:34.940 so traditionally the path scanner needs to move the bed to get the whole body.
00:27:34.940 --> 00:27:37.830 to move the bed to get the whole body.
00:27:37.830 --> 00:27:40.620 to move the bed to get the whole body.
00:27:40.620 --> 00:27:42.212 PET imaging study done,
00:27:42.212 --> 00:27:44.600 but with a total body PAT
00:27:44.600 --> 00:27:46.290 we can collect all the 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 scan 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 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,
00:30:03.076 --> 00:30:06.454 faculty and students at your pet
00:30:06.454 --> 00:30:09.000 center or internal and external
00:30:09.000 --> 00:30:10.980 collaborators and or finding
00:30:10.980 --> 00:30:13.584 agents for supporting our research,
00:30:13.584 --> 00:30:17.216 and this is picture we took last year
00:30:17.220 --> 00:30:19.506 and this is what we look at this year.
00:30:22.390 --> 00:30:24.222 Well, Jason, thank you.
00:30:24.222 --> 00:30:27.281 It was a really terrific review of,
00:30:27.281 --> 00:30:29.147 you know, novel approaches to imaging
00:30:29.147 --> 00:30:31.090 both for clinical care and research.
00:30:31.090 --> 00:30:33.526 And yeah, thank you for changing
00:30:33.526 --> 00:30:36.329 the context of your research group
00:30:36.330 --> 00:30:39.389 photo in terms of the current world.
00:30:39.390 --> 00:30:42.160 You know, Jason, we’re at, why don’t we?
00:30:42.160 --> 00:30:43.900 Why don’t I suggest that for
00:30:43.900 --> 00:30:45.708 folks who have questions for you
NOTE Confidence: 0.7139220458
00:30:45.708 --> 00:30:47.710 to direct them to you offline?
NOTE Confidence: 0.7139220458
00:30:47.710 --> 00:30:49.691 Just 'cause we're at the we're a
NOTE Confidence: 0.7139220458
00:30:49.691 --> 00:30:51.960 little late in the time and I want
NOTE Confidence: 0.7139220458
00:30:51.960 --> 00:30:53.620 to make sure there's time for.
NOTE Confidence: 0.7139220458
00:30:53.620 --> 00:30:57.109 For Zach but Jason thank you for us.
NOTE Confidence: 0.7139220458
00:30:57.109 --> 00:31:01.510 Superb presentation again.
NOTE Confidence: 0.7139220458
00:31:01.593 --> 00:31:04.155 I invite people to submit send
NOTE Confidence: 0.7139220458
00:31:04.160 --> 00:31:05.994 but let me now turn to our.
NOTE Confidence: 0.7139220458
00:31:06.000 --> 00:31:07.431 Our second speaker.
NOTE Confidence: 0.7139220458
00:31:07.431 --> 00:31:09.340 Did Doctor Zachary Corbin,
NOTE Confidence: 0.7139220458
00:31:09.340 --> 00:31:11.908 as many of you know as an
NOTE Confidence: 0.7139220458
00:31:11.908 --> 00:31:13.897 assistant professor of neurology, he.
NOTE Confidence: 0.7139220458
00:31:13.897 --> 00:31:16.519 Received his medical degree at Yale
NOTE Confidence: 0.7139220458
00:31:16.519 --> 00:31:18.823 and thereafter did his residency

42
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.
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.
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.
The transition to methods results.

And our current investigations things

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 when thinking about the disease,
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,
of our country.

And this is John McCain.

Who died of glioblastoma as senator from Arizona?

And so you know.

That was a good introduction to what is a disease that has an annual incidence in the US of 20,000.

Is is glioma in general and glioblastoma in particular has an annual incidence of 11,000.

Actually almost 12,000 / 11,000.

It’s the most common primary malignant brain tumor.

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 an absolutely remarkable, 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.

00:37:37.550 --> 00:37:39.800 But in addition,

00:37:39.800 --> 00:37:41.424 you can see something else that’s

00:37:41.424 --> 00:37:44.172 interesting, which is that.

00:37:44.172 --> 00:37:47.476 There are a number of patients

00:37:47.480 --> 00:37:49.972 And it’s very difficult to predict as

00:37:49.972 --> 00:37:51.970 doctor time mentioned at the start.

00:37:51.970 --> 00:37:54.140 Who is going to come from here

00:37:54.220 --> 00:37:55.279 and still live?

00:37:55.280 --> 00:37:57.940 We don’t have prognostic or

00:37:57.940 --> 00:38:00.600 diagnostic ways of determining this.

00:38:00.600 --> 00:38:06.018 So in order to discuss another related

00:38:06.018 --> 00:38:10.488 but somewhat complementary fact of care for.

00:38:10.490 --> 00:38:12.644 Brain tumors currently is the delayed

NOTE Confidence: 0.856130180909091
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. That really targeted a moderate severity brain tumor, and anaplastic oligodendroglioma OMA and anaplastic oligoastrocytoma although oligo. Astrocytoma is a relatively antiquated term. In this Protocol enrolled patients, and similarly to the Stu Protocol patients received either chemotherapy, and this time with PCV, chemotherapy with radiation,
or radiation alone. And you can see.

Approximately 10 years in 2006, approximately 10 years after the study was started, there was no indication as to which was superior.

10 years later, almost 20 years after the study began, you can actually see a signal, and by this analysis it demonstrated that patients do better with PCV with radiotherapy as compared to radiotherapy alone. So we have.

Two processes going on where you...
00:39:17.342 --> 00:39:19.480 have a substantial burden of a very
NOTE Confidence: 0.856130180909091
00:39:19.480 --> 00:39:20.965 aggressive disease and difficult to
NOTE Confidence: 0.856130180909091
00:39:20.965 --> 00:39:23.208 predict long term survivors in that disease.
NOTE Confidence: 0.856130180909091
00:39:23.210 --> 00:39:26.997 And then less aggressive tumors we have.
NOTE Confidence: 0.856130180909091
00:39:27.000 --> 00:39:28.257 Prolonged 20 years,
NOTE Confidence: 0.856130180909091
00:39:28.257 --> 00:39:30.352 potentially wait between when we
NOTE Confidence: 0.856130180909091
00:39:30.352 --> 00:39:32.695 institute a standard of care or or
NOTE Confidence: 0.856130180909091
00:39:32.695 --> 00:39:34.867 when we are trying to define the
NOTE Confidence: 0.856130180909091
00:39:34.867 --> 00:39:37.198 same care when we have results that
NOTE Confidence: 0.856130180909091
00:39:37.198 --> 00:39:38.698 help us with that standard of care.
NOTE Confidence: 0.856130180909091
00:39:38.700 --> 00:39:41.227 So this is really good fodder for
NOTE Confidence: 0.856130180909091
00:39:41.227 --> 00:39:43.157 exactly what the context today
NOTE Confidence: 0.856130180909091
00:39:43.157 --> 00:39:44.697 is for other ways.
NOTE Confidence: 0.856130180909091
00:39:44.700 --> 00:39:47.930 Biomarkers of measuring this disease.
NOTE Confidence: 0.856130180909091
00:39:47.930 --> 00:39:49.649 So I want to switch gears for a second
NOTE Confidence: 0.856130180909091
00:39:49.649 --> 00:39:51.347 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.

00:40:00.340 --> 00:40:03.484 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.

00:40:13.560 --> 00:40:15.635 And it was raised whether this lesion wasn’t true tumor progression, or whether it was pseudo progression.

00:40:18.172 --> 00:40:20.860 lesion wasn’t true tumor progression, or whether it was pseudo progression.

00:40:22.760 --> 00:40:23.696 Pseudo progression,

00:40:23.696 --> 00:40:25.100 largely in necrosis,
but really a response,

probably by the tumor and also the brain
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 energy 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.

So first I’d like to talk about the deuterium metabolic imaging and then the Warburg index.

So deuterium metabolic imaging.

Really the credit goes to my colleagues at Yale.

Dr Defeater, Hank debater as well as Doctor Robin de Graff who have really done an amazing job in developing this tool.

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. You can see residual chamber. The patient has two voxels that are shown here in the MR spectroscopic spectrum, and 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

Dr. Bendure Ranjit Bindra has really been able to help me understand this better. Isocitrate and ideates wild type pathology. Physiology produces alphabetically and with the IDH mutation, there's a hetero diamond and a heterodimer produces 2-hydroxy butyrate. This has been called an onco metabolite. It may actually be involved in the production of the continuation of tumorigenesis.
Downstream to two hydroxy glutarate in IDH mutant, pathophysiology is methylation changes. DNA hypermethylation in particularly MGMT methylation in gliomas, but also histone methylation. So I actually had the privilege of caring for what is a relatively rare patient who is an IDH mutant glioblastoma and we were able to actually image the tumor with deuterium metabolic imaging. This is prior to the patient having surgery, so this is really a perfect case and so with this case we can see 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. You can see this is the Warburg index, lactate over glutamate. 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
we’re very excited about that
really 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, I’m referring to it as the representation of oxidative phosphorylation or from...
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.
00:51:14.225 --> 00:51:16.133 including the Warburg index.
NOTE Confidence: 0.858992581
00:51:16.140 --> 00:51:18.444 So the Warburg effect being measured
NOTE Confidence: 0.858992581
00:51:18.444 --> 00:51:21.139 with a multi modality image where we
NOTE Confidence: 0.858992581
00:51:21.139 --> 00:51:23.323 have lactate by Mr spectroscopy over
NOTE Confidence: 0.858992581
00:51:23.323 --> 00:51:25.820 the standard uptake value with dog pet
NOTE Confidence: 0.858992581
00:51:25.820 --> 00:51:28.238 and we are saying that that should
NOTE Confidence: 0.858992581
00:51:28.238 --> 00:51:29.968 be relatively equal hopefully to
NOTE Confidence: 0.858992581
00:51:29.968 --> 00:51:32.099 glycolysis over oxidative phosphorylation.
NOTE Confidence: 0.858992581
00:51:32.100 --> 00:51:33.440 Which is the Warburger connectbot.
NOTE Confidence: 0.858992581
00:51:33.440 --> 00:51:35.318 We’re labeling that the Warburg index,
NOTE Confidence: 0.858992581
00:51:35.320 --> 00:51:37.602 ’cause this can be a tool that
NOTE Confidence: 0.858992581
00:51:37.602 --> 00:51:40.027 we could use now in the clinic.
NOTE Confidence: 0.858992581
00:51:40.030 --> 00:51:42.346 So we’re looking forward to starting
NOTE Confidence: 0.858992581
00:51:42.346 --> 00:51:45.573 soon as we transform into a normal
NOTE Confidence: 0.858992581
00:51:45.573 --> 00:51:48.378 process of enrolling patients and
NOTE Confidence: 0.858992581
00:51:48.378 --> 00:51:50.150 observational clinical trials.
00:51:50.150 --> 00:51:54.046 Will have cohorts of 17 and 1788
NOTE Confidence: 0.858992581
00:51:54.046 --> 00:51:56.362 mutant gliomas and 98 well take
NOTE Confidence: 0.858992581
00:51:56.362 --> 00:51:59.332 llamas and will be performing marked
NOTE Confidence: 0.858992581
00:51:59.332 --> 00:52:01.236 prosperity imaging with protons,
NOTE Confidence: 0.858992581
00:52:01.236 --> 00:52:03.474 no label and measure lactate in
NOTE Confidence: 0.858992581
00:52:03.474 --> 00:52:05.816 two hydroxy glutarate and all of
NOTE Confidence: 0.858992581
00:52:05.816 --> 00:52:08.504 these patients and we will also
NOTE Confidence: 0.858992581
00:52:08.504 --> 00:52:11.270 perform FDG PET and and determine
NOTE Confidence: 0.858992581
00:52:11.270 --> 00:52:14.170 the sort of overall glucose demand
NOTE Confidence: 0.858992581
00:52:14.170 --> 00:52:17.020 energy demand from the tumor.
NOTE Confidence: 0.858992581
00:52:17.020 --> 00:52:19.600 Hopefully we’ll be able to enroll
NOTE Confidence: 0.858992581
00:52:19.600 --> 00:52:21.869 these patients in more technical
NOTE Confidence: 0.858992581
00:52:21.869 --> 00:52:24.695 studies where we’ll have really a
NOTE Confidence: 0.858992581
00:52:24.700 --> 00:52:26.365 research standard of the Warburg
NOTE Confidence: 0.858992581
00:52:26.365 --> 00:52:28.030 effect through things like the
NOTE Confidence: 0.858992581
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 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.
IDH mutant glioblastoma and 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, 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. 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 question 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
00:57:46.911 --> 00:57:48.777 clinical measures to be so exciting.
NOTE Confidence: 0.933018215
00:57:48.780 --> 00:57:51.388 This could be put in as an endpoint
NOTE Confidence: 0.933018215
00:57:51.388 --> 00:57:53.420 and potentially a phase two or
NOTE Confidence: 0.933018215
00:57:53.420 --> 00:57:55.055 phase three study very shortly,
NOTE Confidence: 0.933018215
00:57:55.060 --> 00:57:59.758 so hopefully over the next year
NOTE Confidence: 0.933018215
00:57:59.758 --> 00:58:01.048 I'll be able to recruit these
NOTE Confidence: 0.933018215
00:58:01.048 --> 00:58:02.080 cohorts and really have some
NOTE Confidence: 0.933018215
00:58:03.170 --> 00:58:05.866 Great, well I look forward to it Zack.
NOTE Confidence: 0.7861976375
00:58:05.870 --> 00:58:07.920 So it is the top of the hour and I
NOTE Confidence: 0.7861976375
00:58:07.989 --> 00:58:12.184 want to be sensitive to everyone's
NOTE Confidence: 0.7861976375
00:58:09.801 --> 00:58:12.184 time so I wanna thank Zack and
NOTE Confidence: 0.7861976375
00:58:12.184 --> 00:58:15.925 Jason for really 2 outstanding
NOTE Confidence: 0.7861976375
00:58:14.029 --> 00:58:15.925 and informative talks about novel
NOTE Confidence: 0.7861976375
00:58:15.925 --> 00:58:18.235 approaches to imaging for the CNS.
NOTE Confidence: 0.7861976375
00:58:18.240 --> 00:58:20.744 And of course thank all of you for
joining us today and enjoy the rest of your day. Thank you.