Good afternoon, my name is Katie Politi and I'm an associate professor of pathology and of medicine here at the Yale School of Medicine and Awesome Co. Leader of the cancer Signaling Networks Research program at the Yale Cancer Center, Doctor Michael Shen today. Doctor Shen is a professor of medicine, genetics and development, urology and systems biology at Columbia University Medical Center. He received his undergraduate
He then pursued his postdoctoral training with Phil, Doctor Phil, leader at Harvard Medical School, before becoming an independent investigator at Rutgers in 1994 and moved to Columbia University Medical Center in 2007. He is currently the Co leader of the Tumor Biology and Micro Environment Program at the Herbert Irving Comprehensive Cancer Center, as well as the director of Graduate studies in the Columbia Department of Genetics and Development.
Over the past 26 years, Doctor Shen has investigated fundamental mechanisms of mammalian development in cancer using in vivo analysis of genetically engineered mouse models. Recently his lamp has generated novel culture conditions for mouse and human prostate and bladder organized noise, which have led to the creation of a bio Bank of patient arrived bladder tumor organoids. Current work in the lab focuses on understanding molecular mechanisms of cell type differentiation in the normal as well as the transformed prostate epithelium. The epigenetic regulation of linear plasticity in both
bladder and prostate cancer, and the role of the tumor micro environment in modulating treatment response.

Doctor Sen, it really is a pleasure to have you here today and have you visit. I'll be at virtually from Columbia University, so thank you very much and we look forward to your presentation.

Well, thank you Katie. It’s a real pleasure to have this opportunity to speak to. This audience that yell and I wish this were in person, but.
Make do as best as we can,

so I’ll go ahead and

share my screen. Um? And.

Hopefully. You can see my presentation.

Is that true? Can everyone see my?

Yes we can see it.

Thank you. Yes excellent.

So today I’d like to talk.

Take the opportunity to discuss published work, but also a lot of work that can be construed as work in progress.

Much of it focusing on the issue of linc plasticity.

And we’ve been studying this through in vivo analysis in mouse models, but also using organoid models,
and we've been studying this in both the prostate and the bladder. So to start with, what is plasticity? So if we consider that plasticity in the most general definition is the ability of a cell to change from one identity to another, we can think of this in the Waddington model. As you know, sort of balls rolling down a Hill. We start with a stem cell and we have various differentiated cell types and the ability of cells too. Basically change their identity.
is considered to be plasticity and so there are different forms there sort of reprogramming back to a more progenitor state.
There can be transdifferentiation changing from one identity to another etc.
So this is a process that has been studied extensively in both development and cancer and it’s important to think about when we talk about plasticity in cancer to consider that. In order to study plasticity, it’s also essential to understand the normal pathways of differentiation so that one can distinguish what happens in the normal context from
what might happen in a tumor context.
So over many years we’ve been studying these issues in the prostate,
and more recently in the bladder,
and to start with, I just like to consider,
sort of a basic review of the prostate in the mouse.
The prostate has a distinct anatomy there.
It sort of has lobular structure.
There are four different lobes in the mouse.
There’s the anterior prostate,
the dorsal prostate, the lateral prostate,
as well as the ventral prostate.
However, in the human there is
something a little bit different.
The human prostate does not have a distinct lobular structure. Instead, it can be distinguished at the pathological level as having you know, sort of architecture of different regions. So there are zones that have been defined pathologically. The peripheral, central, and transition zones, so the distinct anatomy of the mouse and human prostate has been. Of note, for many years and has been used sort of as an argument as underscoring
the inability perhaps of the mouse to truly model human prostate cancer. Now we’ve known from studies over many years that there are many conserved signaling pathways in the like, but the relationship between the mouse and human prostate still remains somewhat mysterious, both in terms of normal development as well as the cell types can contain. Within the prostate. No. The prostate in the mouse is formed at late stages of fetal development and organic Genesis primarily takes place at neonatal stages.
The prostate form, through a process of ductal budding budding from the urogenital sinus and initial prostate buds are marked by expression of the homeo box. Jinan kicks 3.1 here, visualized by Beta Galactoside. ASA Valax Enoch in that we made a number of years ago and you can see even early on at the time of birth. Their buds that correspond to distinct lobes and at least initially and kicks 3.1, expressed by all of the epithelial cells in the prostate. Prostate formation of course requires androgen signaling,
but the requirements for androgen receptor are actually fairly complex and they involve epithelial mesenchymal interactions. Androgen receptor is actually required in the urogenital mesenchyme for prostate formation. If you delete androgen receptor in the urogenital mesenchyme here in a TFM una testicular feminize mutant. And you perform a tissue recombination assay as was first shown through. The studies of Jerry Kunia about four decades ago now the prostate will not form. However, if you delete androgen receptor in the
epithelium now you will form a prostate.

However, the prostate is not entirely normal. For example, it lacks secretory protein production.

So what are the cell types that are found in the normal adult prostate? Well in both the mouse and the human there’s an array of different cell types in both the epithelium and in the stroma that are just now really being able of being characterized in some detail, but historically we’ve considered the epithelium as containing three basic cell types.

There are the luminal cells which are the tall columnar secretory cells.
That produce the prostate secretions.

There’s an underlying layer of basal cells.

These cells are androgen receptor low or negative,

and express basolateral cytokeratins unlike the luminal cells,

which are high and expressed lumenal cytokeratins.

And then there is a rare third type known as neuroendocrine cells.

These have been very understudied and

I’ll touch upon these later in my talk.

So this is sort of the way we thought

about the prostate epithelium for

many years now, and classically,
bassll cells have always considered have
been considered to be more interesting.
They appear to have more stemlike
properties or does lumenal cells have
been considered to be somewhat boring,
but I think you know for many years
we've thought that lumenal cells are actually the interesting cells.
And now with the advent of single
cell analysis, we see that there's considerable complexity.
In the lumenal population.
So what do bassll cells do?
Well, we believe that there is sort of.
A conserved ancestral role for bassll
cells and that's in wound repair.
So here, for example, in the prostate.

If we damage the luminal cells by deletion of idcat and the basal cells will slough off.

And undergo a notice and the basal cells will actually differentiate into luminal cells to replace the loss luminal cells.

So this is shown in cartoon form here.

So there’s sort of a basal to luminal differentiation that takes place, so we think that this is a conserved function of basal cells in many tissues, and more recently,
work from Cedric Web Con Slab has

What about luminal cells?

Well, luminal cells, as I mentioned,

but in fact,

in ex vivo assays at least one

could see that there are luminal

and generate

organoids that are wholly composed

wholly derived from luminal cells,

then we can see that there are basil cells

that can be formed in these organoids,

and these basil cells are marked.
Indicating their lumenal origin. So of course this is an ex vivo assay and ex vivo cells often display more plasticity than is found in during normal development, and certainly in. Normal context luminal cells are usually impotent, but we think that normal developmental processes, among other things or, can be constrained by the microenvironment and ex vivo assays such as organoid formation can reveal developmental potential that can...
be displayed in specific contexts.

So for example, we think that the ability of luminal cells to display by potency occurs early in organic Genesis. So this is sort of a linear hierarchy as is currently understood, in which there are by potent basil progenitors generating both basal and luminal cells during organic Genesis. But. Luminal progenitors were generally thought of unipotent, but in recent studies we found that in
there is a BI potent luminal progenitor, so if we lineages mark luminal cells. At early postnatal stages using an inducible CK 8 driver, we can then mark luminal cells and then analyzed later. Luminal cells are marked, but also basil cells, and it’s a reasonable fraction of basal cells that are marked, and this by potent progenitor, is fairly short lived. It’s fairly transient, but it can still be detected at a week after birth, but again,
the ability of this by potent progenitor
NOTE Confidence: 0.8089924
quickly disappears thereafter.
NOTE Confidence: 0.8089924
So interesting, Lee,
NOTE Confidence: 0.8089924
both the by potent basil progenitor and
NOTE Confidence: 0.8089924
this by potent luminal progenitor do
NOTE Confidence: 0.8089924
not require androgen receptor function,
NOTE Confidence: 0.8089924
so if we delete androgen receptor.
NOTE Confidence: 0.8089924
In basil cells,
NOTE Confidence: 0.8089924
we find that there’s no effect on
NOTE Confidence: 0.8089924
the formation of luminal cells,
NOTE Confidence: 0.8089924
and similarly if we delete a
NOTE Confidence: 0.8089924
are in the luminal cells,
NOTE Confidence: 0.8089924
we don’t see any effect on the
NOTE Confidence: 0.8089924
generation of basil cells.
NOTE Confidence: 0.8089924
So in cartoon form then what we
NOTE Confidence: 0.8089924
think is going on is that there is
a urogenital epithelial progenitor that gives rise to both basal and luminal progenitors, and initially the basal progenitor can be as potent as well as the luminal progenitor. But that this potency is fairly transient, and then in adulthood both luminal and basal progenitors are generally unipotent. However, this period of potency is actually occurring in the first four weeks after birth, and interestingly, this is a time when androgen levels are very low.
At these pre pubertal stages. Now there is one other interesting aspect of luminal cells, which is that in a series of studies we’ve shown that they are favored as cells of origin for prostate cancer, so we’ve shown this in a number of different transgenic mouse models, as well as a hormonal carcinogenesis model. If we mark Basil cells in these models, for example in the hymec model or a tramp transgenic models of prostate cancer, the basal cells are marked. But they don’t really contribute to tumors. However, we mark Lumenal cells now they
NOTE Confidence: 0.79517823
00:14:50.098 --> 00:14:52.560 readily contribute to tumor formation.
NOTE Confidence: 0.79517823
00:14:52.560 --> 00:14:55.656 So. What we think is going on then
NOTE Confidence: 0.79517823
00:14:55.656 --> 00:14:58.830 is that if we mark luminal cells,
NOTE Confidence: 0.79517823
00:14:58.830 --> 00:15:00.318 they will contribute tumors,
NOTE Confidence: 0.79517823
00:15:00.318 --> 00:15:02.918 and this argues that luminal cells are
NOTE Confidence: 0.79517823
00:15:02.918 --> 00:15:05.039 a cell of origin for prostate cancer.
NOTE Confidence: 0.79517823
00:15:05.040 --> 00:15:06.770 If we mark Basil cells,
NOTE Confidence: 0.79517823
00:15:06.770 --> 00:15:08.490 they don’t contribute to tumors.
NOTE Confidence: 0.79517823
00:15:08.490 --> 00:15:10.560 However, if you explant these cells,
NOTE Confidence: 0.79517823
00:15:10.560 --> 00:15:11.188 they will.
NOTE Confidence: 0.79517823
00:15:11.188 --> 00:15:14.360 You know in this sort of ex vivo context.
NOTE Confidence: 0.79517823
00:15:14.360 --> 00:15:16.334 For example, in a graft undergo a
NOTE Confidence: 0.79517823
00:15:16.334 --> 00:15:18.150 basil to luminal differentiation,
NOTE Confidence: 0.79517823
00:15:18.150 --> 00:15:20.220 and now they can form tumors.
NOTE Confidence: 0.79517823
00:15:20.220 --> 00:15:22.980 So we consider basal cells to be a
NOTE Confidence: 0.79517823
celeb mutation, whereas luminal cells. Are the true cell of origin. And again, we've analyzed this in multiple mouse models of prostate cancer. So because we've observed the same result every time, we think that luminal cells are generally favored as a cell of origin. So we now have this view that luminal cells are generally favored as a cell of origin. We now have this view that luminal cells are generally favored as a cell of origin. So cells are in fact quite interesting, so recently we decided to explore the heterogeneity of the prostate epithelium using single cell approaches. For this we had to really learn how to
dissect the mouse prostate properly.

You might think that’s a bit of an over some bug, an exaggeration, considering we’ve been studying the prostate for over 20 years, but in fact it’s really not a trivial matter of two. Dissect the individual mouse lobes all the way down to their junction with the urethra. This is actually in a green mouse, so you can see the lobes that are dissected. And then we subjected these two.
single cell RNA sequencing both the whole prostate as well as the individual lobes to analyze. We collaborated with Roll Rabadan’s lab, and Raul has developed amazing algorithms that are based upon rather sophisticated mathematical approaches for analyzing single cell data. His laboratory has developed approaches based upon random matrix theory, which demonstrate that these large arrays of data, for example as one generates using single cell RNA sequencing, are mostly noise.
so.
If you consider.
These as giant matrices,
well in fact the distribution of
eigenvalues follows a sort of conserved
mathematical distribution known as
the Marchenko Pastur distribution,
and the deviation for this distribution
is actually where the signal is,
and typically it’s only
about 2 to 3% of the data.
So this is a hypothetical distribution.
This is actually real data.
This is one of our prostate datasets.
And again, here is the signal,
so his laboratory is developed randomly,

an algorithm to isolate these data.

And this proved to be very useful in our analysis,

because it allowed us to identify a cell population that would have been very difficult to identify other ways.

So when we examine an aggregated data set of whole prostate, we observe.

Five different lumenal populations.

First of all,

we only identify one Basil population.

So basil cells are actually not heterogeneous,

but instead there’s heterogeneity

in the lumenal population.
So, first of all, there's four distinct luminal populations that correspond to the populations that are located distally in each prostate lobe and distally in the anterior prostate. Then there is a population that we call Luminal. It is similar in all four lobes and is found more approximately. Finally, there is a population that we call Paraurethral.
This population has both basal and luminal properties, and it is found in the region most adjacent to the urethra. So these are the distinct epithelial properties that we’ve identified. We’ve also identified heterogeneity in the stroma, but I won’t speak to that further. So, as you can note from this sort of illustration, there is diversity along the proximal distal axis. So to give you an idea of what we mean by proximal and distal axis,
Here's an anterior prostate that's been sort of splayed out and cut in histological section when we refer to distal, we're actually referring to this whole region here. That is more than 90% of the volume of the prostate. The proximal region is just this region here. These regions are quite distinct at the level of marker expression as well as. Histology, so here if we go along the proximal distal axis, we have the paraurethral region has specific markers.
Here is the proximal region. It has a distinct Histology and is marked by specific gene expression of specific genes such as this one. PPP, one R1B. Then we have in the distal region other markers that are specific for distal luminal cells. The lume population here, but you will note there are also proxamol cells that are scattered about. They’re not very common, but you can definitely find them in the distal region and then in between. There appears to be a boundary where these regions meet.
If you perform electron micrography of the boundary region, you can see that. These lumit lumayan lumpi cells actually appear to be distinct cell types, so the lume cells again are tall columnar secretory cells. The loopy cells, on the other hand, have a more cuboidal appearance, and they don’t seem to be particularly secretory. At the transcriptomic level, you can analyze the sort of relationships of these populations with each other.
So Luis Aparicio, postdoc INR Lab, who's done these computational analysis, has used. An approach based upon optimal transport theory to calculate Wasserstein distances between these populations, and then relate these populations to each other. You can see that Lumpi is sort of, you know, sort of at the center related to the distal lumenal populations, and then PR you and basil. So in order to investigate the function of these populations, we've observed that there is greater...
00:22:10.018 --> 00:22:12.560 projector potential in the loom PPR.
NOTE Confidence: 0.8025036
00:22:12.560 --> 00:22:14.735 You and basil populations versus
NOTE Confidence: 0.8025036
NOTE Confidence: 0.8025036
NOTE Confidence: 0.8025036
00:22:19.100 --> 00:22:22.285 You can see that the distal luminal
NOTE Confidence: 0.8025036
00:22:22.285 --> 00:22:25.021 populations all have a low efficiency
NOTE Confidence: 0.8025036
00:22:25.021 --> 00:22:28.031 of formation of organoids lumpi as a
NOTE Confidence: 0.8025036
00:22:28.118 --> 00:22:30.960 much greater efficiency and PR you in
NOTE Confidence: 0.8025036
00:22:30.960 --> 00:22:34.670 Basel have a greater efficiency yet.
NOTE Confidence: 0.8025036
00:22:34.670 --> 00:22:36.935 We’ve also isolated these populations
NOTE Confidence: 0.8025036
00:22:36.935 --> 00:22:39.763 by flow cytometry and performed renal
NOTE Confidence: 0.8025036
00:22:39.763 --> 00:22:42.208 grafting assays so in combination
NOTE Confidence: 0.8025036
00:22:42.208 --> 00:22:43.675 with urogenital mesenchyme,
NOTE Confidence: 0.8025036
00:22:43.680 --> 00:22:45.996 these cells were formed renal grafts
NOTE Confidence: 0.8025036
00:22:45.996 --> 00:22:49.360 all be it with different efficiencies,
NOTE Confidence: 0.8025036

36
and then we can analyze the sort of cell types present within these graphs.

So using the markers that we've identified that is specific for each population. In brief, the loom a another distal luminal. Cells can make more of themselves, but not the loom PNP Ru populations, where is the loom PNP? Ru populations can make all of the other different populations, so this supports a sort of a projector. Increased progenitor potential for loom PNP RU populations.

So finally one can ask what is the relationship between
the mouse and human prostate?

After all, anatomically they are quite different and histologically as well, so we've analyzed three independent benign prostatectomy specimens at the single cell level, and again, we can see that there is a single basal population, but they're different lumenal populations that we can relate to. The lumenal populations that we see in the mouse, so there isn't a snare population.
00:23:57.714 --> 00:24:00.235 that seems more closely related to
NOTE Confidence: 0.8025036
00:24:00.235 --> 00:24:02.099 the distal lumenal populations.
NOTE Confidence: 0.8025036
00:24:02.100 --> 00:24:04.180 A ductal populations more proxamol,
NOTE Confidence: 0.8025036
00:24:04.180 --> 00:24:08.156 as well as a PR you like population.
NOTE Confidence: 0.8025036
00:24:08.160 --> 00:24:08.666 Again,
NOTE Confidence: 0.8025036
00:24:08.666 --> 00:24:11.196 using analysis of Wasserstein distances,
NOTE Confidence: 0.8025036
00:24:11.200 --> 00:24:14.384 this time in across species way we can
NOTE Confidence: 0.8025036
00:24:14.384 --> 00:24:18.279 we can definitely show this relationship.
NOTE Confidence: 0.8025036
00:24:18.280 --> 00:24:21.815 So the acinar cells are actually interesting.
NOTE Confidence: 0.8025036
00:24:21.820 --> 00:24:24.260 Lee most closely related to
NOTE Confidence: 0.8025036
00:24:24.260 --> 00:24:27.390 lumenal L cells in the mouse,
NOTE Confidence: 0.8025036
00:24:27.390 --> 00:24:29.920 the ductal cells to loom
NOTE Confidence: 0.8025036
00:24:29.920 --> 00:24:32.450 P&PRU 2P RU in Bloom,
NOTE Confidence: 0.8025036
00:24:32.450 --> 00:24:33.392 P, etc.
NOTE Confidence: 0.8025036
00:24:33.392 --> 00:24:36.689 So this analysis highlights loom L as
NOTE Confidence: 0.8025036
00:24:36.689 --> 00:24:40.879 a population of interest in the mouse.
It perhaps is most closely related to the bulk of the human prostate epithelium. Yet the lateral lobe is understudied in the mouse, and particularly analysis of cancer models. So now I’d like to turn to cancer a little bit and think about plasticity in advanced prostate cancer. So in the current spectrum of prostate cancer where we have. Treatment of with potent anti androgens that are very efficient at suppressing energon receptor function. Now, castration resistant prostate cancer is
displaying a range of different entities. As sort of a spectrum that can be
distinguished perhaps by different differential lineages, plasticity.
So there is prostate cancer that is remains a our pathway positive it
still expresses androgen receptor despite the presence of anti androgens.
And then at the other extreme we have neuroendocrine prostate
cancer which is a are negative and.
He’s most extreme forms can display a small cell phenotype that’s
very aggressive and lethal,
so there’s been considerable interest in the mechanisms of neuroendocrine
differentiation in CR, PC, and so.

There have been studies of CR PC that are trying to distinguish the different entities, and, for example, there is something considered double negative. That is a are negative and neuroendocrine negative, which is defined more by what it is not rather than what it is, but the relationships between these. Distinct entities is unclear, and it may be simple, maybe more complex. But there is widespread agreement that there must be a role for epigenetic reprogramming in this process, and so.
A range of studies have provided evidence that there's an increase in ezh two as PRC. Two activity in this spectrum of plasticity and recently flybot. John Cody’s lab has shown that PRC activity is elevated in double negative prostate cancer etc. But this is all involved studies either in cell lines or in human prostate cancer specimens, so it’s been difficult to sort. You know at a more detailed level and in terms of mechanism as well. So to approach this, we started with a mouse model that we...
had been analyzing in collaboration with Korea Body Schenz lab. So the NPP 53 mouse model uses inducible deletion of P-10 and P53. Of these animals develop a castration resistant prostate cancer that will. Display features of neuroendocrine differentiation and we were able to distinguish what we called focal neuroendocrine differentiation in which the neuroendocrine cells are not proliferative from overt nor endocrine differentiation which often displays a small cell phenotype. These are highly proliferative.
or endocrine cells.

However, since we use lineages marking here, we could show that the neuroendocrine cells are derived from a luminal cell, so the initial.

Tumor induction was from luminal cells and then we have.

Alright, formation of CR PC neuroendocrine differentiation and then there is some type of proliferative switch that we don’t understand that results in this highly proliferative neuroendocrine prostate cancer.

So because we use linear tracing here, we provided evidence that in fact
this was a transdifferentiation of luminal cells to neuron can cells. So when we think about transdifferentiation, there’s sort of a fundamental question both in developmental as well as cancer context, which is what is really going on in terms of the pathways that result in transdifferentiation. Well, it’s possible that this change in identity occurs through a transition that happens normally during development. Alternatively, it’s possible that this change
in identity occurs through a transition that is wholly or at least partially novel that doesn’t really occur in normal development, so there could be a hijacking of an alternative pathway or some other pathway or process that doesn’t occur in normal context. To understand this, of course it is first of all important to discover how neuroendocrine cells differentiate normally. It’s remarkable that there’s very little in the published literature about. Origin in fact,
features of neuroendocrine cells in the normal prostate, enlarged likely because they are quite rare and what is also interesting is that there are different models have been put forth for their origin. So one model says that they actually are of epithelial origin and arise from Basel progenitors. Another model is that they arise from neural Crest and so Cedric Pompons lab published. That they came from basil cells and a more recent paper. From that they’re from their old Crest in both these papers use linear tracing.
In fact, we believe that both of these papers are incorrect and most likely they arise from an early urogenital epithelial progenitor. So neuroendocrine cells are very rare. But what is make some particularly in the mouse, prostate is they’re highly asymmetrically distributed, so nearly all the owner can cells are proximal. They’re very rare distally. And remarkably, neuroendocrine cells, despite their rarity, are heterogeneous.
So about 80% of neuron can cells have adluminal like phenotype. They actually express androgen receptor remarkably and they express luminal cytokeratins and then another 20% of your endocrine cells are basil like they expressed basal cytokeratins and P. They can be detected very early in organic Genesis at burn. Many, most perhaps all Durand Prince cells are actually formed at prepubertal stages, and since neuroendocrine cells I didn’t mention this on previous slide are. But never divide there.
They appear to be post mitotic. We believe that they are made and are not subsequently generated. By lineages tracing, we believe that they have an epithelial origin, so using an NCX Cree driver we can mark most of the prostate epithelial cells and in fact the vast majority of neuroendocrine cells are marked by NCX Creek, so we believe they have a prostate epithelial origin. So there's more than 95% of the neuroendocrine cells are marked in this experiment.
as has been shown in the lung through a pro neural pathway, in which sort of the master regulator at the top of of this of the sort of transcription factor hierarchy is ASE L1. So if we delete ACL one in the mouse prostate, we can actually recover mice that have prostates that completely lack your endocrine cells. And yet the prostate appears to be normal and there is a normal proximal region. So we do have a rare escaper cells in the Periorbital region which are likely due to incomplete deletion by index 3.1.
So our current model for the origin of your endocrine cells is that they likely arise from your original epithelial progenitor, although we haven’t excluded the possibility they arise from an early lumenal progenitor. But in either case progenitor activity coincides with the developmental stages in which androgen levels are very low, and we’re currently studying. The molecular properties of normal neuroendocrine cells. To understand you know in more detail their regulation.
we’ve used the NP 53 mouse model to generate organoid lines that displayed neuroendocrine phenotypes so. This is work from a talented postdoc in my lab, Jolly. She has used NP 53 tumors and established a large number of organoids, some of which have neuroendocrine features. As you can see here, this is the sort of primary tumor, and you’ll note that it’s heterogeneous. These are the organoids are established there, green because of the linear smirking. Here’s a different line that you can
00:34:44.365 --> 00:34:47.409 see the region of small cell Histology.
NOTE Confidence: 0.7690831
00:34:47.410 --> 00:34:49.440 And these organoids are heterogeneous.
NOTE Confidence: 0.7690831
00:34:49.440 --> 00:34:52.520 You can see that they have a
NOTE Confidence: 0.7690831
00:34:52.520 --> 00:34:54.246 neuroendocrine region as well
NOTE Confidence: 0.7690831
00:34:54.246 --> 00:34:56.725 as a non ***** can region that
NOTE Confidence: 0.7690831
00:34:56.725 --> 00:34:58.345 is mesenchymal in nature.
NOTE Confidence: 0.7690831
00:34:58.350 --> 00:35:00.780 So this can be more clearly
NOTE Confidence: 0.7690831
00:35:00.780 --> 00:35:02.400 revealed by marker analysis.
NOTE Confidence: 0.7690831
00:35:02.400 --> 00:35:05.228 It expresses Synaptophysin and Chromogranin
NOTE Confidence: 0.7690831
00:35:05.230 --> 00:35:07.235 a so it has a neuroendocrine phenotype.
NOTE Confidence: 0.7690831
00:35:07.235 --> 00:35:11.080 Here’s a different line that is more
NOTE Confidence: 0.7690831
00:35:11.080 --> 00:35:13.929 heterogeneous there that has sort of
NOTE Confidence: 0.7690831
00:35:13.929 --> 00:35:16.464 mixed expression of neuroendocrine
NOTE Confidence: 0.7690831
00:35:16.464 --> 00:35:20.900 markers as well as androgen receptors.
To some extent, it actually has a double positive or African phenotype. This is a heterogeneous line that I showed you earlier, so it has intermixing of neuroendocrine cells and non endocrine cells that express androgen receptor. Here is a different heterogeneous line again with a similar intermingling. So these new rendering lines, whether homogeneous or heterogeneous or highly stable during passaging, they can be passaged for.
more than 20 passages, and the heterogeneous lines will maintain their heterogeneity.

So we can analyze the heterogeneity using single cell RNA sequencing and so this is the first line I showed you, Interestingly the clusters are sort of grouped together, and we see a similar arrangement of clusters. And this is this is the other heterogeneous line, and we see a similar arrangement of clusters.

So the heterogeneity of these organize is striking because it suggests that we’ve been able to capture
much of the spectrum of CR PC within organoids established organoid lines.

So what can we do with these organoid lines? We can examine, you know, sort of the epigenetic marks that are displayed in these organoid lines. For example, we've been pursuing cut and tag analysis here, looking at H3K27 trimethyl.

What's interesting here is that this is the mark deposited by PRC 2.
00:37:11.815 --> 00:37:13.627 actually the non neuroendocrine
NOTE Confidence: 0.84401006
00:37:13.627 --> 00:37:16.114 lines appear to be have a somewhat
NOTE Confidence: 0.84401006
00:37:16.114 --> 00:37:18.019 higher level of H3K27 trimethyl
NOTE Confidence: 0.84401006
00:37:18.019 --> 00:37:20.119 than the neuroendocrine lines.
NOTE Confidence: 0.84401006
00:37:20.120 --> 00:37:22.670 So that’s something interesting that
NOTE Confidence: 0.84401006
00:37:22.670 --> 00:37:25.530 we are currently following up on.
NOTE Confidence: 0.84401006
00:37:25.530 --> 00:37:28.162 We’ve also been collaborating
NOTE Confidence: 0.84401006
00:37:28.162 --> 00:37:30.794 with Andrea Califano’s laboratory.
NOTE Confidence: 0.84401006
00:37:30.800 --> 00:37:33.716 Which has developed a set of
NOTE Confidence: 0.84401006
00:37:33.716 --> 00:37:35.174 computational systems approaches
NOTE Confidence: 0.84401006
00:37:35.174 --> 00:37:37.658 to identify master regulators
NOTE Confidence: 0.84401006
00:37:37.658 --> 00:37:40.218 that drive biological processes,
NOTE Confidence: 0.84401006
00:37:40.220 --> 00:37:45.624 and so one of the sort of.
NOTE Confidence: 0.84401006
00:37:45.630 --> 00:37:47.354 Analytical approaches that they’ve
NOTE Confidence: 0.84401006
00:37:47.354 --> 00:37:49.940 developed is known as Meta Viper,
NOTE Confidence: 0.84401006
00:37:49.940 --> 00:37:52.376 where we can take single cell
NOTE Confidence: 0.84401006
00:37:52.376 --> 00:37:54.519 RNA sequencing data and analyze
NOTE Confidence: 0.84401006
00:37:54.519 --> 00:37:56.704 this to infer protein activity
NOTE Confidence: 0.84401006
00:37:56.704 --> 00:37:58.990 at the single cell level.
NOTE Confidence: 0.84401006
00:37:58.990 --> 00:38:02.147 So Alessandro Vasi Evo in Andre’s lab
NOTE Confidence: 0.84401006
00:38:02.147 --> 00:38:05.028 postdoc in Andre’s lab has done this,
NOTE Confidence: 0.84401006
00:38:05.030 --> 00:38:07.352 and again using the same organoid
NOTE Confidence: 0.84401006
00:38:07.352 --> 00:38:09.958 line as I showed you earlier
NOTE Confidence: 0.84401006
00:38:09.958 --> 00:38:11.918 here by protein inference,
NOTE Confidence: 0.84401006
00:38:11.920 --> 00:38:14.937 we can see again clustering of ARPU.
NOTE Confidence: 0.84401006
00:38:14.940 --> 00:38:17.860 See any PC and NPC.
NOTE Confidence: 0.84401006
00:38:17.860 --> 00:38:24.400 The the RPC cluster is elevated.
NOTE Confidence: 0.84401006
00:38:24.400 --> 00:38:27.190 Using an androgen receptor signal is
NOTE Confidence: 0.84401006
00:38:27.190 --> 00:38:29.547 is enriched for androgen receptor
NOTE Confidence: 0.84401006
00:38:29.547 --> 00:38:32.061 signature the any PC cluster is
NOTE Confidence: 0.84401006
00:38:32.061 --> 00:38:34.497 enriched for a neuroendocrine signature
NOTE Confidence: 0.84401006
and when we can predict master regulators using this sort of approach.

Notably one of the newer endocrine master regulators that’s predicted is ACL one.

This is a method that we’re employing to identify candidate intrinsic drivers of neuroendocrine differentiation that we’re currently seeking to validate in functional assets.

One of the sort of interesting questions we can ask is does trans differentiation occur at some level in organoid cultures and we have some evidence that that it might
one way that we’ve been looking at this is using single cell a tax seek to examine chromatin Accessibility, and we can see that this is the same line again by single cell, a taxi there, seven clusters, these clusters are. Have open chromatin at chromogranin. A neuron can marker these in a R and what you can see is that there is one cluster here that has open chromatin for both. Chrome Grande are you can see this more readily. Looking at the genomic locus so this cluster seven has accessible chromatin.
at both chromogranin, A&AR and so.

This cluster, we believe, corresponds to a potential transitional population in the process of neuroendocrine differentiation. We’ve also been trying to assay this directly, so this is very preliminary data, but we can isolate non endocrine cells by flow cytometry. Mark them with expression of RFP and then culture than honor in cells, and neurons can sell separately for several passages and they maintain their non **** couldn’t border and can phenotypes if we coculture them together.
However, we now see their rare cells that our RFP positive. But now express neuron could markers such as synaptophysin or Chromogranin A and interesting Lee. They maintain the expression of the Menton. So these appear to be a transitional cell, since phenotype seemingly corresponds to the what the a taxi might predict. OK, so these are some of the approaches that we’ve been employing to study language plasticity in prostate cancer. In the remaining 10 minutes or so,
I’d like to switch over to bladder cancer and explain how we’ve been using organize to study plasticity in bladder cancer. So bladder cancer. Is of course a major health problem. It’s quite understudied. The normal bladder contains again sort of three epithelial cell types, as it were basil cells, intermediate cells, and umbrella cells, and bladder cancer can be roughly divided into non muscle invasive and muscle invasive disease. Historically,
these have been considered to be almost distinct entities, and it’s unclear what the relationship actually is. There are two forms of non muscle invasive bladder cancer, papillary and carcinoma insight, two and carcinoma insight two has been considered to be sort of the precursor to muscle invasive disease. However, there is also some evidence that papillary disease can progress to muscle invasive disease, so we’ve been interested in studying.
progression of bladder cancer and.
To pursue this, we’ve actually established patient derived bladder tumor organoids, and these have been established through collaboration with urologists who perform transurethral resection’s. So what they do is they sort of go in and extract, sort of like the tops of these tumors here. This is what they actually view through the cystoscope. This might look a little uncomfortable for men in the audience, but.
take these samples and we can establish organoid lines in culture, which we can seriously passage. These organoids can also be grafted. This orthotopic grafting it uses ultrasound guided implantation into the bladder wall which is a very efficient process so we can readily interconvert organoids into Xena graphs. We can also take the Xeno grafts and convert them back to organoids, so all of these. Together with the parental tumor can be analyzed by sequencing or histopathology etc. So this just shows you some of the organoid
lines that we established and what is, I think, evident is that the organoids and the Xeno grafts retained the characteristic histology of the parental tumor. We also can establish organoid lines that have less common histological variants, such as squamous cell carcinoma. In recent unpublished work, we’ve now increased our bio bank to approximately 50 organoid lines. We’ve been able to establish organized lines from cystectomy samples, as well as from transferring for receptions, and have also a stab Liszt several lines that contain variant histologies.
So in collaboration with David Solids Group at Memorial Sloan, Kettering Owen, the previous pathology was in collaborate with collaboration with him at all Media Memorial. We’ve analyzed these organoid lines molecularly using the targeted sequencing platform at Memorial MSK impact. We sequenced the organoids parental tumor and normal bloods and we can show generally that the organoids. Display mutational profiles that are concordant with that of the parental tumor. We can examine.
Sort of the mutational profiles of these organoid lines, which really recapitulates sort of the distribution of mutations in human bladder cancer. So we can see that among the common mutations we see mutations in a lot of epigenetic regulators which are frequently mutated in bladder cancer such as KDM 6A, KMT 2C and 2D. As well as ERR2A. Interestingly, we also see we were able to capture mutations that are relatively rare but interesting in bladder cancer, such as mutations and ERB B2 and of note we have very few mutations in RB.
so many bladder cancer cell lines were established from metastatic bladder cancer and contain RB mutations, whereas organoids are generally established from non-muscle invasive bladder cancer or earlier stages of muscle. Invasive disease and lack RB mutations. So what can we do with these organoid lines? One thing we can do is we can examine their drug response, and of particular interest were able to establish organoid lines from patients in a longitudinal fashion. So patients will often undergo
transurethral resection, be treated, and then sometime thereafter, their tumors will unfortunately recur. And then we have an opportunity to establish another organoid line. So here’s an example of a patient. And a pair of organoid lines where patient was not otherwise treated. So the tumor was removed, but the patient was not otherwise treated, and we can see in in terms of response to a range of different drugs that Interestingly, the organoid lines display nearly overlapping drug response profiles. However,
In this case, the different patient was treated with Mitomycin C and BCG. The tumor relapsed after over a year, and now the recurrent organoid line is much more resistant to a range of different drugs. However, displays similar responses to other drugs, so. It’s of interest to us to understand how. Drug response has altered the properties of these organoids. So one thing we’ve started to do is to perform single cell analysis here of this recurrent pair, and Interestingly,
the recurrent organoid line is actually much more heterogeneous than the sort of the parental of the order online from the parental tumor. And what is interesting is if you re aggregate these together now you can identify a cluster that is actually in common between both the between the 1st and the 2nd organoid lines so. This cluster, we believe, corresponds to a transitional population and we can identify markers that are specific for this transitional population, so our hope here is that we can use...
utilized this pair of organoid lines and other examples of recurrent disease that we have to sort of replay in organoid culture. The events that take place during the emergence of treatment. Resistance. So finally I’d like to address the issue of tumor progression in organoid, so non muscle invasive disease you know can be classified into two lumenal categories as well as a basil category. Muscle invasive disease is more complex and again as I mentioned earlier, the relationship between these.
entities has been somewhat unclear. However, there is a question of whether you know if we have progression, whether there might be a switch and subtype specifically.

From sort of Class 2 luminal tumors to Basel to a basal squamous muscle invasive tumor. So we believe that we can recapitulate this in organoid culture. So many of our organoid lines are phenotypic least able and culture. If you look at different markers there stable and organoids as organoid Xena, graphs ansina graph derived graphs and organoids however. Sort of a little over a
00:49:28.500 --> 00:49:30.490 majority of the organoids from.
00:49:30.490 --> 00:49:32.590 Non muscle invasive tumors displayed
00:49:32.590 --> 00:49:34.690 this sort of phenotypic plasticity.
00:49:34.690 --> 00:49:37.690 This is a they start with the luminal
00:49:37.690 --> 00:49:39.934 phenotype here and they become
00:49:39.934 --> 00:49:41.830 basil during organoid culture.
00:49:41.830 --> 00:49:44.350 But notably this phenotype can be
00:49:44.350 --> 00:49:46.030 largely reversed by xenografting,
00:49:46.030 --> 00:49:48.368 so we believe this there’s an effect
00:49:48.368 --> 00:49:50.441 of the tumor micro environment
00:49:50.441 --> 00:49:54.429 that can repress this basil to
00:49:54.429 --> 00:49:55.425 luminal differentiation.
00:49:54.430 --> 00:49:57.542 In fact can reverse it but if we
00:49:57.542 --> 00:50:00.409 remove the tumors again from the.
00:50:00.410 --> 00:50:03.406 In a graph and culture miss organoids,
they will again undergo the space little differentiation.

So John Kristen Terrific Post Document Lab has pursued a small molecule screen to examine organoid lines that display plasticity to see if it’s possible to revert it, and he identified one big hit here GSK. Else one, which is a KTM one inhibitor and it is able to partially revert this plasticity, so the.

I’m not showing this here, but if he knocks out KTM one day, he can also see this effect. So.

He is currently investigating
the mechanisms by which KTM 1A regulates this transition.

In parallel, he’s also been pursuing a taxi. Can Alesis to examine sort of the epigenetic States and eventually the epigenetic marks that are associated with this plasticity. So if you examine, for example, these three organoid lines, this is adluminal line. This is a basil line and this is what we call a plastic line. The plastic line looks like a basil line, although it started with a luminal phenotype. So we’ve performed a taxi.
Can Alesis and we can cluster these so you see that the lumenal lines clustered together. The basil lines clustered together and these are the plastic lines which in the first principle component cluster together with basil. But they’re separated along the second principle component. So now if we look at, you know, sort of genomic tracks, you can see that at basil markers such as keratin 14, the basil lines of course have open chromatin and the plastic lines also have open chromatin, which of course is to be expected.
because they have a basal phenotype.

But what’s interesting is that lumenal markers.

Such as gotta three.

We see that the plastic organoid lines seem to have partially open chromatin,

so they retain an epigenetic memory of their lumenal origin.

So we are currently pursuing studies to determine whether we can actually detect this epigenetic memory in human prostate tumors,

which might indicate.

A specific pacifically base of the basal squamous category to determine
whether they may have in fact originated from more lumenal tumor. Finally, we’re also pursuing motif discovery approaches to identify candidate transcription factors that might be driving this transition, and we’re coupling this with other computational approaches. We think that this really is modeling something that’s happening during, you know. Sort of transition to muscle invasive disease because. As has been noted in breast cancer for Andy Walt, what we’ve found is at the at the invasive front of these tumors.
Now we see the expression of a basal marker cytokeratin 14 at the invasive front, but this is not expressed within the tumor body. So in closing, then I’d like to underscore that we think these organoids represent a model system for studying tumor plasticity. So we can identify transitional populations in patients in order rates from patients with recurrent disease, and we think that the sort of plasticity we’re studying culture can reflect processings of disease progression in vivo, and we’re using computational...
A systems approach is to identify the drivers of plasticity. And more generally, we believe that organoid models are incredibly useful because they will allow mechanistic studies of complex questions in cancer biology that may be inaccessible. Of course, the work that I’ve described involved large team of terrific scientists really did all the work. So notably, Laura Crowley is a graduate student who led the single cell.
analysis of the prostate epithelium together with Francesco Comma, Boolean, former postdoc Moshe Botton, now at George Washington University. The work on normal neuroendocrine differentiation was performed by graduate student gave alone. Jolly a terrific postdoc in the lab. Then former lab members soup soup. Lee started the bladder organized. John Kristen is a current post Doc who’s played a major role in continuing this project. We’ve had terrific collaborators.
Roll Rabadan Andrea Califano for computational systems biology.

Jim McKiernan, whole team of talented urologists who provided samples.

We've collaborated with Korea Body Shen, in analysis of Mouse models, which how Lewin, epigenetic analysis.

Need help search for pathology as well as Max load at Cornell.

For pathological analysis and a great group of collaborators at Memorial Sloan Kettering.

David Solid Hickman to Marty and Barry Taylor.

So thank you very much and I'll
00:56:01.846 --> 00:56:03.980 be happy to take any questions.

NOTE Confidence: 0.83516306

00:56:05.490 --> 00:56:07.270 Thank you very much, Michael.

NOTE Confidence: 0.91066235

00:56:07.270 --> 00:56:09.734 That was a wonderful talk and really

NOTE Confidence: 0.91066235

00:56:09.734 --> 00:56:12.273 amazing to see all of these models

NOTE Confidence: 0.91066235

00:56:12.273 --> 00:56:14.385 and everything that can be done

NOTE Confidence: 0.91066235

00:56:14.390 --> 00:56:16.810 with all of these different models.

NOTE Confidence: 0.91066235

00:56:16.810 --> 00:56:19.960 I would like to remind the audience

NOTE Confidence: 0.91066235

00:56:20.040 --> 00:56:22.146 that they can type questions in

NOTE Confidence: 0.91066235

00:56:22.146 --> 00:56:24.720 the chat and I will read them

NOTE Confidence: 0.91066235

00:56:24.720 --> 00:56:26.904 out and ask them to Michael.

NOTE Confidence: 0.91066235

00:56:26.910 --> 00:56:29.718 I will get started

NOTE Confidence: 0.91066235

00:56:29.718 --> 00:56:31.590 with a question Michael.

NOTE Confidence: 0.91066235

00:56:31.590 --> 00:56:34.950 One of the things that you see in

NOTE Confidence: 0.91066235

00:56:34.950 --> 00:56:38.472 the organoids and I was thinking in

NOTE Confidence: 0.91066235

00:56:38.472 --> 00:56:41.062 particular about the prostate cancer

NOTE Confidence: 0.91066235

88
00:56:41.159 --> 00:56:43.841 ones is there’s a the heterogeneity
NOTE Confidence: 0.91066235
00:56:43.841 --> 00:56:46.642 and I was just wondering whether
NOTE Confidence: 0.91066235
00:56:46.642 --> 00:56:49.678 you see shifts in the heterogeneity
NOTE Confidence: 0.91066235
00:56:49.678 --> 00:56:52.936 or of the organoids themselves when
NOTE Confidence: 0.91066235
00:56:52.936 --> 00:56:56.176 you use different types of media.
NOTE Confidence: 0.91066235
00:56:56.180 --> 00:56:59.281 So can you see shifts based on
NOTE Confidence: 0.91066235
00:56:59.281 --> 00:57:01.230 how you grow them?
NOTE Confidence: 0.91066235
00:57:01.230 --> 00:57:04.086 And then I was also wondering whether
NOTE Confidence: 0.91066235
00:57:04.086 --> 00:57:06.864 you have applied certain types of
NOTE Confidence: 0.91066235
00:57:06.864 --> 00:57:09.319 therapies to those prostate cancer
NOTE Confidence: 0.91066235
00:57:09.319 --> 00:57:12.229 organoids and whether you see changes
NOTE Confidence: 0.91066235
00:57:12.229 --> 00:57:14.995 in that heterogeneity and shifts when
NOTE Confidence: 0.91066235
00:57:15.000 --> 00:57:17.748 you when you use different different
NOTE Confidence: 0.8553434
00:57:17.750 --> 00:57:19.130 types of treatments.
NOTE Confidence: 0.8553434
00:57:19.130 --> 00:57:22.486 OK, so Katie, that’s a great question.
NOTE Confidence: 0.8553434
00:57:22.486 --> 00:57:24.462 Well questions so first
question regarding media so.

One of the things that I forgot to mention is that we use our own sort of homegrown media for all of these organoid experiments. This is a complex medium containing hepatocyte media and serum. You know we. Develop this years ago to grow mouse prostate organoids so it’s quite different from the ENR based media that many groups use to pursue organoid assays. You might imagine that some of the
growth factors involved are in common.

There are undoubtedly differences between the media compositions in terms of what’s actually going on.

We know that, anecdotally, it is probably easier to establish patient derived organoids using our media than in our based media.

And we also know that you can transition organoid lines from one media to the other, but it may not be that straightforward.

So we have some experience with DNR based media, but all the analysis that I’ve showed you today were done in our sort of homegrown media.
So do we observe shifts in composition in different media? We have not really examined that. In part because it can be different, it can be difficult to transition organ lines from one medium to another. In terms of drug treatment, we have only started to do this with respect to the prostate organoids. Bladder organizer, something that we’ve been examining in more detail. We’ve been particularly interested in mechanisms of cisplatin resistance, which, of course is of considerable
translational interest.

So those are studies that are currently being pursued to examine how cisplatin treatment alters the phenotype, and perhaps the heterogeneity of the organized, but I don’t have any results yet.

Great, thank you.

There’s a question from Gefsky. Are you been able to analyze human lumenal bladder tumors for plasticity, and correlate those results with subsequent development?
01:00:10.476 --> 01:00:12.500 of muscle invasive tumors?

01:00:14.420 --> 01:00:16.410 So that’s a great question.

01:00:16.410 --> 01:00:18.498 Obviously we want to extend what

01:00:18.498 --> 01:00:20.448 we’ve been doing in organoid

01:00:20.448 --> 01:00:22.780 culture to human specimens, so.

01:00:25.700 --> 01:00:28.220 I have to confess that this work that we’ve

01:00:28.220 --> 01:00:32.798 only recently gotten started, so we don’t.

01:00:32.800 --> 01:00:35.152 Part of the problem is actually

01:00:35.152 --> 01:00:37.282 having a cohort of patients

01:00:37.282 --> 01:00:39.697 that’s suitable for this so.

01:00:39.700 --> 01:00:42.738 Yeah, we are now in the process

01:00:42.738 --> 01:00:45.465 of trying to assemble patient

01:00:45.465 --> 01:00:48.775 cohorts where we can actually.

01:00:48.780 --> 01:00:53.720 Have samples are sort of launch eternal

01:00:53.720 --> 01:00:56.590 from patients who have progressed,

NOTE Confidence: 0.9077339
01:00:56.590 --> 01:00:59.887 say from high grade non muscle invasive
NOTE Confidence: 0.9077339
01:00:59.887 --> 01:01:02.789 disease to muscle invasive disease.
NOTE Confidence: 0.9077339
01:01:02.790 --> 01:01:05.886 Assembling these cohorts is very nontrivial.
NOTE Confidence: 0.9077339
01:01:05.890 --> 01:01:08.778 Fortunately we are part
NOTE Confidence: 0.9077339
01:01:08.778 --> 01:01:11.666 of a large collaboration.
NOTE Confidence: 0.9077339
01:01:11.670 --> 01:01:14.340 Led by Corey Body Shan,
NOTE Confidence: 0.9077339
01:01:14.340 --> 01:01:16.930 together with collaborators at Memorial
NOTE Confidence: 0.9077339
01:01:16.930 --> 01:01:20.210 Sloan Kettering and at Johns Hopkins,
NOTE Confidence: 0.9077339
01:01:20.210 --> 01:01:22.346 so collaborates Atmore Memorial
NOTE Confidence: 0.9077339
01:01:22.346 --> 01:01:25.016 include David Solid and colleagues,
NOTE Confidence: 0.9077339
01:01:25.020 --> 01:01:27.690 as well as you know,
NOTE Confidence: 0.9077339
01:01:27.690 --> 01:01:29.822 people like Jonathan Rosenberg,
NOTE Confidence: 0.9077339
01:01:29.822 --> 01:01:31.960 DeAndre Jordan, Barry Wagner,
NOTE Confidence: 0.9077339
01:01:31.960 --> 01:01:35.170 Bernie Buckner, and at Johns Hopkins.
NOTE Confidence: 0.9077339
01:01:35.170 --> 01:01:37.186 Led by David Mcconkey,
NOTE Confidence: 0.9077339
01:01:37.186 --> 01:01:39.706 Nojan and others to try
01:01:39.706 --> 01:01:42.368 to gather together the.
01:01:42.370 --> 01:01:44.220 Cohorts that are essential to
01:01:44.220 --> 01:01:46.070 address this type of question
01:01:46.134 --> 01:01:48.329 because they don’t currently exist,
01:01:48.330 --> 01:01:51.095 and these types of samples are rare.
01:01:52.640 --> 01:01:55.070 Thank you we have another question
01:01:55.070 --> 01:01:58.228 from Mike Hurwitz who says great talk
01:01:58.228 --> 01:02:00.668 within the different luminal subtypes.
01:02:00.670 --> 01:02:03.196 Do you think some are more
01:02:03.196 --> 01:02:05.570 likely to develop into cancer?
01:02:05.570 --> 01:02:07.800 Any correlate in human prostates?
01:02:08.910 --> 01:02:11.024 OK, so this is a question about
01:02:11.024 --> 01:02:13.136 prostate and of course we’re very
01:02:13.136 --> 01:02:15.026 interested in cell of origin.
01:02:15.030 --> 01:02:17.375 You know, we’ve always been sort of
dissatisfied with our previous analysis of Cell of Origin because you know you have luminal cells and basil cells. There’s only so much you can say, but we think that there’s still something to explore here because. This is well known phenomenon in which 85 to 90% of prostate cancer patients. With sort of intermediate risk disease, you know a will actually have indolent. Prostate cancer, whereas the remaining 10 to 15% of patients actually have aggressive disease and it’s difficult to distinguish between the indolent and aggressive tumors and
despite a lot of molecular analysis, they haven’t tremendously improved over. Just simple histological police and grading. So we think that it remains possible that cell of origin could explain at least partially. The difference between indolent and aggressive disease. And so that’s something we’re very interested in pursuing. The. We know already that you know from the literature that both proximal and distal luminal cells can be cells of origin in mouse models. But that does not necessarily answer
the question because you know they may be different in terms of their phenotype or response to treatment or.

Ultimate outcomes so you know we’re in the process of pursuing these types of studies.

It’s not really clear what’s going on in the human prostate.

And again, there’s a lot more work that needs to be done there.

Well, thank you very much Michael for
this visit for this fascinating talk.

I know it made me think of a lot of things or some parallels in the world of lung cancer.

So it was really great to think about this so thank you very much for visiting us today and thank you everybody also who joined and have a wonderful afternoon.

Well, thank you Katie. Thank you every.