WEBVTT

NOTE duration:"00:23:45.2610000" language:en-us

NOTE Confidence: 0.854451835155487

00:00:07.150 --> 00:00:27.150 Thank you again. Thank you all for being here. It's almost amazing to see how much we can still learn from studying DNA T 2 more viruses, so before I begin user. My disclosures have received some research funding from Astra Zeneca and so for the purpose of this talk today, I wanted.

NOTE Confidence: 0.907916963100433

00:00:27.950 --> 00:00:47.950 Of our interests longstanding interest in understanding the mechanisms of metastasis and then the recent couple of years. We've been focusing on the problem of brain metastasis or metastasis. The central nervous system and here's the clinical challenge, so bring that ass is can arise from multiple types of tumors predominantly long rest and melanoma.

NOTE Confidence: 0.884256660938263

00:00:48.750 --> 00:01:08.750 Are responding to systemic therapy but eventually relap sing the incidence of CNS relapse? Is predicted to increase over the next couple of years as 1 of my good close colleagues. Veronica showing always tells me I always listen to her when she when she tells me anything, it's actually been very difficult to study brain metastasis.

NOTE Confidence: 0.910400211811066

00:01:09.550 --> 00:01:29.550 Incidence is relatively high very few of these patients are actually less than 10% undergo surgical resection's and therefore obtaining tissue to study this disease is difficult from a biological standpoint. I think what's fascinating me is encapsulated here by these 2 images taken from the clinical literature, where you can see that In addition to originate NG from.

NOTE Confidence: 0.864826321601868

00:01:30.350 --> 00:01:50.350 Answers brain Mets can also manifest representing different heterogeneous patterns of disease progression so for instance, some tumors are well circumscribed and focal where there's other brain Mets appears multiple disease with various patterns of invasion of brain pragma and So what are the mechanisms that drive this are the genetic and if they are are?

NOTE Confidence: 0.850683450698853

00:01:51.150 --> 00:02:11.150 Dad with the private tumors or unique to the brain metastasis can be be epigenetic. And if so are these epigenetic changes intrinsic to the cell types tumor cell types or they induced by the tumor microenvironment and finally in the case of relapse is due to poor predator penetration of systemic drugs or other factors from the microphone and so the uh.

NOTE Confidence: 0.880239248275757

00:02:11.950 --> 00:02:31.950 To study brain metastasis are really 2 to 3 fold, the first is that in collaboration with Veronica Chang. I'll be Patel and several others involvement lung cancer spore word leveraging cerebral spinal fluid biopsies from patients identify drivers of CNS metastasis. This is a new initiative. I won't have time to discuss this today, when I like to focus on.

NOTE Confidence: 0.903188586235046

00:02:32.750 --> 00:02:52.750 And also pre clinical approaches to identifying adaptive mechanisms of brain metastasis outgrowth and drug resistance using preclinical models. Another major thrust in my lab is we're interested in the relationship between developmental pathways and how these drive tumor progression, particularly in lung cancer and I'll only touch.

NOTE Confidence: 0.882470548152924

00:02:53.550 --> 00:03:13.550 Insofar, as it is relevant to the discussion of brain metastasis so in my lab, we use several different models. I like this? How all my training is that when they come into the lab that were not model Nazis were equal opportunists. Recognizing both the advantages and limitations of each of these models.

NOTE Confidence: 0.884166479110718

00:03:14.350 --> 00:03:34.350 Patient arrives in a graph and also syngenetic models one of the approaches. I do want to mention in a bit more detail to study metastasis is while it's easy to document or relatively easy to document metastasis. It's another thing to actually quantify these events and the approach that we use here is that we can take tumor cells label them.

NOTE Confidence: 0.876201331615448

00:03:35.150 --> 00:03:55.150 Porters and inject them into circulation of mice and what this allows us to do is a quantified document and quantify with some accuracy. Some of the very early steps of metathesis, which include reaching the blood brain barrier. Co option of the CNS blood vasculature latency of these disseminated tumor cells as Micro Mets that persists.

NOTE Confidence: 0.878097414970398

00:03:56.100 --> 00:04:16.100 Before they start to go out as Macro Metastasis and I just want to mention that experimentally and we believe that this happens in humans as well. Most of the attrition of tumor cells or the bottleneck as well occurs during these early steps and these early steps are not radiologically detectable and in fact, is not till later in these model systems.

NOTE Confidence: 0.832951784133911

00:04:16.900 --> 00:04:36.900 See large macro metastasis and by MRI as you might in humans and this is done in collaboration with famine. Haider in his former postdoc medicines panel so really the challenge. Here is how do we

identify adaptive mechanisms at these early stages? Which we would argue R rated limiting for brain metastasis so?

NOTE Confidence: 0.897610306739807

00:04:37.700 --> 00:04:57.700 We are also interested in optimizing or leveraging several types of transcriptomic approaches and we use a really simply have really simple idea, which is goes as follows. Can we leverage recent advances in our ability to map transcripts of low abundance and the species specific manner and tissues and secondly.

NOTE Confidence: 0.859788596630096

00:04:58.500 --> 00:05:18.500 Which is in a graph models could we differentiate or discern gene expression changes that are coming from the tumor cells because these would be human jeans that are coming from the human tumor cells that are then transplanted into marine hosts and therefore the stroma will be represented by changes in metering jeans and so this is a proof of principle experiment, which take a well characterized.

NOTE Confidence: 0.857770025730133

00:05:19.340 --> 00:05:39.340 And in this context and you grow them in culture and you treat them with the drug. You can see that they're equally sensitive to the tyrosine kinase inhibitor similar. I see 50s and if you re transplant them into the brain. You can reproducibly show. This resistance phenotype that is preferential in the brain and that's enhanced by the tumor microenvironment and again if we apply are are.

NOTE Confidence: 0.883866012096405

00:05:40.140 --> 00:06:00.140 Pipeline we see is that certainly while you can find gene signatures that differentiate these resistant cells from these sensitive cells when they're grown in culture. You can see the number of jeans and the magnitude of these gene responses increases significantly in these tumor. Cells are grown inside the brain. Obviously these patients still develop GK resistant disease and we can model this so I can hear you.

NOTE Confidence: 0.856820285320282

00:06:00.940 --> 00:06:20.940 That are growing in the brain that we're quantifying here. These animals are on your treatment. We can have tumors that grow preferentially in the brain under continuous treatment of a synonym. They can be compared here to tumors that share a similar linear. I won't get into the details of how these were generated but essentially these tumors can be compared to.

NOTE Confidence: 0.867581903934479

00:06:21.740 --> 00:06:41.740 And what's rather interesting is if you take the tumor cells out of the brain in this context, and you grow them in culture and you treat them with the drug. You can see that they're equally sensitive to

the tyrosine kinase inhibitor similar. I see 50s. But if you re transplant them into the brain. You can reproducibly show. This resistance phenotype that is preferential in the brain and that's enhanced by the tumor.

NOTE Confidence: 0.888478219509125

00:06:42.700 --> 00:07:02.700 And again if we apply are are sequencing pipeline that we see is that certainly while you can find gene signatures that differentiate these resistant cells from these sensitive cells when they're grown in culture. You can see the number of jeans and the magnitude of these gene responses increases significantly on these tumor. Cells are grown inside the brain, obviously these patients still develop.

NOTE Confidence: 0.846430063247681

00:07:03.500 --> 00:07:23.500 Disease and we can model this so and here you're looking at tumors that are growing in the brain that we're quantifying here. These animals are on your treatment. We can have tumors that grow preferentially in the brain under continuous treatment of most alert him that can be compared here to tumors that share a similar linear. I won't get into the details of how the?

NOTE Confidence: 0.869457721710205

00:07:24.300 --> 00:07:44.300 Essentially, these tumors can be compared to one another and what's rather interesting is if you take the tumor cells out of the brain in this context, and you grow them in culture and you treat them with the drug. You can see that they're equally sensitive to that are some Chinese inhibitor similar. I see 50s. But if you re transplant them into the brain you can reproducibly show this resistance phenotype that.

NOTE Confidence: 0.881043553352356

00:07:45.100 --> 00:08:05.100 In the brain and that's enhanced by the tumor microenvironment and again. If we apply. Our sequencing pipeline. We see is that certainly while you can find gene signatures that differentiate these resistant cells from these sensitive cells when they're grown in culture. You can see the number of jeans and the magnitude of these gene responses increases significantly on these tumor cells are grown.

NOTE Confidence: 0.838469564914703

00:08:05.130 --> 00:08:25.130 Inside the brain, obviously these patients still develop GK resistant disease and we can model this so and here you're looking at tumors that are growing in the brain that we're quantifying here. These animals are on your treatment. We can have tumors that grow preferentially in the brain under continuous treatment of a synonym they can be compared here, too, too.

NOTE Confidence: 0.891959249973297

00:08:25.930 --> 00:08:45.930 Share a similar linear I won't get into the details of how these were generated but essentially these tumors can be compared to one another and what's rather interesting is if you take the tumor cells out of the brain in this context, and you grow them in culture and you treat them with the drug. You can see that they're equally sensitive to the tyrosine kinase inhibitor similar. I see 50s. But if you re transplant them into the brain.

NOTE Confidence: 0.865682303905487

00:08:46.730 --> 00:09:06.730 We show this, this resistance phenotype that is preferential in the brain and that's enhanced by the tumor microenvironment and again. If we apply are are sequencing pipeline that we see is that certainly while you can find gene signatures that differentiate these resistant cells from these sensitive cells when they're grown in culture. You can see the number of jeans and the magnitude.

NOTE Confidence: 0.859366774559021

00:09:07.530 --> 00:09:27.530 This increases significantly when these tumor cells are grown inside the brain. Obviously these patients still develop GK resistant disease and we can model this so and here you're looking at tumors that are growing in the brain that we're quantifying here. These animals are on your treatment. We can have tumors that grow preferentially in the brain under continuous treatment of OCD, alerting him.

NOTE Confidence: 0.884845316410065

00:09:27.780 --> 00:09:47.780 At least they can be compared here to tumors that share a similar linear. I won't get into the details of how these were generated but essentially these tumors can be compared to one another and once rather interesting is if you take the tumor cells out of the brain in this context and you grow them in culture and you treat them with the drug. You can see that they're equally sensitive to that are some Chinese and.

NOTE Confidence: 0.860025942325592

00:09:48.580 --> 00:10:08.580 Well, I see 50s and if you re transplant them into the brain. You can reproducibly show. This resistance phenotype that is preferential in the brain and that's enhanced by the tumor microenvironment and again. If we apply. Our sequencing pipeline. We see is that certainly while you can find gene signatures that differentiate these resistant cells from these sensitive.

NOTE Confidence: 0.869504153728485

00:10:09.380 --> 00:10:29.380 We don't in culture, you can see the number of jeans and the magnitude of these gene responses increases significantly when these tumor. Cells are grown inside the brain again, suggesting that this in C to approach can capture some of these adaptive responses in the brain micropump. It so I don't think I needed to show you all that for you to for us to conclude.

NOTE Confidence: 0.888698101043701

00:10:30.180 --> 00:10:50.180 For Michael employment matters So what I want to do for the rest of the talk is focused on a couple of more specific sets of findings. The first vignette is will be for those of you that are lumpers and so here what we would like to show is some of the top line analysis that this approach that we've used to look at Jean responses in Brainerd.

NOTE Confidence: 0.878473818302155

00:10:50.220 --> 00:11:10.220 This models that originate from multiple diseases long breast and melanoma and for the splitters. I'd like to also describe a little bit later, an interesting phenomenon of Lenny Edge Plasticity in the context of lung cancer and brain metastasis so in this proof of principle experiment? What we decided to do is take.

NOTE Confidence: 0.878920435905457

00:11:10.250 --> 00:11:30.250 3 well describe models that are representative of triple negative breast cancer. B rap mutant melanoma and care ass P 53. Newton lung cancers in this case non small cell lung cancer and then subject established brain metastasis models from all 3 controlling for the location in this case growing in the forebrain and uh.

NOTE Confidence: 0.853996753692627

00:11:31.050 --> 00:11:51.050 Subject these 2 are on BMX seek pipeline and in this case, we're looking first and stromal gene responses that are differentially induced in the stroma tumor bearing brain versus control brain controlling for the region of the brain and so it was somewhat surprising to me is that there was a lot of differences in the strong response of these tumors again, even if we count for.

NOTE Confidence: 0.885184049606323

00:11:51.850 --> 00:12:11.850 To my birds location with the breast cancer model in lung cancer model showing the most significant overlap, however, if you focus on the core group of jeans here that are commonly disregulated in the stroma of these brain. Max would you find is a number of inflammatory molecules perhaps not too surprisingly?

NOTE Confidence: 0.865237414836884

00:12:12.650 --> 00:12:32.650 Expressing your name immune cells, but was kind of intriguing to us was that we saw significant upregulation of 2 receptors in particular. Lag 3 and HABCR 2 also known as Tim 3 and so for most of you in the audience. You'll probably are aware of the significance of these 2 receptors because they are generally thought is being expressed on.

NOTE Confidence: 0.850481808185577

00:12:33.560 --> 00:12:53.560 And function as checkpoint receptors and their part of this new wave of checkpoint receptors that are being targeted for therapy. This is intriguing because this is as you will call this was done in Azina graph model. These animals do not have T cells. And so why are these jeans being expressed in the stroma of these brain metathesis and so if we look at?

NOTE Confidence: 0.84907740354538

00:12:53.600 --> 00:13:13.600 And the reason is because we think that M 3 in Lancair also expressed on brain metastasis associated microglia. So this is Emmanuel standing to confirm some of our bulk. Transcriptomic analysis where you can see and yellow here. Basically, Tim 3 in lag 3 overlapping with fiber. One positive tumor associated macrophages, so in the brain IBA one can.

NOTE Confidence: 0.838839828968048

00:13:14.400 --> 00:13:34.400 Or my Lord cells that either derived from resident pool of Micro Glea or also potentially from the bone marrow. We think that these cells are mostly in these brain Mets at least derived from resident microglia because the over the coast in with the microglial specific marker team M 119. Although not all of them are also to me.

NOTE Confidence: 0.874523878097534

00:13:35.200 --> 00:13:55.200 So so this is also somewhat consistent with some observations that are made in the field of neural degeneration and information were some glial cell types of neurons can also express these receptors quite interesting. So we've also confirmed this in patient arrives in the graph models and more importantly, looking at the matched patient brain biopsy.

NOTE Confidence: 0.823973715305328

00:13:56.000 --> 00:14:16.000 See consistent standing up 103 on eyeball one positive cells and this is work done in collaboration with Veronica Chang and Katie Pelini and several others. We've Sutter. Tomasi collection patient arrives in a graph from brain metastasis patients and then finally we convert confirm this in Syngenetic models in a competent models.

NOTE Confidence: 0.866159379482269

00:14:16.800 --> 00:14:36.800 Well, so we turn our attention to some of the gene responses from the tumors from the same eyes. Same samples were going to see a little bit more overlap and what we can do with some of this data, now is integrate this with some of the stromal gene responses to kind of infer what would be the signaling pathways that are emanating from the brain, Marco Environment and that might be driving brain metastasis.

NOTE Confidence: 0.879835069179535

00:14:36.830 --> 00:14:56.830 And So what you see here many of you will recognize immediately several components of the Canonical went pathway. And this is interesting for us because in the past, we had. I'm not showing the data here.

It's been published which shown that this pathway is functionally required for brain metastasis in several models. But we were never certain whether not the activation of this pathway was cell intrinsic.

NOTE Confidence: 0.838176846504211

00:14:57.630 --> 00:15:17.630 From this trauma in this case this model is predicting that a lot of these wind. Liggins our went Co ligands are induced in the stroma of these brain metastasis meeting to activation of the pathway in tumor cells and so one prediction from this is that this pathway might be reversible. In fact, Emily did this very elegant experiment.

NOTE Confidence: 0.9114830493927

00:15:17.690 --> 00:15:37.690 Interesting findings and insights into the mechanisms of brain metastasis and the chief advantage of this, I would argue is that we really are not discussing the cells from their host environment and those single cell technologies are very powerful. There are certainly some technical limitations that could introduce artifacts in some of these and.

NOTE Confidence: 0.859883606433868

00:15:39.010 --> 00:15:59.010 Tumor cells within a tumor and non small cell lung cancers. They have there are in this epigenetic state that is permissive for the activation of neurons are coming like gene expression programs. Once there in the brain, presumably be due to some signals that are coming from this Sharma. We have are obvious candidates based on some of the the prior data.

NOTE Confidence: 0.893693268299103

00:15:59.880 --> 00:16:19.880 Looking at the straw more components and stromal changes in this task. This models so to summarize what I've shown you today. I think that just like everyone else were definitely interested in single cell on your sequencing approaches and we have plans to integrate this with some of our analysis here. But I think the point is even with a very simplistic bulk trance.

NOTE Confidence: 0.898800253868103

00:16:20.680 --> 00:16:40.680 We can infer some some interesting findings and insights into the mechanisms of brain metastasis and the chief advantage of this, I would argue is that we really are not discussing the cells from their host environment and those single cell technologies are very powerful there are certainly some technical limit.

NOTE Confidence: 0.872376382350922

00:16:41.480 --> 00:17:01.480 Introduce artifacts in some of these analysis tumor cells within a tumor and non small cell lung cancers. They have there are in this epigenetic state that is permissive for the activation of neuroendocrine like gene expression programs. Once there in the brain, presumably be due to some signals that are coming from this trauma. We have are obvious candidates.

NOTE Confidence: 0.885210394859314

00:17:01.510 --> 00:17:21.510 Based on some of the the prior data that I showed you looking at the straw more components and struggle changes in these tasks as models. So to summarize what I've shown you today. I think that just like everyone else were definitely interested in single cell. RNA sequencing approaches and we have plans to integrate this with some of our analysis here, but

NOTE Confidence: 0.894889175891876

00:17:22.310 --> 00:17:42.310 Point is even with a very simplistic bulk transcriptomic approach. We can infer some interesting findings and insights into the mechanisms of brain metastasis and the chief advantage of this, I would argue is that we really are not discussing the cells from their host environment and those single cell tech.

NOTE Confidence: 0.875499427318573

00:17:43.110 --> 00:18:03.110 Powerful there are certainly some technical limitations that could introduce artifacts in some of these analysis tumor cells within a tumor and non small cell lung cancers. They have there are in this epigenetic state that is permissive for the activation of neuroendocrine like gene expression programs. Once there in the brain, presumably be do.

NOTE Confidence: 0.872207462787628

00:18:03.910 --> 00:18:23.910 Those that are coming from this trauma. We have are obvious candidates based on some of the the prior data that I showed you looking at the stromal components and struggle changes in this task. This models so to summarize what I've shown you today. I think that just like everyone else were definitely interested in single cell on your sequencing approaches and we

NOTE Confidence: 0.91275817155838

00:18:23.970 --> 00:18:43.970 I have plans to integrate this with some of our analysis here. But I think the point is even with a very simplistic bulk transcriptomic approach. We can infer some interesting findings and insights into the mechanisms of brain metastasis and the chief advantage of this, I would argue is that we really are not discussing the cells from there.

NOTE Confidence: 0.891046822071075

00:18:44.860 --> 00:19:04.860 Host environment and those single cell technologies are very powerful. There are certainly some technical limitations. That could introduce artifacts in some of these analysis tumor cells within a tumor and non small cell lung cancers. They have there are in this epigenetic state that is permissive for the activation of neurons.

NOTE Confidence: 0.861212015151978

00:19:05.660 --> 00:19:25.660 Social programs once there in the brain, presumably be due to some signals that are coming from this Sharma. We have are obvious candidates based on some of the the prior data that I showed you looking at the straw more components and struggle changes in these tests models. So to summarize what I've shown you today. I think that just like everyone else were.

NOTE Confidence: 0.90739232301712

00:19:26.460 --> 00:19:46.460 In single cell RNA sequencing approaches and we have plans to integrate this with some of our analysis here. But I think the point is even with a very simplistic bulk transcriptomic approach. We can infer some interesting findings and insights into the mechanisms of brain metastasis and the chief advantage of this, I would.

NOTE Confidence: 0.887103140354156

00:19:47.260 --> 00:20:07.260 We really are not discussing the cells from their host environment and those single cell technologies are very powerful. There are certainly some technical limitations. That could introduce artifacts in some of these analysis tumor cells within a tumor and non small cell lung cancers. They have there are in this epigenetic state.

NOTE Confidence: 0.852473974227905

00:20:07.290 --> 00:20:27.290 That is permissive for the activation of no undercutting like gene expression programs. Once there in the brain, presumably be due to some signals that are coming from this Sharma. We have are obvious candidates based on some of the the prior data that I showed you looking at the store more components and stromal changes in this task this model so to sum.

NOTE Confidence: 0.912777304649353

00:20:28.090 --> 00:20:48.090 Today I think that just like everyone else were definitely interested in single cell on your sequencing approaches and we have plans to integrate this with some of our analysis here. But I think the point is even with a very simplistic bulk transcriptomic approach. We can infer some interesting findings and insights into the mechanism.

NOTE Confidence: 0.887141704559326

00:20:48.890 --> 00:21:08.890 Success and the chief advantage of this, I would argue is that we really are not discussing the cells from their host environment and those single cell technologies are very powerful. There are certainly some technical limitations. That could introduce artifacts in some of these analysis finger cells within a tumor and.

NOTE Confidence: 0.873072504997253

00:21:09.690 --> 00:21:29.690 Answers they have there are in this epigenetic state that is permissive for the activation of neuroendocrine like gene expression programs. Once there in the brain, presumably be due to some signals that are

coming from this Sharma. We have are obvious candidates based on some of the the prior data that I showed you looking at the straw more components and strong willed.

NOTE Confidence: 0.8967564702034

00:21:30.490 --> 00:21:50.490 We test this models so to summarize what I've shown you today. I think that just like everyone else were definitely interested in single cell on your sequencing approaches and we have plans to integrate this with some of our analysis here. But I think the point is even with a very simplistic bulk transcriptomic approach, we can infer some.

NOTE Confidence: 0.912000775337219

00:21:51.290 --> 00:22:11.290 Findings and insights into the mechanisms of brain metastasis and the chief advantage of this, I would argue is that we really are not discussing the cells from their host environment and those single cell technologies are very powerful. There are certainly some technical limitations that could introduce artifacts in some of these analysis.

NOTE Confidence: 0.861500084400177

00:22:12.230 --> 00:22:32.230 Tumor cells within a tumor and non small cell lung cancers. They have there are in this epigenetic state that is permissive for the activation of neuroendocrine like gene expression programs. Once there in the brain, presumably be due to some signals that are coming from this Sharma. We have are obvious candidates based on some of the the prior data that.

NOTE Confidence: 0.897432148456573

00:22:33.090 --> 00:22:53.090 Looking at the straw more components and struggle changes in this task. This models so to summarize what I've shown you today. I think that just like everyone else were definitely interested in single cell RNA sequencing approaches and we have plans to integrate this with some of our analysis here. But I think the point is even with a very simplistic bulk trash.

NOTE Confidence: 0.898587942123413

00:22:53.890 --> 00:23:13.890 We can infer some some interesting findings and insights into the mechanisms of brain metastasis and the chief advantage of this, I would argue is that we really are not discussing the cells from their host environment and those single cell technologies are very powerful there are certainly some technical limit.

NOTE Confidence: 0.87698894739151

00:23:14.690 --> 00:23:34.690 We introduce artifacts in some of these analysis and we're particularly interested in deploying this in the context of drug resistance. So I'll finish with that and just mention that pending some temperamental editors and referees. We looking forward to releasing a lot of this data.

NOTE Confidence: 0.856521308422089

00:23:35.490 --> 00:23:45.230 This rich data set through web portal that will be accessible by anyone so stay tuned and feel free to contact me, so that I'll take any questions like this like.