WEBVTT

NOTE duration:"01:04:58.1550000"

NOTE language:en-us

NOTE Confidence: 0.83967113

00:00:00.000 --> 00:00:03.129 Good afternoon, my

NOTE Confidence: 0.83967113

00:00:03.130 --> 00:00:06.735 name is Katie Politi and I'm an

NOTE Confidence: 0.83967113

00:00:06.735 --> 00:00:08.876 associate professor of pathology

NOTE Confidence: 0.83967113

00:00:08.876 --> 00:00:12.348 and of medicine here at the Yale

NOTE Confidence: 0.83967113

00:00:12.348 --> 00:00:15.727 School of Medicine and Awesome Co.

NOTE Confidence: 0.83967113

00:00:15.730 --> 00:00:18.832 Leader of the cancer Signaling Networks

NOTE Confidence: 0.83967113

00:00:18.832 --> 00:00:22.549 Research program at the Yale Cancer Center,

NOTE Confidence: 0.83967113

00:00:22.550 --> 00:00:26.603 and it is my pleasure to introduce

NOTE Confidence: 0.83967113

00:00:26.603 --> 00:00:29.090 Doctor Michael Shen today.

NOTE Confidence: 0.83967113

00:00:29.090 --> 00:00:32.408 Doctor Shen is a professor of medicine,

NOTE Confidence: 0.83967113

00:00:32.410 --> 00:00:34.129 genetics and development,

NOTE Confidence: 0.83967113

00:00:34.129 --> 00:00:36.994 urology and systems biology at

NOTE Confidence: 0.83967113

00:00:36.994 --> 00:00:39.350 Columbia University Medical Center.

NOTE Confidence: 0.83967113

00:00:39.350 --> 00:00:41.538 He received his undergraduate

NOTE Confidence: 0.83967113

00:00:41.538 --> 00:00:44.273 degree from Harvard University and

NOTE Confidence: 0.83967113

00:00:44.273 --> 00:00:47.317 his PhD from Cambridge University.

NOTE Confidence: 0.83967113

00:00:47.320 --> 00:00:49.930 He then pursued his postdoctoral

NOTE Confidence: 0.83967113

00:00:49.930 --> 00:00:52.542 training with Phil, Doctor Phil,

NOTE Confidence: 0.83967113

00:00:52.542 --> 00:00:55.147 leader at Harvard Medical School,

NOTE Confidence: 0.83967113

00:00:55.150 --> 00:00:57.965 before becoming an independent investigator

NOTE Confidence: 0.83967113

00:00:57.965 --> 00:01:01.980 at Rutgers in 1994 and moved to

NOTE Confidence: 0.83967113

00:01:01.980 --> 00:01:05.310 Columbia University Medical Center in 2007.

NOTE Confidence: 0.83967113

00:01:05.310 --> 00:01:07.368 He is currently the Co leader

NOTE Confidence: 0.83967113

00:01:07.368 --> 00:01:09.798 of the Tumor Biology and Micro

NOTE Confidence: 0.83967113

00:01:09.798 --> 00:01:12.268 Environment Program at the Herbert

NOTE Confidence: 0.83967113

00:01:12.268 --> 00:01:14.300 Irving Comprehensive Cancer Center,

NOTE Confidence: 0.83967113

00:01:14.300 --> 00:01:17.191 as well as the director of Graduate

NOTE Confidence: 0.83967113

00:01:17.191 --> 00:01:19.841 studies in the Columbia Department

NOTE Confidence: 0.83967113

00:01:19.841 --> 00:01:22.485 of Genetics and Development.

NOTE Confidence: 0.83967113

00:01:22.490 --> 00:01:25.000 Over the past 26 years,

NOTE Confidence: 0.83967113

00:01:25.000 --> 00:01:27.870 Doctor Shen has investigated fundamental

NOTE Confidence: 0.83967113

00:01:27.870 --> 00:01:30.166 mechanisms of mammalian development

NOTE Confidence: 0.83967113

00:01:30.166 --> 00:01:33.821 in cancer using in vivo analysis of

NOTE Confidence: 0.83967113

00:01:33.821 --> 00:01:35.825 genetically engineered mouse models.

NOTE Confidence: 0.83967113

00:01:35.830 --> 00:01:38.192 Recently his lamp has generated novel

NOTE Confidence: 0.83967113

00:01:38.192 --> 00:01:40.550 culture conditions for mouse and human,

NOTE Confidence: 0.83967113

00:01:40.550 --> 00:01:42.510 prostate and bladder organized noise,

NOTE Confidence: 0.83967113

00:01:42.510 --> 00:01:45.970 which have led to the creation of a bio Bank

NOTE Confidence: 0.83967113

00:01:46.049 --> 00:01:49.427 of patient arrived bladder tumor organoids.

NOTE Confidence: 0.83967113

00:01:49.430 --> 00:01:52.769 Current work in the lab focuses on

NOTE Confidence: 0.83967113

00:01:52.769 --> 00:01:55.001 understanding molecular mechanisms of cell

NOTE Confidence: 0.83967113

00:01:55.001 --> 00:01:57.197 type differentiation in the normal as

NOTE Confidence: 0.83967113

00:01:57.197 --> 00:02:00.489 well as the transformed prostate epithelium.

NOTE Confidence: 0.83967113

00:02:00.490 --> 00:02:02.250 The epigenetic regulation of

NOTE Confidence: 0.83967113

00:02:02.250 --> 00:02:04.010 linear plasticity in both

NOTE Confidence: 0.83967113

00:02:04.010 --> 00:02:06.030 bladder and prostate cancer,

NOTE Confidence: 0.83967113

00:02:06.030 --> 00:02:10.166 and the role of the tumor micro environment

NOTE Confidence: 0.83967113

00:02:10.166 --> 00:02:13.019 in modulating treatment response.

NOTE Confidence: 0.83967113

00:02:13.020 --> 00:02:13.694 Doctor Sen,

NOTE Confidence: 0.83967113

00:02:13.694 --> 00:02:16.053 it really is a pleasure to have

NOTE Confidence: 0.83967113

00:02:16.053 --> 00:02:18.620 you here today and have you visit.

NOTE Confidence: 0.83967113

00:02:18.620 --> 00:02:20.370 I'll be at virtually from

NOTE Confidence: 0.83967113

00:02:20.370 --> 00:02:21.070 Columbia University,

NOTE Confidence: 0.83967113

00:02:21.070 --> 00:02:23.430 so thank you very much and we look

NOTE Confidence: 0.83967113

00:02:23.430 --> 00:02:25.269 forward to your presentation.

NOTE Confidence: 0.9015736

00:02:26.830 --> 00:02:28.438 Well, thank you Katie.

NOTE Confidence: 0.9015736

00:02:28.438 --> 00:02:30.850 It's a real pleasure to have

NOTE Confidence: 0.9015736

00:02:30.932 --> 00:02:33.217 this opportunity to speak to.

NOTE Confidence: 0.9015736

00:02:33.220 --> 00:02:34.852 This audience that yell and I

NOTE Confidence: 0.9015736

00:02:34.852 --> 00:02:38.260 wish this were in person, but.

NOTE Confidence: 0.9015736

00:02:38.260 --> 00:02:40.416 Make do as best as we can,

NOTE Confidence: 0.9015736

00:02:40.420 --> 00:02:42.330 so I'll go ahead and

NOTE Confidence: 0.9015736

00:02:42.330 --> 00:02:46.610 share my screen. Um? And.

NOTE Confidence: 0.9336113

00:02:50.290 --> 00:02:54.410 Hopefully. You can see my presentation.

NOTE Confidence: 0.9336113

00:02:54.410 --> 00:02:57.868 Is that true? Can everyone see my?

NOTE Confidence: 0.9336113

00:02:57.868 --> 00:02:59.708 Yes we can see it.

NOTE Confidence: 0.9336113

00:02:59.708 --> 00:03:01.180 Thank you. Yes excellent.

NOTE Confidence: 0.9336113

00:03:01.180 --> 00:03:03.388 So today I'd like to talk.

NOTE Confidence: 0.9336113

00:03:03.390 --> 00:03:05.598 Take the opportunity to discuss published

NOTE Confidence: 0.9336113

00:03:05.598 --> 00:03:08.754 work, but also a lot of work that can

NOTE Confidence: 0.9336113

00:03:08.754 --> 00:03:11.119 be construed as work in progress.

NOTE Confidence: 0.9336113

00:03:11.120 --> 00:03:13.730 Much of it focusing on the

NOTE Confidence: 0.9336113

00:03:13.730 --> 00:03:15.470 issue of linic plasticity.

NOTE Confidence: 0.9336113

00:03:15.470 --> 00:03:18.116 And we've been studying this through

NOTE Confidence: 0.9336113

00:03:18.116 --> 00:03:20.989 in vivo analysis in mouse models,

NOTE Confidence: 0.9336113

00:03:20.990 --> 00:03:23.290 but also using organoid models,

NOTE Confidence: 0.9336113

00:03:23.290 --> 00:03:26.320 and we've been studying this in

NOTE Confidence: 0.9336113

00:03:26.320 --> 00:03:29.580 both the prostate and the bladder.

NOTE Confidence: 0.9336113

00:03:29.580 --> 00:03:32.457 So to start with, what is plasticity?

NOTE Confidence: 0.9336113

00:03:32.460 --> 00:03:34.890 So if we consider that plasticity

NOTE Confidence: 0.9336113

00:03:34.890 --> 00:03:37.351 in the most general definition is

NOTE Confidence: 0.9336113

00:03:37.351 --> 00:03:40.025 the ability of a cell to change

NOTE Confidence: 0.9336113

00:03:40.025 --> 00:03:42.318 from one identity to another,

NOTE Confidence: 0.9336113

00:03:42.320 --> 00:03:45.197 we can think of this in the.

NOTE Confidence: 0.9336113

00:03:45.200 --> 00:03:47.660 You know, perhaps cliched Waddington model.

NOTE Confidence: 0.9336113

00:03:47.660 --> 00:03:48.893 As you know,

NOTE Confidence: 0.9336113

00:03:48.893 --> 00:03:51.770 sort of balls rolling down a Hill.

NOTE Confidence: 0.9336113

00:03:51.770 --> 00:03:54.594 We start with a stem cell and we

NOTE Confidence: 0.9336113

00:03:54.594 --> 00:03:56.340 have various differentiated cell

NOTE Confidence: 0.9336113

00:03:56.340 --> 00:03:59.693 types and the ability of cells too.

NOTE Confidence: 0.9336113

00:03:59.700 --> 00:04:01.620 Basically change their identity

NOTE Confidence: 0.9336113

00:04:01.620 --> 00:04:04.020 is considered to be plasticity

NOTE Confidence: 0.9336113

00:04:04.020 --> 00:04:06.790 and so there are different forms

NOTE Confidence: 0.9336113

00:04:06.790 --> 00:04:09.005 there sort of reprogramming back

NOTE Confidence: 0.9336113

00:04:09.086 --> 00:04:11.046 to a more progenitor state.

NOTE Confidence: 0.9336113

00:04:11.050 --> 00:04:13.380 There can be transdifferentiation changing

NOTE Confidence: 0.9336113

00:04:13.380 --> 00:04:16.040 from one identity to another etc.

NOTE Confidence: 0.9336113

00:04:16.040 --> 00:04:19.480 So this is a process that has been

NOTE Confidence: 0.9336113

00:04:19.480 --> 00:04:21.804 studied extensively in both development

NOTE Confidence: 0.9336113

00:04:21.804 --> 00:04:24.570 and cancer and it's important to

NOTE Confidence: 0.9336113

00:04:24.570 --> 00:04:27.390 think about when we talk about

NOTE Confidence: 0.9336113

00:04:27.390 --> 00:04:30.158 plasticity in cancer to consider that.

NOTE Confidence: 0.9336113

00:04:30.158 --> 00:04:32.648 In order to study plasticity,

NOTE Confidence: 0.9336113

00:04:32.650 --> 00:04:35.878 it's also essential to understand the

NOTE Confidence: 0.9336113

00:04:35.878 --> 00:04:38.030 normal pathways of differentiation

NOTE Confidence: 0.9336113

00:04:38.109 --> 00:04:40.527 so that one can distinguish what

NOTE Confidence: 0.9336113

00:04:40.527 --> 00:04:43.051 happens in the normal context from

NOTE Confidence: 0.9336113

00:04:43.051 --> 00:04:45.956 what might happen in a tumor context.

NOTE Confidence: 0.9336113

00:04:45.960 --> 00:04:48.529 So over many years we've been studying

NOTE Confidence: 0.9336113

00:04:48.529 --> 00:04:50.589 these issues in the prostate,

NOTE Confidence: 0.9336113

00:04:50.590 --> 00:04:52.906 and more recently in the bladder,

NOTE Confidence: 0.9336113

00:04:52.910 --> 00:04:56.375 and to start with, I just like to consider,

NOTE Confidence: 0.9336113

00:04:56.380 --> 00:04:57.156 you know,

NOTE Confidence: 0.9336113

00:04:57.156 --> 00:04:59.872 sort of a basic review of the

NOTE Confidence: 0.9336113

00:04:59.872 --> 00:05:01.400 prostate in the mouse.

NOTE Confidence: 0.9336113

00:05:01.400 --> 00:05:04.095 The prostate has a distinct anatomy there.

NOTE Confidence: 0.9336113

00:05:04.100 --> 00:05:06.416 It sort of has lobular structure.

NOTE Confidence: 0.9336113

00:05:06.420 --> 00:05:09.508 There are four different lobes in the mouse.

NOTE Confidence: 0.9336113

00:05:09.510 --> 00:05:11.050 There's the anterior prostate,

NOTE Confidence: 0.9336113

00:05:11.050 --> 00:05:13.599 the dorsal prostate, the lateral prostate,

NOTE Confidence: 0.9336113

00:05:13.599 --> 00:05:16.377 as well as the ventral prostate.

NOTE Confidence: 0.9336113

00:05:16.380 --> 00:05:19.098 However, in the human there is

NOTE Confidence: 0.9336113

00:05:19.098 --> 00:05:21.850 something a little bit different.

NOTE Confidence: 0.9336113

00:05:21.850 --> 00:05:24.832 The human prostate does not have

NOTE Confidence: 0.9336113

00:05:24.832 --> 00:05:26.820 a distinct lobular structure.

NOTE Confidence: 0.9336113

00:05:26.820 --> 00:05:29.850 Instead, it can be distinguished at

NOTE Confidence: 0.9336113

00:05:29.850 --> 00:05:33.278 the pathological level as having you know,

NOTE Confidence: 0.9336113

00:05:33.280 --> 00:05:36.256 sort of architecture of different regions.

NOTE Confidence: 0.9336113

00:05:36.260 --> 00:05:39.236 So there are zones that have

NOTE Confidence: 0.9336113

00:05:39.236 --> 00:05:40.724 been defined pathologically.

NOTE Confidence: 0.9336113

00:05:40.730 --> 00:05:42.224 The peripheral, central,

NOTE Confidence: 0.9336113

00:05:42.224 --> 00:05:43.718 and transition zones,

NOTE Confidence: 0.9336113

00:05:43.720 --> 00:05:46.786 so the distinct anatomy of the

NOTE Confidence: 0.9336113

00:05:46.786 --> 00:05:49.770 mouse and human prostate has been.

NOTE Confidence: 0.9336113

00:05:49.770 --> 00:05:50.136 Um?

NOTE Confidence: 0.9336113

00:05:50.136 --> 00:05:50.868 Of note,

NOTE Confidence: 0.9336113

00:05:50.868 --> 00:05:54.002 for many years and has been used sort

NOTE Confidence: 0.9336113

00:05:54.002 --> 00:05:56.930 of as an argument as underscoring

NOTE Confidence: 0.9336113

00:05:56.930 --> 00:05:59.836 the inability perhaps of the mouse

NOTE Confidence: 0.9336113

00:05:59.836 --> 00:06:02.548 to truly model human prostate cancer.

NOTE Confidence: 0.9336113

00:06:02.550 --> 00:06:05.224 Now we've known from studies over many

NOTE Confidence: 0.9336113

00:06:05.224 --> 00:06:07.754 years that there are many conserved

NOTE Confidence: 0.9336113

00:06:07.754 --> 00:06:09.929 signaling pathways in the like,

NOTE Confidence: 0.9336113

00:06:09.930 --> 00:06:11.755 but the relationship between the

NOTE Confidence: 0.9336113

00:06:11.755 --> 00:06:13.580 mouse and human prostate still

NOTE Confidence: 0.9336113

00:06:13.638 --> 00:06:15.258 remains somewhat mysterious,

NOTE Confidence: 0.9336113

00:06:15.260 --> 00:06:18.046 both in terms of normal development as

NOTE Confidence: 0.9336113

00:06:18.046 --> 00:06:21.147 well as the cell types can contain.

NOTE Confidence: 0.9336113

00:06:21.150 --> 00:06:22.682 Within the prostate. No.

NOTE Confidence: 0.9336113

00:06:22.682 --> 00:06:25.508 The prostate in the mouse is formed

NOTE Confidence: 0.9336113

00:06:25.508 --> 00:06:28.196 at late stages of fetal development

NOTE Confidence: 0.9336113

00:06:28.196 --> 00:06:29.540 and organic Genesis

NOTE Confidence: 0.81583895576923

00:06:29.621 --> 00:06:32.585 primarily takes place at neonatal stages.

NOTE Confidence: 0.81583895576923

00:06:32.590 --> 00:06:33.739 The prostate form,

NOTE Confidence: 0.81583895576923

00:06:33.739 --> 00:06:36.037 through a process of ductal budding

NOTE Confidence: 0.81583895576923

00:06:36.037 --> 00:06:38.022 budding from the urogenital sinus

NOTE Confidence: 0.81583895576923

00:06:38.022 --> 00:06:40.320 and initial prostate bugs are marked

NOTE Confidence: 0.81583895576923

00:06:40.391 --> 00:06:42.305 by expression of the homeo box.

NOTE Confidence: 0.81583895576923

00:06:42.310 --> 00:06:43.802 Jinan kicks 3.1 here,

NOTE Confidence: 0.81583895576923

00:06:43.802 --> 00:06:45.294 visualized by Beta Galactoside.

NOTE Confidence: 0.81583895576923

00:06:45.300 --> 00:06:48.268 ASA Valax Enoch in that we made a

NOTE Confidence: 0.81583895576923

00:06:48.268 --> 00:06:51.283 number of years ago and you can see

NOTE Confidence: 0.81583895576923

00:06:51.283 --> 00:06:54.379 even early on at the time of birth.

NOTE Confidence: 0.81583895576923

00:06:54.380 --> 00:06:56.702 Their buds that correspond to distinct

NOTE Confidence: 0.81583895576923

00:06:56.702 --> 00:06:59.948 lobes and at least initially and kicks 3.1,

NOTE Confidence: 0.81583895576923

00:06:59.950 --> 00:07:02.686 is expressed by all of the

NOTE Confidence: 0.81583895576923

00:07:02.686 --> 00:07:05.430 epithelial cells in the prostate.

NOTE Confidence: 0.81583895576923

00:07:05.430 --> 00:07:07.670 Prostate formation of course

NOTE Confidence: 0.81583895576923

00:07:07.670 --> 00:07:09.350 requires androgen signaling,

NOTE Confidence: 0.81583895576923

00:07:09.350 --> 00:07:12.380 but the requirements for androgen receptor

NOTE Confidence: 0.81583895576923

00:07:12.380 --> 00:07:15.756 are actually fairly complex and they

NOTE Confidence: 0.81583895576923

00:07:15.756 --> 00:07:18.308 involve epithelial mesenchymal interactions.

NOTE Confidence: 0.81583895576923

00:07:18.310 --> 00:07:21.020 So androgen receptor is actually

NOTE Confidence: 0.81583895576923

00:07:21.020 --> 00:07:23.188 required in the urogenital

NOTE Confidence: 0.81583895576923

00:07:23.188 --> 00:07:25.588 mesenchyme for prostate formation.

NOTE Confidence: 0.81583895576923

00:07:25.590 --> 00:07:29.748 So if you delete androgen receptor in

NOTE Confidence: 0.81583895576923

00:07:29.748 --> 00:07:33.216 the urogenital mesenchyme here in a

NOTE Confidence: 0.81583895576923

00:07:33.216 --> 00:07:35.866 TFM una testicular feminize mutant.

NOTE Confidence: 0.81583895576923

00:07:35.870 --> 00:07:39.650 And you perform a a tissue recombination

NOTE Confidence: 0.81583895576923

00:07:39.650 --> 00:07:43.419 assay as was first shown through.

NOTE Confidence: 0.81583895576923

00:07:43.420 --> 00:07:46.220 The studies of Jerry Kunia about four

NOTE Confidence: 0.81583895576923

00:07:46.220 --> 00:07:49.540 decades ago now the prostate will not form.

NOTE Confidence: 0.81583895576923

00:07:49.540 --> 00:07:49.971 However,

NOTE Confidence: 0.81583895576923

00:07:49.971 --> 00:07:52.988 if you delete androgen receptor in the

NOTE Confidence: 0.81583895576923

00:07:52.988 --> 00:07:55.656 epithelium now you will form a prostate.

NOTE Confidence: 0.81583895576923

00:07:55.660 --> 00:07:58.516 However, the prostate is not entirely normal.

NOTE Confidence: 0.81583895576923

00:07:58.520 --> 00:07:59.800 For example,

NOTE Confidence: 0.81583895576923

00:07:59.800 --> 00:08:03.000 it lacks secretory protein production.

NOTE Confidence: 0.81583895576923

00:08:03.000 --> 00:08:05.776 So what are the cell types that are

NOTE Confidence: 0.81583895576923

00:08:05.776 --> 00:08:08.608 found in the normal adult prostate?

NOTE Confidence: 0.81583895576923

00:08:08.610 --> 00:08:11.546 Well in both the mouse and the human

NOTE Confidence: 0.81583895576923

00:08:11.546 --> 00:08:14.108 there's an array of different cell

NOTE Confidence: 0.81583895576923

00:08:14.108 --> 00:08:17.576 types in both the epithelium and in the

NOTE Confidence: 0.81583895576923

00:08:17.576 --> 00:08:20.250 stroma that are just now really being

NOTE Confidence: 0.81583895576923

00:08:20.250 --> 00:08:23.046 able of being characterized in some detail,

NOTE Confidence: 0.81583895576923

00:08:23.050 --> 00:08:24.702 but historically we've considered

NOTE Confidence: 0.81583895576923

00:08:24.702 --> 00:08:26.354 the epithelium as containing

NOTE Confidence: 0.81583895576923

00:08:26.354 --> 00:08:27.859 three basic cell types.

NOTE Confidence: 0.81583895576923

00:08:27.860 --> 00:08:30.814 There are the luminal cells which are

NOTE Confidence: 0.81583895576923

00:08:30.814 --> 00:08:33.389 the tall columnar secretory cells.

NOTE Confidence: 0.81583895576923

00:08:33.390 --> 00:08:35.916 That produce the the prostate secretions.

NOTE Confidence: 0.81583895576923

00:08:35.920 --> 00:08:38.860 There's an underlying layer of basil cells.

NOTE Confidence: 0.81583895576923

00:08:38.860 --> 00:08:40.965 These cells are androgen receptor

NOTE Confidence: 0.81583895576923

00:08:40.965 --> 00:08:42.228 low or negative,

NOTE Confidence: 0.81583895576923

00:08:42.230 --> 00:08:43.914 and express basil cytokeratins

NOTE Confidence: 0.81583895576923

00:08:43.914 --> 00:08:45.598 unlike the luminal cells,

NOTE Confidence: 0.81583895576923

00:08:45.600 --> 00:08:48.126 which are a are high and

NOTE Confidence: 0.81583895576923

00:08:48.126 --> 00:08:49.389 expressed lumenal cytokeratins.

NOTE Confidence: 0.81583895576923

00:08:49.390 --> 00:08:52.814 And then there is a rare third type

NOTE Confidence: 0.81583895576923

00:08:52.814 --> 00:08:55.809 known as neuroendocrine cells.

NOTE Confidence: 0.81583895576923

00:08:55.810 --> 00:08:58.462 These have been very understudied and

NOTE Confidence: 0.81583895576923

00:08:58.462 --> 00:09:01.578 I'll touch upon these later in my talk.

NOTE Confidence: 0.81583895576923

00:09:01.580 --> 00:09:04.442 So this is sort of the way we thought

NOTE Confidence: 0.81583895576923

00:09:04.442 --> 00:09:06.653 about the prostate epithelium for

NOTE Confidence: 0.81583895576923

00:09:06.653 --> 00:09:08.816 many years now, and classically,

NOTE Confidence: 0.81583895576923

00:09:08.816 --> 00:09:11.204 basil cells have always considered have

NOTE Confidence: 0.81583895576923

00:09:11.204 --> 00:09:13.330 been considered to be more interesting.

NOTE Confidence: 0.81583895576923

00:09:13.330 --> 00:09:15.562 They appear to have more stemlike

NOTE Confidence: 0.81583895576923

00:09:15.562 --> 00:09:17.870 properties or does luminal cells have

NOTE Confidence: 0.81583895576923

00:09:17.870 --> 00:09:20.144 been considered to be somewhat boring,

NOTE Confidence: 0.81583895576923

00:09:20.150 --> 00:09:22.718 but I think you know for many years

NOTE Confidence: 0.81583895576923

00:09:22.718 --> 00:09:24.755 we've thought that luminal cells

NOTE Confidence: 0.81583895576923

00:09:24.755 --> 00:09:26.965 are actually the interesting cells.

NOTE Confidence: 0.81583895576923

00:09:26.970 --> 00:09:29.616 And now with the advent of single

NOTE Confidence: 0.81583895576923

00:09:29.616 --> 00:09:30.372 cell analysis,

NOTE Confidence: 0.81583895576923

00:09:30.380 --> 00:09:32.780 we see that there's considerable complexity.

NOTE Confidence: 0.81583895576923

00:09:32.780 --> 00:09:34.648 In the lumenal population.

NOTE Confidence: 0.81583895576923

00:09:34.648 --> 00:09:37.450 So what do basil cells do?

NOTE Confidence: 0.81583895576923

00:09:37.450 --> 00:09:41.130 Well, we believe that there is sort of.

NOTE Confidence: 0.81583895576923

00:09:41.130 --> 00:09:43.656 A conserved ancestral role for basil

NOTE Confidence: 0.81583895576923

00:09:43.656 --> 00:09:46.399 cells and that's in wound repair.

NOTE Confidence: 0.81583895576923

00:09:46.400 --> 00:09:49.466 So here, for example, in the prostate.

NOTE Confidence: 0.81583895576923

00:09:49.470 --> 00:09:52.326 If we damage the luminal cells by

NOTE Confidence: 0.81583895576923

00:09:52.326 --> 00:09:55.030 deletion of idcat here in inducible

NOTE Confidence: 0.81583895576923

00:09:55.030 --> 00:09:57.814 deletion of ekit here and the

NOTE Confidence: 0.81583895576923

00:09:57.814 --> 00:10:00.127 epithelial cells will Slough off.

NOTE Confidence: 0.81583895576923

00:10:00.130 --> 00:10:02.412 And undergo a notice and the basil

NOTE Confidence: 0.81583895576923

00:10:02.412 --> 00:10:03.862 cells will actually differentiate

NOTE Confidence: 0.81583895576923

00:10:03.862 --> 00:10:05.887 into luminal cells to replace

NOTE Confidence: 0.81583895576923

00:10:05.887 --> 00:10:07.507 the loss luminal cells.

NOTE Confidence: 0.8089924

00:10:07.510 --> 00:10:10.454 So this is shown in cartoon form here.

NOTE Confidence: 0.8089924

00:10:10.460 --> 00:10:13.348 So there's sort of a basil to luminal

NOTE Confidence: 0.8089924

00:10:13.348 --> 00:10:14.889 differentiation that takes place,

NOTE Confidence: 0.8089924

00:10:14.890 --> 00:10:17.650 so we think that this is a conserved

NOTE Confidence: 0.8089924

00:10:17.650 --> 00:10:20.430 function of basil cells in many tissues,

NOTE Confidence: 0.8089924

00:10:20.430 --> 00:10:21.606 and more recently,

NOTE Confidence: 0.8089924

00:10:21.606 --> 00:10:24.350 work from Cedric Web Con Slab has

NOTE Confidence: 0.8089924

00:10:24.425 --> 00:10:27.288 demonstrated that is in fact the case.

NOTE Confidence: 0.8089924

00:10:27.290 --> 00:10:28.826 What about luminal cells?

NOTE Confidence: 0.8089924

00:10:28.826 --> 00:10:31.120 Well, luminal cells, as I mentioned,

NOTE Confidence: 0.8089924

00:10:31.120 --> 00:10:33.794 have been considered to be somewhat boring,

NOTE Confidence: 0.8089924

00:10:33.800 --> 00:10:34.760 but in fact,

NOTE Confidence: 0.8089924

00:10:34.760 --> 00:10:37.000 in ex vivo assays at least one

NOTE Confidence: 0.8089924

00:10:37.076 --> 00:10:39.572 could see that there are luminal

NOTE Confidence: 0.8089924

00:10:39.572 --> 00:10:41.840 progenitors that are by potent.

NOTE Confidence: 0.8089924

00:10:41.840 --> 00:10:43.796 So if we perform lineages marking

NOTE Confidence: 0.8089924

00:10:43.796 --> 00:10:45.598 of luminal cells and generate

NOTE Confidence: 0.8089924

00:10:45.598 --> 00:10:47.743 organoids that are wholly composed

NOTE Confidence: 0.8089924

00:10:47.743 --> 00:10:49.890 wholly derived from luminal cells,

NOTE Confidence: 0.8089924

00:10:49.890 --> 00:10:53.085 then we can see that there are basil cells

NOTE Confidence: 0.8089924

00:10:53.085 --> 00:10:56.019 that can be formed in these organoids,

NOTE Confidence: 0.8089924

00:10:56.020 --> 00:10:58.390 and these basil cells are marked.

NOTE Confidence: 0.8089924

00:10:58.390 --> 00:11:00.618 Indicating their lumenal origin.

NOTE Confidence: 0.8089924

00:11:00.618 --> 00:11:05.065 So of course this is an ex vivo

NOTE Confidence: 0.8089924

00:11:05.065 --> 00:11:08.053 assay and ex vivo cells often

NOTE Confidence: 0.8089924

00:11:08.053 --> 00:11:11.166 display more plasticity than is

NOTE Confidence: 0.8089924

00:11:11.166 --> 00:11:14.526 found in during normal development,

NOTE Confidence: 0.8089924

00:11:14.530 --> 00:11:17.329 and certainly in.

NOTE Confidence: 0.8089924

00:11:17.330 --> 00:11:19.278 Normal context luminal cells

NOTE Confidence: 0.8089924

00:11:19.278 --> 00:11:21.226 are usually you'd impotent,

NOTE Confidence: 0.8089924

00:11:21.230 --> 00:11:23.665 but we think that normal

NOTE Confidence: 0.8089924

00:11:23.665 --> 00:11:24.639 developmental processes,

NOTE Confidence: 0.8089924

00:11:24.640 --> 00:11:26.380 among other things or,

NOTE Confidence: 0.8089924

00:11:26.380 --> 00:11:28.990 can be constrained by the micro

NOTE Confidence: 0.8089924

00:11:29.077 --> 00:11:32.029 environment and ex vivo assays such

NOTE Confidence: 0.8089924

00:11:32.029 --> 00:11:34.677 as organoid formation can reveal

NOTE Confidence: 0.8089924

00:11:34.677 --> 00:11:37.065 developmental potential that can

NOTE Confidence: 0.8089924

00:11:37.065 --> 00:11:40.050 be displayed in specific contexts.

NOTE Confidence: 0.8089924

00:11:40.050 --> 00:11:41.490 So for example,

NOTE Confidence: 0.8089924

00:11:41.490 --> 00:11:44.370 we think that the ability of

NOTE Confidence: 0.8089924

00:11:44.370 --> 00:11:47.260 luminal cells to display by potency

NOTE Confidence: 0.8089924

00:11:47.260 --> 00:11:50.173 to be able to generate basil

NOTE Confidence: 0.8089924

00:11:50.173 --> 00:11:53.221 cells is actually an ability that

NOTE Confidence: 0.8089924

00:11:53.221 --> 00:11:55.652 occurs early in organic Genesis.

NOTE Confidence: 0.8089924

00:11:55.652 --> 00:11:58.809 So this is sort of a linear

NOTE Confidence: 0.8089924

00:11:58.809 --> 00:12:01.607 hierarchy as is currently understood,

NOTE Confidence: 0.8089924

00:12:01.610 --> 00:12:04.893 in which there are by potent basil

NOTE Confidence: 0.8089924

00:12:04.893 --> 00:12:07.397 progenitors generating both basal and

NOTE Confidence: 0.8089924

00:12:07.397 --> 00:12:09.937 luminal cells during organic Genesis.

NOTE Confidence: 0.8089924

00:12:09.940 --> 00:12:10.382 But.

NOTE Confidence: 0.8089924

00:12:10.382 --> 00:12:11.708 Luminal progenitors were

NOTE Confidence: 0.8089924

00:12:11.708 --> 00:12:13.476 generally thought of unipotent,

NOTE Confidence: 0.8089924

00:12:13.480 --> 00:12:16.680 but in recent studies we found that in

NOTE Confidence: 0.8089924

00:12:16.680 --> 00:12:20.347 fact there is a BI potent luminal progenitor,

NOTE Confidence: 0.8089924

00:12:20.350 --> 00:12:24.095 so if we lineages mark luminal cells.

NOTE Confidence: 0.8089924

00:12:24.100 --> 00:12:26.340 At early postnatal stages

NOTE Confidence: 0.8089924

00:12:26.340 --> 00:12:29.700 using an inducible CK 8 driver,

NOTE Confidence: 0.8089924

00:12:29.700 --> 00:12:33.402 we can then mark luminal cells

NOTE Confidence: 0.8089924

00:12:33.402 --> 00:12:35.870 and then analyzed later.

NOTE Confidence: 0.8089924

00:12:35.870 --> 00:12:37.450 Luminal cells are marked,

NOTE Confidence: 0.8089924

00:12:37.450 --> 00:12:39.030 but also basil cells,

NOTE Confidence: 0.8089924

00:12:39.030 --> 00:12:41.364 and it's it's a reasonable fraction

NOTE Confidence: 0.8089924

00:12:41.364 --> 00:12:43.770 of basal cells that are marked,

NOTE Confidence: 0.8089924

00:12:43.770 --> 00:12:45.750 and this by potent progenitor,

NOTE Confidence: 0.8089924

00:12:45.750 --> 00:12:47.326 is fairly short lived.

NOTE Confidence: 0.8089924

00:12:47.326 --> 00:12:48.508 It's fairly transient,

NOTE Confidence: 0.8089924

00:12:48.510 --> 00:12:51.135 but it can still be detected at

NOTE Confidence: 0.8089924

00:12:51.135 --> 00:12:53.694 a week after birth, but again,

NOTE Confidence: 0.8089924

00:12:53.694 --> 00:12:56.613 the ability of this by potent progenitor

NOTE Confidence: 0.8089924

00:12:56.613 --> 00:12:58.660 quickly disappears thereafter.

NOTE Confidence: 0.8089924

00:12:58.660 --> 00:12:59.881 So interesting, Lee,

NOTE Confidence: 0.8089924

00:12:59.881 --> 00:13:02.730 both the by potent basil progenitor and

NOTE Confidence: 0.8089924

00:13:02.801 --> 00:13:05.489 this by potent luminal progenitor do

NOTE Confidence: 0.8089924

00:13:05.489 --> 00:13:07.960 not require androgen receptor function,

NOTE Confidence: 0.8089924

00:13:07.960 --> 00:13:11.380 so if we delete androgen receptor.

NOTE Confidence: 0.8089924

00:13:11.380 --> 00:13:12.493 In basil cells,

NOTE Confidence: 0.8089924

00:13:12.493 --> 00:13:15.090 we find that there's no effect on

NOTE Confidence: 0.8089924

00:13:15.170 --> 00:13:17.520 the formation of luminal cells,

NOTE Confidence: 0.8089924

00:13:17.520 --> 00:13:19.860 and similarly if we delete a

NOTE Confidence: 0.8089924

00:13:19.860 --> 00:13:22.010 are in the luminal cells,

NOTE Confidence: 0.8089924

00:13:22.010 --> 00:13:25.384 we don't see any effect on the

NOTE Confidence: 0.8089924

00:13:25.384 --> 00:13:27.510 generation of basil cells.

NOTE Confidence: 0.8089924

00:13:27.510 --> 00:13:30.219 So in cartoon form then what we

NOTE Confidence: 0.8089924

00:13:30.219 --> 00:13:33.946 think is going on is that there is

NOTE Confidence: 0.8089924

00:13:33.946 --> 00:13:35.930 a urogenital epithelial progenitor

NOTE Confidence: 0.8089924

00:13:35.930 --> 00:13:39.091 that gives rise to both basal

NOTE Confidence: 0.8089924

00:13:39.091 --> 00:13:40.636 and luminal progenitors,

NOTE Confidence: 0.8089924

00:13:40.640 --> 00:13:42.915 and initially the basil progenitor

NOTE Confidence: 0.8089924

00:13:42.915 --> 00:13:46.237 can be by potent as as well

NOTE Confidence: 0.8089924

00:13:46.237 --> 00:13:48.149 as the luminal progenitor.

NOTE Confidence: 0.8089924

00:13:48.150 --> 00:13:51.894 But that this by potency is fairly transient,

NOTE Confidence: 0.8089924

00:13:51.900 --> 00:13:54.060 and then in adulthood both

NOTE Confidence: 0.8089924

00:13:54.060 --> 00:13:56.220 luminal and basal progenitors are

NOTE Confidence: 0.79517823

00:13:56.298 --> 00:13:57.740 generally unipotent.

NOTE Confidence: 0.79517823

00:13:57.740 --> 00:14:00.350 However, this period of by potency

NOTE Confidence: 0.79517823

00:14:00.350 --> 00:14:02.571 is actually occurring in the

NOTE Confidence: 0.79517823

00:14:02.571 --> 00:14:04.596 first four weeks after birth,

NOTE Confidence: 0.79517823

00:14:04.600 --> 00:14:07.864 and Interestingly, this is a time

NOTE Confidence: 0.79517823

00:14:07.864 --> 00:14:10.980 when androgen levels are very low.

NOTE Confidence: 0.79517823

00:14:10.980 --> 00:14:13.530 At these pre pubertal stages.

NOTE Confidence: 0.79517823

00:14:13.530 --> 00:14:15.774 Now there is one other interesting

NOTE Confidence: 0.79517823

00:14:15.774 --> 00:14:17.270 aspect of luminal cells,

NOTE Confidence: 0.79517823

00:14:17.270 --> 00:14:20.006 which is that in a series of studies

NOTE Confidence: 0.79517823

00:14:20.006 --> 00:14:22.657 we've shown that they are favored as

NOTE Confidence: 0.79517823

00:14:22.657 --> 00:14:25.120 cells of origin for prostate cancer,

NOTE Confidence: 0.79517823

00:14:25.120 --> 00:14:27.976 so we've shown this in a number of

NOTE Confidence: 0.79517823

00:14:27.976 --> 00:14:29.610 different transgenic mouse models,

NOTE Confidence: 0.79517823

00:14:29.610 --> 00:14:32.228 as well as a hormonal carcinogenesis model.

NOTE Confidence: 0.79517823

00:14:32.230 --> 00:14:35.214 If we mark Basil cells in these models,

NOTE Confidence: 0.79517823

00:14:35.220 --> 00:14:38.091 for example in the hymec model or a tramp

NOTE Confidence: 0.79517823

00:14:38.091 --> 00:14:40.458 model which are well characterized,

NOTE Confidence: 0.79517823

00:14:40.460 --> 00:14:42.330 transgenic models of prostate cancer,

NOTE Confidence: 0.79517823

00:14:42.330 --> 00:14:44.330 the basal cells are marked.

NOTE Confidence: 0.79517823

00:14:44.330 --> 00:14:47.130 But they don't really contribute to tumors.

NOTE Confidence: 0.79517823

00:14:47.130 --> 00:14:50.098 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

00:15:22.980 --> 00:15:24.774 celeb mutation, whereas luminal cells.

NOTE Confidence: 0.79517823

00:15:24.774 --> 00:15:26.982 Are the true cell of origin.

NOTE Confidence: 0.79517823

00:15:26.990 --> 00:15:27.662 And again,

NOTE Confidence: 0.79517823

00:15:27.662 --> 00:15:29.342 we've analyzed this in multiple

NOTE Confidence: 0.79517823

00:15:29.342 --> 00:15:31.340 mouse models of prostate cancer.

NOTE Confidence: 0.79517823

00:15:31.340 --> 00:15:33.155 So because we've observed the

NOTE Confidence: 0.79517823

00:15:33.155 --> 00:15:34.607 same result every time,

NOTE Confidence: 0.79517823

00:15:34.610 --> 00:15:37.262 we think that luminal cells are

NOTE Confidence: 0.79517823

00:15:37.262 --> 00:15:40.350 generally favored as a cell of origin.

NOTE Confidence: 0.79517823

00:15:40.350 --> 00:15:42.050 So.

NOTE Confidence: 0.79517823

00:15:42.050 --> 00:15:44.640 We now have this view that lumenal

NOTE Confidence: 0.79517823

00:15:44.640 --> 00:15:47.638 cells are in fact quite interesting,

NOTE Confidence: 0.79517823

00:15:47.640 --> 00:15:49.854 so recently we decided to explore

NOTE Confidence: 0.79517823

00:15:49.854 --> 00:15:51.919 the heterogeneity of the prostate

NOTE Confidence: 0.79517823

00:15:51.919 --> 00:15:54.519 epithelium using single cell approaches.

NOTE Confidence: 0.79517823

00:15:54.520 --> 00:15:58.642 For this we had to really learn how to

NOTE Confidence: 0.79517823

00:15:58.642 --> 00:16:01.989 dissect the mouse prostate properly.

NOTE Confidence: 0.79517823

00:16:01.990 --> 00:16:04.244 You might think that's a bit of

NOTE Confidence: 0.79517823

00:16:04.244 --> 00:16:06.264 an over some bug, an exaggeration,

NOTE Confidence: 0.79517823

00:16:06.264 --> 00:16:07.632 considering we've been studying

NOTE Confidence: 0.79517823

00:16:07.632 --> 00:16:09.490 the prostate for over 20 years,

NOTE Confidence: 0.79517823

00:16:09.490 --> 00:16:11.428 but in fact it's really not

NOTE Confidence: 0.79517823

00:16:11.428 --> 00:16:13.070 a trivial matter of two.

NOTE Confidence: 0.79517823

00:16:13.070 --> 00:16:14.282 Dissect the individual mouse

NOTE Confidence: 0.79517823

00:16:14.282 --> 00:16:16.520 lobes all the way down to their

NOTE Confidence: 0.79517823

00:16:16.520 --> 00:16:17.956 junction with the urethra.

NOTE Confidence: 0.79517823

00:16:17.960 --> 00:16:21.099 So this is sort of a view of sort of how

NOTE Confidence: 0.79517823

00:16:21.099 --> 00:16:23.829 we can dissect the weight mouse lobes.

NOTE Confidence: 0.79517823

00:16:23.830 --> 00:16:26.105 This is actually in a green mouse,

NOTE Confidence: 0.79517823

00:16:26.110 --> 00:16:30.079 so you can see the lobes that are dissected.

NOTE Confidence: 0.79517823

00:16:30.080 --> 00:16:32.942 And then we subjected these two

NOTE Confidence: 0.79517823

00:16:32.942 --> 00:16:35.393 single cell RNA sequencing both

NOTE Confidence: 0.79517823

00:16:35.393 --> 00:16:38.111 the whole prostate as well as

NOTE Confidence: 0.79517823

00:16:38.111 --> 00:16:40.573 the individual lobes to analyze

NOTE Confidence: 0.79517823

00:16:40.573 --> 00:16:43.123 the results we collaborated with

NOTE Confidence: 0.79517823

00:16:43.123 --> 00:16:47.270 Roll Rabadan's lab Raul has.

NOTE Confidence: 0.79517823

00:16:47.270 --> 00:16:48.683 Developed you know,

NOTE Confidence: 0.79517823

00:16:48.683 --> 00:16:51.509 amazing algorithms that are based upon

NOTE Confidence: 0.79517823

00:16:51.509 --> 00:16:53.306 rather sophisticated mathematical

NOTE Confidence: 0.79517823

00:16:53.306 --> 00:16:57.056 approaches for analyzing single cell data.

NOTE Confidence: 0.79517823

00:16:57.060 --> 00:16:58.662 So in particular,

NOTE Confidence: 0.79517823

00:16:58.662 --> 00:17:01.332 his laboratory has developed approaches

NOTE Confidence: 0.79517823

00:17:01.332 --> 00:17:04.130 based upon random matrix theory,

NOTE Confidence: 0.79517823

00:17:04.130 --> 00:17:06.310 which demonstrate that these

NOTE Confidence: 0.79517823

00:17:06.310 --> 00:17:08.490 large arrays of data,

NOTE Confidence: 0.79517823

00:17:08.490 --> 00:17:11.927 for example as one generates using so

NOTE Confidence: 0.79517823

00:17:11.927 --> 00:17:16.097 single cell RNA sequencing are mostly noise,

NOTE Confidence: 0.79517823

00:17:16.100 --> 00:17:16.756 so.

NOTE Confidence: 0.79517823

00:17:16.756 --> 00:17:18.724 If you consider.

NOTE Confidence: 0.79517823

00:17:18.724 --> 00:17:21.348 These as giant matrices,

NOTE Confidence: 0.79517823

00:17:21.350 --> 00:17:23.768 well in fact the distribution of

NOTE Confidence: 0.79517823

00:17:23.768 --> 00:17:26.579 eigenvalues follows a sort of conserved

NOTE Confidence: 0.79517823

00:17:26.579 --> 00:17:28.823 mathematical distribution known as

NOTE Confidence: 0.79517823

00:17:28.823 --> 00:17:31.067 the Marchenko Pastur distribution,

NOTE Confidence: 0.849921

00:17:31.070 --> 00:17:34.034 and the deviation for this distribution

NOTE Confidence: 0.849921

00:17:34.034 --> 00:17:36.909 is actually where the signal is,

NOTE Confidence: 0.849921

00:17:36.910 --> 00:17:38.850 and typically it's only

NOTE Confidence: 0.849921

00:17:38.850 --> 00:17:42.248 about 2 to 3% of the data.

NOTE Confidence: 0.849921

00:17:42.248 --> 00:17:45.164 So this is a hypothetical distribution.

NOTE Confidence: 0.849921

00:17:45.170 --> 00:17:47.600 This is actually real data.

NOTE Confidence: 0.849921

00:17:47.600 --> 00:17:51.310 This is one of our prostate datasets.

NOTE Confidence: 0.849921

00:17:51.310 --> 00:17:53.926 And again, here is the signal,

NOTE Confidence: 0.849921

00:17:53.930 --> 00:17:56.546 so his laboratory is developed randomly,

NOTE Confidence: 0.849921

00:17:56.550 --> 00:18:00.498 an algorithm to isolate these data.

NOTE Confidence: 0.849921

00:18:00.500 --> 00:18:02.408 And this proved to be very

NOTE Confidence: 0.849921

00:18:02.408 --> 00:18:03.680 useful in our analysis,

NOTE Confidence: 0.849921

00:18:03.680 --> 00:18:06.039 because it allowed us to identify a

NOTE Confidence: 0.849921

00:18:06.039 --> 00:18:08.198 cell population that would have been

NOTE Confidence: 0.849921

00:18:08.198 --> 00:18:10.364 very difficult to identify other ways.

NOTE Confidence: 0.849921

00:18:10.370 --> 00:18:13.359 So when we examine an aggregated data

NOTE Confidence: 0.849921

00:18:13.359 --> 00:18:17.780 set of whole prostate, we observe.

NOTE Confidence: 0.849921

00:18:17.780 --> 00:18:19.548 Five different lumenal populations.

NOTE Confidence: 0.849921

00:18:19.548 --> 00:18:20.874 First of all,

NOTE Confidence: 0.849921

00:18:20.880 --> 00:18:23.538 we only identify one Basil population.

NOTE Confidence: 0.849921

00:18:23.540 --> 00:18:25.750 So basil cells are actually

NOTE Confidence: 0.849921

00:18:25.750 --> 00:18:26.634 not heterogeneous,

NOTE Confidence: 0.849921

00:18:26.640 --> 00:18:28.408 but instead there's heterogeneity

NOTE Confidence: 0.849921

00:18:28.408 --> 00:18:30.176 in the lumenal population.

NOTE Confidence: 0.849921

00:18:30.180 --> 00:18:31.968 So, first of all,

NOTE Confidence: 0.849921

00:18:31.968 --> 00:18:33.756 there's four distinct lumenal

NOTE Confidence: 0.849921

00:18:33.756 --> 00:18:35.984 populations that correspond to the

NOTE Confidence: 0.849921

00:18:35.984 --> 00:18:38.498 that are located distally in each

NOTE Confidence: 0.849921

00:18:38.498 --> 00:18:40.334 prostate lobes alumet population

NOTE Confidence: 0.849921

00:18:40.334 --> 00:18:42.569 distally in the anterior prostate

NOTE Confidence: 0.849921

00:18:42.569 --> 00:18:46.015 loom D in the distal dorsal prostate

NOTE Confidence: 0.849921

00:18:46.015 --> 00:18:49.460 lumel the lateral movie and eventual.

NOTE Confidence: 0.849921

00:18:49.460 --> 00:18:51.422 Then there is a population that

NOTE Confidence: 0.849921

00:18:51.422 --> 00:18:53.400 we call Lumpi for proxamol.

NOTE Confidence: 0.849921

00:18:53.400 --> 00:18:56.536 It is similar in all four lobes and

NOTE Confidence: 0.849921

00:18:56.536 --> 00:19:00.376 it is it is found more approximately.

NOTE Confidence: 0.849921

00:19:00.380 --> 00:19:00.807 Finally,

NOTE Confidence: 0.849921

00:19:00.807 --> 00:19:02.942 there is a population that

NOTE Confidence: 0.849921

00:19:02.942 --> 00:19:04.223 we call Paraurethral.

NOTE Confidence: 0.849921

00:19:04.230 --> 00:19:05.942 This population has both

NOTE Confidence: 0.849921

00:19:05.942 --> 00:19:07.654 basal and luminal properties,

NOTE Confidence: 0.849921

00:19:07.660 --> 00:19:11.090 and it is found in the region

NOTE Confidence: 0.849921

00:19:11.090 --> 00:19:13.949 most adjacent to the urethra.

NOTE Confidence: 0.849921

00:19:13.950 --> 00:19:16.410 So these are the distinct epithelial

NOTE Confidence: 0.849921

00:19:16.410 --> 00:19:18.050 properties that we've identified.

NOTE Confidence: 0.849921

00:19:18.050 --> 00:19:19.690 We've also identified heterogeneity

NOTE Confidence: 0.849921

00:19:19.690 --> 00:19:20.920 in the stroma,

NOTE Confidence: 0.849921

00:19:20.920 --> 00:19:23.790 but I won't speak to that further.

NOTE Confidence: 0.849921

00:19:23.790 --> 00:19:24.200 So,

NOTE Confidence: 0.849921

00:19:24.200 --> 00:19:26.660 as you can note from this

NOTE Confidence: 0.849921

00:19:26.660 --> 00:19:27.890 sort of illustration,

NOTE Confidence: 0.849921

00:19:27.890 --> 00:19:29.882 there is diversity along

NOTE Confidence: 0.849921

00:19:29.882 --> 00:19:31.874 the proximal distal axis.

NOTE Confidence: 0.849921

00:19:31.880 --> 00:19:34.562 So to give you an idea of what we

NOTE Confidence: 0.849921

00:19:34.562 --> 00:19:37.148 mean by proximal and distal axis,

NOTE Confidence: 0.849921

00:19:37.150 --> 00:19:38.935 here's an anterior prostate that's

NOTE Confidence: 0.849921

00:19:38.935 --> 00:19:41.795 been sort of splayed out and cut in

NOTE Confidence: 0.849921

00:19:41.795 --> 00:19:44.161 histological section when we refer to distal,

NOTE Confidence: 0.849921

00:19:44.170 --> 00:19:45.220 we're actually referring

NOTE Confidence: 0.849921

00:19:45.220 --> 00:19:46.970 to this whole region here.

NOTE Confidence: 0.849921

00:19:46.970 --> 00:19:49.080 That is more than 90% of

NOTE Confidence: 0.849921

00:19:49.080 --> 00:19:50.830 the volume of the prostate.

NOTE Confidence: 0.849921

00:19:50.830 --> 00:19:54.630 The proximal region is just this region here.

NOTE Confidence: 0.849921

00:19:54.630 --> 00:19:57.094 And these regions are quite distinct at

NOTE Confidence: 0.849921

00:19:57.094 --> 00:20:00.189 the level of marker expression as well as.

NOTE Confidence: 0.849921

00:20:00.190 --> 00:20:00.608 Histology,

NOTE Confidence: 0.849921

00:20:00.608 --> 00:20:03.534 so here if we go along the

NOTE Confidence: 0.849921

00:20:03.534 --> 00:20:04.850 proximal distal axis,

NOTE Confidence: 0.849921

00:20:04.850 --> 00:20:06.550 we have the paraurethral

NOTE Confidence: 0.849921

00:20:06.550 --> 00:20:08.250 region has specific markers.

NOTE Confidence: 0.849921

00:20:08.250 --> 00:20:10.370 Here is the proximal region.

NOTE Confidence: 0.849921

00:20:10.370 --> 00:20:13.212 It has a distinct Histology and is

NOTE Confidence: 0.849921

00:20:13.212 --> 00:20:15.378 marked by specific gene expression

NOTE Confidence: 0.849921

00:20:15.378 --> 00:20:18.416 of specific genes such as this one.

NOTE Confidence: 0.849921

00:20:18.420 --> 00:20:20.808 PPP, one R1B.

NOTE Confidence: 0.849921

00:20:20.810 --> 00:20:22.922 Then we have in the distal

NOTE Confidence: 0.849921

00:20:22.922 --> 00:20:24.826 region other markers that are

NOTE Confidence: 0.849921

00:20:24.826 --> 00:20:26.966 specific for distal luminal cells.

NOTE Confidence: 0.849921

00:20:26.970 --> 00:20:28.370 The lume population here,

NOTE Confidence: 0.849921

00:20:28.370 --> 00:20:30.968 but you will note there are also

NOTE Confidence: 0.849921

00:20:30.968 --> 00:20:33.518 proxamol cells that are scattered about.

NOTE Confidence: 0.849921

00:20:33.520 --> 00:20:35.116 They're not very common,

NOTE Confidence: 0.849921

00:20:35.116 --> 00:20:37.938 but you can definitely find them in

NOTE Confidence: 0.849921

00:20:37.938 --> 00:20:40.444 the distal region and then in between.

NOTE Confidence: 0.849921

00:20:40.450 --> 00:20:43.540 There appears to be a boundary

NOTE Confidence: 0.849921

00:20:43.540 --> 00:20:45.600 where these regions meet.

NOTE Confidence: 0.849921

00:20:45.600 --> 00:20:47.840 If you perform electron micrography

NOTE Confidence: 0.849921

00:20:47.840 --> 00:20:51.310 micrography of sort of the boundary region,

NOTE Confidence: 0.849921

00:20:51.310 --> 00:20:54.458 you can see that.

NOTE Confidence: 0.849921

00:20:54.460 --> 00:20:56.872 These lumit lumayan lumpi cells actually

NOTE Confidence: 0.849921

00:20:56.872 --> 00:20:59.260 appear to be distinct cell types,

NOTE Confidence: 0.849921

00:20:59.260 --> 00:21:01.660 so the lume cells again are

NOTE Confidence: 0.849921

00:21:01.660 --> 00:21:03.260 tall columnar secretory cells.

NOTE Confidence: 0.849921

00:21:03.260 --> 00:21:04.460 The loopy cells,

NOTE Confidence: 0.849921

00:21:04.460 --> 00:21:06.060 on the other hand,

NOTE Confidence: 0.849921

00:21:06.060 --> 00:21:08.060 have a more cuboidal appearance,

NOTE Confidence: 0.74194753

00:21:08.060 --> 00:21:11.870 and they don't seem to be

NOTE Confidence: 0.74194753

00:21:11.870 --> 00:21:13.140 particularly secretory.

NOTE Confidence: 0.74194753

00:21:13.140 --> 00:21:14.920 At the transcriptomic level,

NOTE Confidence: 0.74194753

00:21:14.920 --> 00:21:18.253 you can analyze the sort of relationships

NOTE Confidence: 0.74194753

00:21:18.253 --> 00:21:21.727 of these populations with each other.

NOTE Confidence: 0.74194753

00:21:21.730 --> 00:21:24.760 So Luis Aparicio, postdoc INR Lab,

NOTE Confidence: 0.74194753

00:21:24.760 --> 00:21:27.790 who who's done these computational analysis,

NOTE Confidence: 0.74194753

00:21:27.790 --> 00:21:32.075 has used. An approach based upon optimal

NOTE Confidence: 0.74194753

00:21:32.075 --> 00:21:34.050 transport theory to calculate Wasserstein

NOTE Confidence: 0.74194753

00:21:34.105 --> 00:21:36.077 distances between these populations,

NOTE Confidence: 0.74194753

00:21:36.080 --> 00:21:37.784 and then relate these

NOTE Confidence: 0.74194753

00:21:37.784 --> 00:21:39.488 populations to each other.

NOTE Confidence: 0.74194753

00:21:39.490 --> 00:21:42.906 You can see that Lumpi is sort of,

NOTE Confidence: 0.74194753

00:21:42.910 --> 00:21:45.670 you know, sort of at the center related

NOTE Confidence: 0.74194753

00:21:45.670 --> 00:21:48.460 to the distal lumenal populations,

NOTE Confidence: 0.74194753

00:21:48.460 --> 00:21:51.808 and then PR you and basil.

NOTE Confidence: 0.74194753

00:21:51.810 --> 00:21:56.076 So in order to investigate the

NOTE Confidence: 0.74194753

00:21:56.076 --> 00:21:59.630 function of these populations, we've.

NOTE Confidence: 0.8025036

00:22:02.530 --> 00:22:04.738 And so, as you might imagine

NOTE Confidence: 0.8025036

00:22:04.738 --> 00:22:07.330 from this sort of relationship,

NOTE Confidence: 0.8025036

00:22:07.330 --> 00:22:10.018 we observed that there is greater

NOTE Confidence: 0.8025036

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

00:22:14.735 --> 00:22:16.475 the distal lumenal population.

NOTE Confidence: 0.8025036

00:22:16.480 --> 00:22:19.096 So here's an organoid formation assay.

NOTE Confidence: 0.8025036

00:22:19.100 --> 00:22:22.285 You can see that the distal lumenal

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

00:22:49.360 --> 00:22:53.040 and then we can analyze the sort of

NOTE Confidence: 0.8025036

00:22:53.040 --> 00:22:56.860 cell types present within these graphs.

NOTE Confidence: 0.8025036

00:22:56.860 --> 00:22:59.471 So using the markers that we've identified

NOTE Confidence: 0.8025036

00:22:59.471 --> 00:23:01.918 that is specific for each population.

NOTE Confidence: 0.8025036

00:23:01.920 --> 00:23:02.696 In brief,

NOTE Confidence: 0.8025036

00:23:02.696 --> 00:23:05.024 the loom a another distal luminal.

NOTE Confidence: 0.8025036

00:23:05.030 --> 00:23:07.358 Cells can make more of themselves,

NOTE Confidence: 0.8025036

00:23:07.360 --> 00:23:10.090 but not the loom PNP Ru populations,

NOTE Confidence: 0.8025036

00:23:10.090 --> 00:23:12.030 where is the loom PNP?

NOTE Confidence: 0.8025036

00:23:12.030 --> 00:23:14.364 Ru populations can make all of

NOTE Confidence: 0.8025036

00:23:14.364 --> 00:23:15.920 the other different populations,

NOTE Confidence: 0.8025036

00:23:15.920 --> 00:23:20.640 so this supports a sort of a projector.

NOTE Confidence: 0.8025036

00:23:20.640 --> 00:23:22.719 Increased progenitor potential

NOTE Confidence: 0.8025036

00:23:22.719 --> 00:23:26.184 for loom PNP RU populations.

NOTE Confidence: 0.8025036

00:23:26.190 --> 00:23:28.374 So finally one can ask what

NOTE Confidence: 0.8025036

00:23:28.374 --> 00:23:29.830 is the relationship between

NOTE Confidence: 0.8025036

00:23:29.906 --> 00:23:31.826 the mouse and human prostate?

NOTE Confidence: 0.8025036

00:23:31.830 --> 00:23:32.592 After all,

NOTE Confidence: 0.8025036

00:23:32.592 --> 00:23:34.497 anatomically they are quite different

NOTE Confidence: 0.8025036

00:23:34.497 --> 00:23:35.970 and histologically as well,

NOTE Confidence: 0.8025036

00:23:35.970 --> 00:23:37.970 so we've.

NOTE Confidence: 0.8025036

00:23:37.970 --> 00:23:39.646 Analyzed three independent benign

NOTE Confidence: 0.8025036

00:23:39.646 --> 00:23:41.322 prostatectomy specimens at the

NOTE Confidence: 0.8025036

00:23:41.322 --> 00:23:43.258 single cell level, and again,

NOTE Confidence: 0.8025036

00:23:43.258 --> 00:23:45.736 we can see that there is a

NOTE Confidence: 0.8025036

00:23:45.736 --> 00:23:47.540 single basil population,

NOTE Confidence: 0.8025036

00:23:47.540 --> 00:23:49.204 but they're different lumenal

NOTE Confidence: 0.8025036

00:23:49.204 --> 00:23:51.700 populations that we can relate to.

NOTE Confidence: 0.8025036

00:23:51.700 --> 00:23:52.945 The lumenal populations

NOTE Confidence: 0.8025036

00:23:52.945 --> 00:23:55.435 that we see in the mouse,

NOTE Confidence: 0.8025036

00:23:55.440 --> 00:23:57.714 so there isn't a snare population

NOTE Confidence: 0.8025036

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.

NOTE Confidence: 0.8025036

00:24:40.880 --> 00:24:43.743 It perhaps is most closely related to

NOTE Confidence: 0.8025036

00:24:43.743 --> 00:24:47.559 the bulk of the human prostate epithelium.

NOTE Confidence: 0.8025036

00:24:47.560 --> 00:24:50.416 Yet the lateral lobe is understudied

NOTE Confidence: 0.8025036

00:24:50.416 --> 00:24:51.844 in the mouse,

NOTE Confidence: 0.8025036

00:24:51.850 --> 00:24:56.386 and particularly analysis of cancer models.

NOTE Confidence: 0.8025036

00:24:56.390 --> 00:25:00.395 So now I'd like to turn to cancer a

NOTE Confidence: 0.8025036

00:25:00.395 --> 00:25:04.436 little bit and think about plasticity

NOTE Confidence: 0.8025036

00:25:04.436 --> 00:25:07.220 in advanced prostate cancer.

NOTE Confidence: 0.8025036

00:25:07.220 --> 00:25:11.609 So in the current spectrum of of.

NOTE Confidence: 0.8025036

00:25:11.610 --> 00:25:14.910 Prostate cancer where we have.

NOTE Confidence: 0.8025036

00:25:14.910 --> 00:25:17.265 Treatment of with potent anti

NOTE Confidence: 0.8025036

00:25:17.265 --> 00:25:20.314 androgens that are very efficient at

NOTE Confidence: 0.8025036

00:25:20.314 --> 00:25:22.766 suppressing energon receptor function.

NOTE Confidence: 0.8025036

00:25:22.770 --> 00:25:23.252 Now,

NOTE Confidence: 0.8025036

00:25:23.252 --> 00:25:25.662 castration resistant prostate cancer is

NOTE Confidence: 0.8025036

00:25:25.662 --> 00:25:29.060 displaying a range of different entities.

NOTE Confidence: 0.8025036

00:25:29.060 --> 00:25:32.604 As sort of a spectrum that can be

NOTE Confidence: 0.8025036

00:25:32.604 --> 00:25:34.979 distinguished perhaps by different

NOTE Confidence: 0.8025036

00:25:34.979 --> 00:25:36.854 differential lineages, plasticity.

NOTE Confidence: 0.8025036

00:25:36.854 --> 00:25:40.102 So there is prostate cancer that is

NOTE Confidence: 0.8025036

00:25:40.102 --> 00:25:43.356 remains a our pathway positive it

NOTE Confidence: 0.8025036

00:25:43.356 --> 00:25:45.600 still expresses androgen receptor

NOTE Confidence: 0.8025036

00:25:45.600 --> 00:25:49.008 despite the presence of anti androgens.

NOTE Confidence: 0.8025036

00:25:49.010 --> 00:25:52.670 And then at the other extreme

NOTE Confidence: 0.8025036

00:25:52.670 --> 00:25:55.110 we have neuroendocrine prostate

NOTE Confidence: 0.8025036

00:25:55.210 --> 00:25:58.710 cancer which is a are negative and.

NOTE Confidence: 0.8025036

00:25:58.710 --> 00:26:00.852 He's most extreme forms can display

NOTE Confidence: 0.8025036

00:26:00.852 --> 00:26:02.764 a small cell phenotype that's

NOTE Confidence: 0.8025036

00:26:02.764 --> 00:26:04.440 very aggressive and lethal,

NOTE Confidence: 0.8413423

00:26:04.440 --> 00:26:06.325 so there's been considerable interest

NOTE Confidence: 0.8413423

00:26:06.325 --> 00:26:08.210 in the mechanisms of neuroendocrine

NOTE Confidence: 0.8413423

00:26:08.271 --> 00:26:10.325 differentiation in CR, PC, and so.

NOTE Confidence: 0.8413423

00:26:10.325 --> 00:26:13.469 There have been studies of CR PC that are

NOTE Confidence: 0.8413423

00:26:13.469 --> 00:26:16.277 trying to distinguish the different entities,

NOTE Confidence: 0.8413423

00:26:16.280 --> 00:26:18.572 and, for example, there is something

NOTE Confidence: 0.8413423

00:26:18.572 --> 00:26:19.718 considered double negative.

NOTE Confidence: 0.8413423

00:26:19.720 --> 00:26:22.012 That is a are negative and

NOTE Confidence: 0.8413423

00:26:22.012 --> 00:26:22.776 neuroendocrine negative,

NOTE Confidence: 0.8413423

00:26:22.780 --> 00:26:25.503 which is defined more by what it

NOTE Confidence: 0.8413423

00:26:25.503 --> 00:26:28.120 is not rather than what it is,

NOTE Confidence: 0.8413423

00:26:28.120 --> 00:26:30.200 but the relationships between these.

NOTE Confidence: 0.8413423

00:26:30.200 --> 00:26:32.624 Distinct entities is unclear,

NOTE Confidence: 0.8413423

00:26:32.624 --> 00:26:39.128 and it may be simple, maybe more complex.

NOTE Confidence: 0.8413423

00:26:39.130 --> 00:26:41.152 But there is widespread agreement that

NOTE Confidence: 0.8413423

00:26:41.152 --> 00:26:43.904 there must be a role for epigenetic

NOTE Confidence: 0.8413423

00:26:43.904 --> 00:26:46.700 reprogramming in this process, and so.

NOTE Confidence: 0.8413423

00:26:46.700 --> 00:26:50.235 A range of studies have provided evidence

NOTE Confidence: 0.8413423

00:26:50.235 --> 00:26:54.105 that there's increase in ezh two as PRC.

NOTE Confidence: 0.8413423

00:26:54.110 --> 00:26:56.888 Two activity in this spectrum of

NOTE Confidence: 0.8413423

00:26:56.888 --> 00:26:58.740 plasticity and recently flybot

NOTE Confidence: 0.8413423

00:26:58.818 --> 00:27:01.387 John Cody's lab has shown that PRC

NOTE Confidence: 0.8413423

00:27:01.387 --> 00:27:04.081 one activity is elevated in double

NOTE Confidence: 0.8413423

00:27:04.081 --> 00:27:06.097 negative prostate cancer etc.

NOTE Confidence: 0.8413423

00:27:06.100 --> 00:27:08.554 But this is all involved studies

NOTE Confidence: 0.8413423

00:27:08.554 --> 00:27:11.731 either in cell lines or in human

NOTE Confidence: 0.8413423

00:27:11.731 --> 00:27:13.195 prostate cancer specimens,

NOTE Confidence: 0.8413423

00:27:13.200 --> 00:27:16.698 so it's been difficult to sort

NOTE Confidence: 0.8413423

00:27:16.698 --> 00:27:19.030 of study these things.

NOTE Confidence: 0.8413423

00:27:19.030 --> 00:27:22.320 You know at a more detailed level

NOTE Confidence: 0.8413423

00:27:22.320 --> 00:27:25.989 and in terms of mechanism as well.

NOTE Confidence: 0.8413423

00:27:25.990 --> 00:27:27.938 So to approach this,

NOTE Confidence: 0.8413423

00:27:27.938 --> 00:27:32.115 we started with a mouse model that we

NOTE Confidence: 0.8413423

00:27:32.115 --> 00:27:34.990 had been analyzing in collaboration

NOTE Confidence: 0.8413423

00:27:34.990 --> 00:27:37.889 with Korea Body Schenz lab.

NOTE Confidence: 0.8413423

00:27:37.890 --> 00:27:41.768 So the NPP 53 mouse model uses

NOTE Confidence: 0.8413423

00:27:41.768 --> 00:27:44.929 inducible deletion of P-10 and P53.

NOTE Confidence: 0.8413423

00:27:44.930 --> 00:27:48.680 Of these animals develop a castration

NOTE Confidence: 0.8413423

00:27:48.680 --> 00:27:51.740 resistant prostate cancer that will.

NOTE Confidence: 0.8413423

00:27:51.740 --> 00:27:53.364 Display features of neuroendocrine

NOTE Confidence: 0.8413423

00:27:53.364 --> 00:27:55.800 differentiation and we were able to

NOTE Confidence: 0.8413423

00:27:55.862 --> 00:27:58.067 distinguish what we called focal

NOTE Confidence: 0.8413423

00:27:58.067 --> 00:27:59.390 neuroendocrine differentiation in

NOTE Confidence: 0.8413423

00:27:59.390 --> 00:28:01.775 which the neuroendocrine cells are

NOTE Confidence: 0.8413423

00:28:01.775 --> 00:28:04.180 not proliferative from overt nor

NOTE Confidence: 0.8413423

00:28:04.180 --> 00:28:06.044 endocrine differentiation which often

NOTE Confidence: 0.8413423

00:28:06.044 --> 00:28:08.279 displays a small cell phenotype.

NOTE Confidence: 0.8413423

00:28:08.280 --> 00:28:10.068 These are highly proliferative

NOTE Confidence: 0.8413423

00:28:10.068 --> 00:28:11.409 or endocrine cells.

NOTE Confidence: 0.8413423

00:28:11.410 --> 00:28:14.539 However, since we use lineages marking here,

NOTE Confidence: 0.8413423

00:28:14.540 --> 00:28:17.288 we could show that the neuroendocrine

NOTE Confidence: 0.8413423

00:28:17.288 --> 00:28:20.349 cells are derived from a luminal cell,

NOTE Confidence: 0.8413423

00:28:20.350 --> 00:28:22.540 so the initial.

NOTE Confidence: 0.8413423

00:28:22.540 --> 00:28:26.190 Tumor induction was from luminal

NOTE Confidence: 0.8413423

00:28:26.190 --> 00:28:29.420 cells and then we have.

NOTE Confidence: 0.8413423

00:28:29.420 --> 00:28:29.939 Alright,

NOTE Confidence: 0.8413423

00:28:29.939 --> 00:28:32.534 formation of CR PC neuroendocrine

NOTE Confidence: 0.8413423

00:28:32.534 --> 00:28:35.123 differentiation and then there is

NOTE Confidence: 0.8413423

00:28:35.123 --> 00:28:37.293 some type of proliferative switch

NOTE Confidence: 0.8413423

00:28:37.293 --> 00:28:39.680 that we don't understand that

NOTE Confidence: 0.8413423

00:28:39.680 --> 00:28:42.565 results in this highly proliferative

NOTE Confidence: 0.8413423

00:28:42.565 --> 00:28:44.296 neuroendocrine prostate cancer.

NOTE Confidence: 0.8413423

00:28:44.300 --> 00:28:47.555 So because we use linear tracing here,

NOTE Confidence: 0.8413423

00:28:47.560 --> 00:28:50.788 we provided evidence that in fact

NOTE Confidence: 0.8413423

00:28:50.788 --> 00:28:53.470 this was a transdifferentiation of

NOTE Confidence: 0.8413423

00:28:53.470 --> 00:28:56.098 luminal cells to neuron can cells.

NOTE Confidence: 0.8413423

00:28:56.100 --> 00:28:58.788 So when we think about transdifferentiation,

NOTE Confidence: 0.8413423

00:28:58.790 --> 00:29:01.060 there's sort of a fundamental

NOTE Confidence: 0.8413423

00:29:01.060 --> 00:29:02.876 question both in developmental

NOTE Confidence: 0.8413423

00:29:02.876 --> 00:29:05.058 as well as cancer context,

NOTE Confidence: 0.8413423

00:29:05.060 --> 00:29:07.070 which is what is really going

NOTE Confidence: 0.8413423

00:29:07.070 --> 00:29:10.361 on in terms of the pathways that

NOTE Confidence: 0.8413423

00:29:10.361 --> 00:29:12.230 result in transdifferentiation.

NOTE Confidence: 0.8413423

00:29:12.230 --> 00:29:12.679 Well,

NOTE Confidence: 0.8413423

00:29:12.679 --> 00:29:15.373 it's possible that this change in

NOTE Confidence: 0.8413423

00:29:15.373 --> 00:29:18.447 identity occurs through a transition that

NOTE Confidence: 0.8413423

00:29:18.447 --> 00:29:20.647 happens normally during development.

NOTE Confidence: 0.8413423

00:29:20.650 --> 00:29:21.133 Alternatively,

NOTE Confidence: 0.8413423

00:29:21.133 --> 00:29:23.548 it's possible that this change

NOTE Confidence: 0.8413423

00:29:23.548 --> 00:29:25.919 in identity occurs through a

NOTE Confidence: 0.8413423

00:29:25.919 --> 00:29:28.133 transition that is wholly or at

NOTE Confidence: 0.8413423

00:29:28.133 --> 00:29:30.228 least partially novel that doesn't

NOTE Confidence: 0.8413423

00:29:30.228 --> 00:29:32.528 really occur in normal development,

NOTE Confidence: 0.8413423

00:29:32.530 --> 00:29:35.890 so there could be a hijacking of

NOTE Confidence: 0.8413423

00:29:35.890 --> 00:29:38.843 an alternative pathway or or some

NOTE Confidence: 0.8413423

00:29:38.843 --> 00:29:41.203 other pathway or process that

NOTE Confidence: 0.8413423

00:29:41.203 --> 00:29:43.808 doesn't occur in normal context.

NOTE Confidence: 0.8413423

00:29:43.810 --> 00:29:45.082 To understand this,

NOTE Confidence: 0.8413423

00:29:45.082 --> 00:29:48.915 of course it is first of all important

NOTE Confidence: 0.8413423

00:29:48.915 --> 00:29:52.007 to discover how neuroendocrine

NOTE Confidence: 0.8413423

00:29:52.007 --> 00:29:54.326 cells differentiate normally.

NOTE Confidence: 0.8413423

00:29:54.330 --> 00:29:54.791 So.

NOTE Confidence: 0.8413423

00:29:54.791 --> 00:29:57.096 It's remarkable that there's very

NOTE Confidence: 0.8413423

00:29:57.096 --> 00:30:00.309 little in the published literature about.

NOTE Confidence: 0.8413423

00:30:00.310 --> 00:30:01.591 Origin in fact,

NOTE Confidence: 0.8413423

00:30:01.591 --> 00:30:03.299 features of neuroendocrine cells

NOTE Confidence: 0.8413423

00:30:03.299 --> 00:30:05.270 in the normal prostate,

NOTE Confidence: 0.834509

00:30:05.270 --> 00:30:07.832 enlarged likely because they are quite

NOTE Confidence: 0.834509

00:30:07.832 --> 00:30:10.574 rare and what is also interesting

NOTE Confidence: 0.834509

00:30:10.574 --> 00:30:13.418 is that there are different models

NOTE Confidence: 0.834509

00:30:13.418 --> 00:30:16.550 have been put forth for their origin.

NOTE Confidence: 0.834509

00:30:16.550 --> 00:30:19.004 So one model says that they

NOTE Confidence: 0.834509

00:30:19.004 --> 00:30:21.230 actually are of epithelial origin

NOTE Confidence: 0.834509

00:30:21.230 --> 00:30:23.760 and arise from Basel progenitors.

NOTE Confidence: 0.834509

00:30:23.760 --> 00:30:27.488 Another model is that they arise from neural

NOTE Confidence: 0.834509

00:30:27.488 --> 00:30:31.268 Crest and so Cedric Pompons lab published.

NOTE Confidence: 0.834509

00:30:31.270 --> 00:30:32.625 That they came from basil

NOTE Confidence: 0.834509

00:30:32.625 --> 00:30:34.370 cells and a more recent paper.

NOTE Confidence: 0.834509

00:30:34.370 --> 00:30:36.512 From that they're from their old Crest

NOTE Confidence: 0.834509

00:30:36.512 --> 00:30:39.018 in both these papers use linear tracing.

NOTE Confidence: 0.834509

00:30:39.020 --> 00:30:41.316 In fact, we believe that both of

NOTE Confidence: 0.834509

00:30:41.316 --> 00:30:43.595 these papers are incorrect and most

NOTE Confidence: 0.834509

00:30:43.595 --> 00:30:46.043 likely they arise from an early

NOTE Confidence: 0.834509

00:30:46.043 --> 00:30:48.000 urogenital epithelial progenitor.

NOTE Confidence: 0.834509

00:30:48.000 --> 00:30:50.436 So neuroendocrine cells are very rare.

NOTE Confidence: 0.834509

00:30:50.440 --> 00:30:52.888 But what is make some particularly

NOTE Confidence: 0.834509

00:30:52.888 --> 00:30:55.338 in the mouse, prostate is they're

NOTE Confidence: 0.834509

00:30:55.338 --> 00:30:56.556 highly asymmetrically distributed,

NOTE Confidence: 0.834509

00:30:56.560 --> 00:30:59.824 so they are mostly found in the proximal

NOTE Confidence: 0.834509

00:30:59.824 --> 00:31:02.280 region, which I showed you earlier.

NOTE Confidence: 0.834509

00:31:02.280 --> 00:31:04.722 So nearly all the owner can

NOTE Confidence: 0.834509

00:31:04.722 --> 00:31:05.943 cells are proxamol.

NOTE Confidence: 0.834509

00:31:05.950 --> 00:31:09.078 They're very rare distally.

NOTE Confidence: 0.834509

00:31:09.080 --> 00:31:10.896 And remarkably, neuroendocrine cells,

NOTE Confidence: 0.834509

00:31:10.896 --> 00:31:12.258 despite their rarity,

NOTE Confidence: 0.834509

00:31:12.260 --> 00:31:13.488 are heterogeneous.

NOTE Confidence: 0.834509

00:31:13.488 --> 00:31:17.174 So about 80% of neuron can cells

NOTE Confidence: 0.834509

00:31:17.174 --> 00:31:19.018 have adluminal like phenotype.

NOTE Confidence: 0.834509

00:31:19.020 --> 00:31:21.400 They actually express androgen receptor

NOTE Confidence: 0.834509

00:31:21.400 --> 00:31:23.780 remarkably and they express lumenal

NOTE Confidence: 0.834509

00:31:23.845 --> 00:31:26.387 cytokeratins and then another 20% of

NOTE Confidence: 0.834509

00:31:26.387 --> 00:31:29.069 your endocrine cells are basil like

NOTE Confidence: 0.834509

00:31:29.069 --> 00:31:31.929 they expressed basal cytokeratins and P.

NOTE Confidence: 0.834509

00:31:31.930 --> 00:31:34.210 63.

NOTE Confidence: 0.834509

00:31:34.210 --> 00:31:36.826 They can be detected very early

NOTE Confidence: 0.834509

00:31:36.826 --> 00:31:39.070 in organic Genesis at burn.

NOTE Confidence: 0.7690831

00:31:45.930 --> 00:31:49.157 Many, most perhaps all Durand Prince cells

NOTE Confidence: 0.7690831

00:31:49.157 --> 00:31:52.260 are actually formed at prepubertal stages,

NOTE Confidence: 0.7690831

00:31:52.260 --> 00:31:55.740 and since neuroendocrine cells I didn't

NOTE Confidence: 0.7690831

00:31:55.740 --> 00:31:59.059 mention this on previous slide are.

NOTE Confidence: 0.7690831

00:31:59.060 --> 00:32:00.492 But never divide there.

NOTE Confidence: 0.7690831

00:32:00.492 --> 00:32:02.640 They appear to be post mitotic.

NOTE Confidence: 0.7690831

00:32:02.640 --> 00:32:05.615 We believe that they are made and

NOTE Confidence: 0.7690831

00:32:05.615 --> 00:32:07.760 are not subsequently generated.

NOTE Confidence: 0.7690831

00:32:07.760 --> 00:32:09.995 By lineages tracing, we believe

NOTE Confidence: 0.7690831

00:32:09.995 --> 00:32:12.830 that they have an epithelial origin,

NOTE Confidence: 0.7690831

00:32:12.830 --> 00:32:15.846 so using an NCX Cree driver we can

NOTE Confidence: 0.7690831

00:32:15.846 --> 00:32:18.503 mark most of the prostate epithelial

NOTE Confidence: 0.7690831

00:32:18.503 --> 00:32:22.399 cells and in fact the vast majority of

NOTE Confidence: 0.7690831

00:32:22.399 --> 00:32:26.193 neuroendocrine cells are marked by NCX Creek,

NOTE Confidence: 0.7690831

00:32:26.200 --> 00:32:28.966 so we believe they have a

NOTE Confidence: 0.7690831

00:32:28.966 --> 00:32:30.349 prostate epithelial origin.

NOTE Confidence: 0.7690831

00:32:30.350 --> 00:32:33.806 So there's more than 95% of the

NOTE Confidence: 0.7690831

00:32:33.806 --> 00:32:36.118 neuroendocrine cells are marked

NOTE Confidence: 0.7690831

00:32:36.118 --> 00:32:37.852 in this experiment.

NOTE Confidence: 0.7690831

00:32:37.860 --> 00:32:43.080 Can finally neuroendocrine cells you know?

NOTE Confidence: 0.7690831

00:32:43.080 --> 00:32:43.944 Likely arise,

NOTE Confidence: 0.7690831

00:32:43.944 --> 00:32:46.968 as has been shown in the lung

NOTE Confidence: 0.7690831

00:32:46.968 --> 00:32:49.269 through a pro neural pathway,

NOTE Confidence: 0.7690831

00:32:49.270 --> 00:32:52.518 in which sort of the master regulator

NOTE Confidence: 0.7690831

00:32:52.518 --> 00:32:57.796 at the top of of this of the sort of

NOTE Confidence: 0.7690831

00:32:57.796 --> 00:33:00.489 transcription factor hierarchy is ASE L1.

NOTE Confidence: 0.7690831

00:33:00.490 --> 00:33:03.521 So if we delete ACL one in

NOTE Confidence: 0.7690831

00:33:03.521 --> 00:33:04.820 the mouse prostate,

NOTE Confidence: 0.7690831

00:33:04.820 --> 00:33:07.376 we can actually recover mice that

NOTE Confidence: 0.7690831

00:33:07.376 --> 00:33:09.080 have prostates that completely

NOTE Confidence: 0.7690831

00:33:09.149 --> 00:33:10.877 lack your endocrine cells.

NOTE Confidence: 0.7690831

00:33:10.880 --> 00:33:14.192 And yet the prostate appears to be normal

NOTE Confidence: 0.7690831

00:33:14.192 --> 00:33:17.380 and there is a normal proximal region.

NOTE Confidence: 0.7690831

00:33:17.380 --> 00:33:20.926 So we do have a rare escaper cells in

NOTE Confidence: 0.7690831

00:33:20.926 --> 00:33:24.545 the Periorbital region which are likely

NOTE Confidence: 0.7690831

00:33:24.545 --> 00:33:28.730 due to incomplete deletion by index 3.1.

NOTE Confidence: 0.7690831

00:33:28.730 --> 00:33:31.022 So our current model for the

NOTE Confidence: 0.7690831

00:33:31.022 --> 00:33:33.503 origin of your endocrine cells is

NOTE Confidence: 0.7690831

00:33:33.503 --> 00:33:36.137 that they likely arise from your

NOTE Confidence: 0.7690831

00:33:36.137 --> 00:33:37.890 original epithelial progenitor,

NOTE Confidence: 0.7690831

00:33:37.890 --> 00:33:39.490 although we haven't excluded

NOTE Confidence: 0.7690831

00:33:39.490 --> 00:33:41.490 the possibility they arise from

NOTE Confidence: 0.7690831

00:33:41.490 --> 00:33:43.550 an early lumenal progenitor.

NOTE Confidence: 0.7690831

00:33:43.550 --> 00:33:46.406 But in either case progenitor activity

NOTE Confidence: 0.7690831

00:33:46.406 --> 00:33:48.758 coincides with the developmental stages

NOTE Confidence: 0.7690831

00:33:48.758 --> 00:33:51.397 in which androgen levels are very low,

NOTE Confidence: 0.7690831

00:33:51.400 --> 00:33:53.764 and we're currently studying.

NOTE Confidence: 0.7690831

00:33:53.764 --> 00:33:56.128 The molecular properties of

NOTE Confidence: 0.7690831

00:33:56.128 --> 00:33:57.840 normal neuroendocrine cells.

NOTE Confidence: 0.7690831

00:33:57.840 --> 00:34:02.028 To understand you know in more

NOTE Confidence: 0.7690831

00:34:02.028 --> 00:34:04.122 detail their regulation.

NOTE Confidence: 0.7690831

00:34:04.130 --> 00:34:05.994 Moving on to cancer,

NOTE Confidence: 0.7690831

00:34:05.994 --> 00:34:09.655 we've used the NP 53 mouse model

NOTE Confidence: 0.7690831

00:34:09.655 --> 00:34:13.470 to generate organoid lines that

NOTE Confidence: 0.7690831

00:34:13.470 --> 00:34:16.522 displayed neuroendocrine phenotypes so.

NOTE Confidence: 0.7690831

00:34:16.530 --> 00:34:18.924 This is work from a talented

NOTE Confidence: 0.7690831

00:34:18.924 --> 00:34:20.895 postdoc in my lab, Jolly.

NOTE Confidence: 0.7690831

00:34:20.895 --> 00:34:23.895 She has used NP 53 tumors and established

NOTE Confidence: 0.7690831

00:34:23.895 --> 00:34:26.898 a large number of organ would lines,

NOTE Confidence: 0.7690831

00:34:26.900 --> 00:34:29.300 some of which have neuroendocrine features.

NOTE Confidence: 0.7690831

00:34:29.300 --> 00:34:31.290 As you can see here,

NOTE Confidence: 0.7690831

00:34:31.290 --> 00:34:34.090 this is the sort of primary tumor,

NOTE Confidence: 0.7690831

00:34:34.090 --> 00:34:36.478 and you'll note that it's heterogeneous.

NOTE Confidence: 0.7690831

00:34:36.480 --> 00:34:38.072 These are the organoids

NOTE Confidence: 0.7690831

00:34:38.072 --> 00:34:39.266 are established there,

NOTE Confidence: 0.7690831

00:34:39.270 --> 00:34:41.670 green because of the linear smirking.

NOTE Confidence: 0.7690831

00:34:41.670 --> 00:34:44.365 Here's a different line that you can

NOTE Confidence: 0.7690831

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 --> 00:35:04.420 So here's a line that's

NOTE Confidence: 0.7690831

00:35:04.420 --> 00:35:05.228 relatively homogeneous.

NOTE Confidence: 0.7690831

00:35:05.230 --> 00:35:07.235 It expresses Synaptophysin and Chromogranin

NOTE Confidence: 0.7690831

00:35:07.235 --> 00:35:11.080 a so it has a neuroendocrine phenotype.

NOTE Confidence: 0.7690831

00:35:11.080 --> 00:35:13.929 Here's a different line that is more

NOTE Confidence: 0.7690831

00:35:13.929 --> 00:35:16.464 heterogeneous there that has sort of

NOTE Confidence: 0.7690831

00:35:16.464 --> 00:35:18.120 mixed expression of neuroendocrine

NOTE Confidence: 0.7690831

00:35:18.120 --> 00:35:20.900 markers as well as androgen receptors.

NOTE Confidence: 0.7690831

00:35:20.900 --> 00:35:22.238 To some extent,

NOTE Confidence: 0.7690831

00:35:22.238 --> 00:35:24.914 it actually has a double positive

NOTE Confidence: 0.7690831

00:35:24.914 --> 00:35:27.000 or African phenotype.

NOTE Confidence: 0.7690831

00:35:27.000 --> 00:35:29.520 This is a heterogeneous line that

NOTE Confidence: 0.7690831

00:35:29.520 --> 00:35:31.200 I showed you earlier,

NOTE Confidence: 0.7690831

00:35:31.200 --> 00:35:33.797 so it is it has intermixing of

NOTE Confidence: 0.7690831

00:35:33.797 --> 00:35:35.924 neuroendocrine cells and non your

NOTE Confidence: 0.7690831

00:35:35.924 --> 00:35:37.812 endocrine cells that express

NOTE Confidence: 0.7690831

00:35:37.812 --> 00:35:38.756 androgen receptor.

NOTE Confidence: 0.84401006

00:35:38.760 --> 00:35:41.466 Here is a different heterogeneous line

NOTE Confidence: 0.84401006

00:35:41.466 --> 00:35:44.420 again with a similar intermingling.

NOTE Confidence: 0.84401006

00:35:44.420 --> 00:35:46.690 So these new rendering lines,

NOTE Confidence: 0.84401006

00:35:46.690 --> 00:35:48.506 whether homogeneous or heterogeneous

NOTE Confidence: 0.84401006

00:35:48.506 --> 00:35:50.776 or highly stable during passaging,

NOTE Confidence: 0.84401006

00:35:50.780 --> 00:35:53.045 they can be passaged for

NOTE Confidence: 0.84401006

00:35:53.045 --> 00:35:54.857 more than 20 passages,

NOTE Confidence: 0.84401006

00:35:54.860 --> 00:35:57.825 and the heterogeneous lines will

NOTE Confidence: 0.84401006

00:35:57.825 --> 00:35:59.604 maintain their heterogeneity.

NOTE Confidence: 0.84401006

00:35:59.610 --> 00:36:01.848 So we can analyze the heterogeneity

NOTE Confidence: 0.84401006

00:36:01.848 --> 00:36:04.046 using single cell RNA sequencing and

NOTE Confidence: 0.84401006

00:36:04.046 --> 00:36:06.940 so this is the first line I showed you,

NOTE Confidence: 0.84401006

00:36:06.940 --> 00:36:08.332 and Interestingly the clusters

NOTE Confidence: 0.84401006

00:36:08.332 --> 00:36:10.072 are sort of grouped together,

NOTE Confidence: 0.84401006

00:36:10.080 --> 00:36:13.550 so we have an ARPU C cluster on any PC

NOTE Confidence: 0.84401006

00:36:13.646 --> 00:36:17.666 cluster and and and and a grouping of DN PC.

NOTE Confidence: 0.84401006

00:36:17.670 --> 00:36:20.220 And this is this is the

NOTE Confidence: 0.84401006

00:36:20.220 --> 00:36:21.495 other heterogeneous line,

NOTE Confidence: 0.84401006

00:36:21.500 --> 00:36:25.716 and we see a similar arrangement of clusters.

NOTE Confidence: 0.84401006

00:36:25.720 --> 00:36:28.720 So the heterogeneity of these organize

NOTE Confidence: 0.84401006

00:36:28.720 --> 00:36:31.691 is striking because it suggests that

NOTE Confidence: 0.84401006

00:36:31.691 --> 00:36:34.349 we've been we're able to capture

NOTE Confidence: 0.84401006

00:36:34.349 --> 00:36:38.563 much of the spectrum of CR PC within

NOTE Confidence: 0.84401006

00:36:38.563 --> 00:36:40.727 organoids established organoid lines.

NOTE Confidence: 0.84401006

00:36:40.730 --> 00:36:44.015 So what can we do with these organoid lines?

NOTE Confidence: 0.84401006

00:36:44.020 --> 00:36:46.948 Well, we can do a number of things.

NOTE Confidence: 0.84401006

00:36:46.950 --> 00:36:49.860 One thing is we can examine, you know,

NOTE Confidence: 0.84401006

00:36:49.860 --> 00:36:52.345 sort of the epigenetic marks that are

NOTE Confidence: 0.84401006

00:36:52.345 --> 00:36:54.267 displayed in these organoid lines.

NOTE Confidence: 0.84401006

00:36:54.270 --> 00:36:55.362 So for example,

NOTE Confidence: 0.84401006

00:36:55.362 --> 00:36:57.546 we've been pursuing cut and tag

NOTE Confidence: 0.84401006

00:36:57.546 --> 00:36:58.300 analysis here,

NOTE Confidence: 0.84401006

00:36:58.300 --> 00:37:00.396 looking at H3K27 trimethyl.

NOTE Confidence: 0.84401006

00:37:00.396 --> 00:37:04.469 So this is the mark deposited by PRC 2.

NOTE Confidence: 0.84401006

00:37:04.470 --> 00:37:07.277 And so I'll just show you just

NOTE Confidence: 0.84401006

00:37:07.277 --> 00:37:09.549 little this little tidbit here.

NOTE Confidence: 0.84401006

00:37:09.550 --> 00:37:11.815 What's interesting here is that

NOTE Confidence: 0.84401006

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

00:38:34.497 --> 00:38:37.791 and when we can predict master

NOTE Confidence: 0.84401006

00:38:37.791 --> 00:38:40.826 regulators using this sort of approach.

NOTE Confidence: 0.84401006

00:38:40.826 --> 00:38:44.378 Notably one of the newer endocrine master

NOTE Confidence: 0.84401006

00:38:44.378 --> 00:38:47.726 regulators that's predicted is ACL one.

NOTE Confidence: 0.84401006

00:38:47.730 --> 00:38:50.946 So this is a way that we are.

NOTE Confidence: 0.84401006

00:38:50.950 --> 00:38:53.547 This is a method that we're employing

NOTE Confidence: 0.84401006

00:38:53.547 --> 00:38:55.770 to identify candidate intrinsic drivers

NOTE Confidence: 0.84401006

00:38:55.770 --> 00:38:57.336 of neuroendocrine differentiation

NOTE Confidence: 0.84401006

00:38:57.336 --> 00:38:59.946 that we're currently seeking to

NOTE Confidence: 0.84401006

00:39:00.012 --> 00:39:01.900 validate in functional assets.

NOTE Confidence: 0.84401006

00:39:01.900 --> 00:39:02.331 So.

NOTE Confidence: 0.84401006

00:39:02.331 --> 00:39:04.917 One of the sort of interesting

NOTE Confidence: 0.84401006

00:39:04.917 --> 00:39:08.188 questions we can ask is does trans

NOTE Confidence: 0.84401006

00:39:08.188 --> 00:39:10.553 differentiation occur at some level

NOTE Confidence: 0.84401006

00:39:10.553 --> 00:39:13.480 in organoid cultures and we have

NOTE Confidence: 0.84401006

00:39:13.480 --> 00:39:16.214 some evidence that that it might

NOTE Confidence: 0.84401006

00:39:16.214 --> 00:39:18.762 one way that we've been looking at

NOTE Confidence: 0.84401006

00:39:18.762 --> 00:39:22.481 this is using single cell a tax seek

NOTE Confidence: 0.84401006

00:39:22.481 --> 00:39:24.421 to examine chromatin Accessibility,

NOTE Confidence: 0.84401006

00:39:24.430 --> 00:39:27.558 and we can see that this is the

NOTE Confidence: 0.84401006

00:39:27.558 --> 00:39:30.437 same line again by single cell,

NOTE Confidence: 0.8348551

00:39:30.440 --> 00:39:32.580 a taxi there, seven clusters,

NOTE Confidence: 0.8348551

00:39:32.580 --> 00:39:34.272 and these clusters are.

NOTE Confidence: 0.8348551

00:39:34.272 --> 00:39:36.387 Have open chromatin at chromogranin.

NOTE Confidence: 0.8348551

00:39:36.390 --> 00:39:39.530 A neuron can marker these in a R and what

NOTE Confidence: 0.8348551

00:39:39.611 --> 00:39:42.716 you can see is that there is one cluster

NOTE Confidence: 0.8348551

00:39:42.716 --> 00:39:45.665 here that has open chromatin for both.

NOTE Confidence: 0.8348551

00:39:45.670 --> 00:39:48.385 Chrome Grande are you can

NOTE Confidence: 0.8348551

00:39:48.385 --> 00:39:50.557 see this more readily.

NOTE Confidence: 0.8348551

00:39:50.560 --> 00:39:53.703 Looking at the genomic locus so this

NOTE Confidence: 0.8348551

00:39:53.703 --> 00:39:56.532 cluster seven has accessible chromatin

NOTE Confidence: 0.8348551

00:39:56.532 --> 00:40:00.520 at both chromogranin, A&AR and so.

NOTE Confidence: 0.8348551

00:40:00.520 --> 00:40:02.768 This cluster, we believe,

NOTE Confidence: 0.8348551

00:40:02.768 --> 00:40:05.238 corresponds to a potential transitional

NOTE Confidence: 0.8348551

00:40:05.238 --> 00:40:08.303 population in the process of

NOTE Confidence: 0.8348551

00:40:08.303 --> 00:40:09.807 neuroendocrine differentiation.

NOTE Confidence: 0.8348551

00:40:09.810 --> 00:40:11.510 We've also been trying

NOTE Confidence: 0.8348551

00:40:11.510 --> 00:40:13.210 to assay this directly,

NOTE Confidence: 0.8348551

00:40:13.210 --> 00:40:15.760 so this is very preliminary data,

NOTE Confidence: 0.8348551

00:40:15.760 --> 00:40:18.070 but we can isolate non your

NOTE Confidence: 0.8348551

00:40:18.070 --> 00:40:20.440 endocrine cells by flow cytometry.

NOTE Confidence: 0.8348551

00:40:20.440 --> 00:40:23.415 Mark them with expression of RFP and

NOTE Confidence: 0.8348551

00:40:23.415 --> 00:40:25.959 then culture than honor in cells,

NOTE Confidence: 0.8348551

00:40:25.960 --> 00:40:28.492 and neurons can sell separately for

NOTE Confidence: 0.8348551

00:40:28.492 --> 00:40:30.665 several passages and they maintain

NOTE Confidence: 0.8348551

00:40:30.665 --> 00:40:33.610 their non ***** couldn't border and can

NOTE Confidence: 0.8348551

00:40:33.610 --> 00:40:36.160 phenotypes if we coculture them together.

NOTE Confidence: 0.8348551

00:40:36.160 --> 00:40:36.566 However,

NOTE Confidence: 0.8348551

00:40:36.566 --> 00:40:39.002 we now see their rare cells

NOTE Confidence: 0.8348551

00:40:39.002 --> 00:40:41.360 that that our RFP positive.

NOTE Confidence: 0.8348551

00:40:41.360 --> 00:40:43.440 But now express neuron could

NOTE Confidence: 0.8348551

00:40:43.440 --> 00:40:45.520 markers such as synaptophysin or

NOTE Confidence: 0.8348551

00:40:45.598 --> 00:40:47.988 Chromogranin A and interesting Lee.

NOTE Confidence: 0.8348551

00:40:47.990 --> 00:40:51.077 They maintain the expression of the Menton.

NOTE Confidence: 0.8348551

00:40:51.080 --> 00:40:54.616 So these appear to be a transitional cell,

NOTE Confidence: 0.8348551

00:40:54.620 --> 00:40:56.832 since phenotype seemingly corresponds

NOTE Confidence: 0.8348551

00:40:56.832 --> 00:41:01.540 to the what the a taxi might predict.

NOTE Confidence: 0.8348551

00:41:01.540 --> 00:41:01.854 OK,

NOTE Confidence: 0.8348551

00:41:01.854 --> 00:41:04.052 so these are some of the approaches

NOTE Confidence: 0.8348551

00:41:04.052 --> 00:41:06.499 that we've been employing to study

NOTE Confidence: 0.8348551

00:41:06.499 --> 00:41:08.694 language plasticity in prostate cancer.

NOTE Confidence: 0.8348551

00:41:08.700 --> 00:41:11.339 In the remaining 10 minutes or so,

NOTE Confidence: 0.8348551

00:41:11.340 --> 00:41:13.937 I'd like to switch over to bladder

NOTE Confidence: 0.8348551

00:41:13.937 --> 00:41:15.960 cancer and explain how we've

NOTE Confidence: 0.8348551

00:41:15.960 --> 00:41:18.060 been using organize to study

NOTE Confidence: 0.8348551

00:41:18.060 --> 00:41:19.880 plasticity in bladder cancer.

NOTE Confidence: 0.8348551

00:41:19.880 --> 00:41:23.540 So bladder cancer.

NOTE Confidence: 0.8348551

00:41:23.540 --> 00:41:26.977 Is of course a major health problem.

NOTE Confidence: 0.8348551

00:41:26.980 --> 00:41:28.411 It's quite understudied.

NOTE Confidence: 0.8348551

00:41:28.411 --> 00:41:30.796 The normal bladder contains again

NOTE Confidence: 0.8348551

00:41:30.796 --> 00:41:33.849 sort of three epithelial cell types,

NOTE Confidence: 0.8348551

00:41:33.850 --> 00:41:36.310 as it were basil cells,

NOTE Confidence: 0.8348551

00:41:36.310 --> 00:41:37.290 intermediate cells,

NOTE Confidence: 0.8348551

00:41:37.290 --> 00:41:38.760 and umbrella cells,

NOTE Confidence: 0.8348551

00:41:38.760 --> 00:41:41.370 and bladder cancer can be roughly

NOTE Confidence: 0.8348551

00:41:41.370 --> 00:41:43.758 divided into non muscle invasive

NOTE Confidence: 0.8348551

00:41:43.758 --> 00:41:46.618 disease and muscle invasive disease.

NOTE Confidence: 0.8348551

00:41:46.620 --> 00:41:47.111 Historically,

NOTE Confidence: 0.8348551

00:41:47.111 --> 00:41:49.566 these have been considered to

NOTE Confidence: 0.8348551

00:41:49.566 --> 00:41:51.530 be almost distinct entities,

NOTE Confidence: 0.8348551

00:41:51.530 --> 00:41:54.145 and it's unclear what the

NOTE Confidence: 0.8348551

00:41:54.145 --> 00:41:56.237 relationship actually is so.

NOTE Confidence: 0.8348551

00:41:56.240 --> 00:41:59.000 There are two forms of non

NOTE Confidence: 0.8348551

00:41:59.000 --> 00:42:00.840 muscle invasive bladder cancer,

NOTE Confidence: 0.8348551

00:42:00.840 --> 00:42:02.776 papillary and carcinoma insight,

NOTE Confidence: 0.8348551

00:42:02.776 --> 00:42:05.680 two and carcinoma insight two has

NOTE Confidence: 0.8348551

00:42:05.753 --> 00:42:08.469 been considered to be sort of the

NOTE Confidence: 0.8348551

00:42:08.469 --> 00:42:10.959 precursor to muscle invasive disease.

NOTE Confidence: 0.8348551

00:42:10.960 --> 00:42:11.367 However,

NOTE Confidence: 0.8348551

00:42:11.367 --> 00:42:14.623 there is also sorry there is also some

NOTE Confidence: 0.8348551

00:42:14.623 --> 00:42:17.147 evidence that papillary disease can

NOTE Confidence: 0.8348551

00:42:17.147 --> 00:42:19.692 progress to muscle invasive disease,

NOTE Confidence: 0.8348551

00:42:19.700 --> 00:42:23.126 so we've been interested in studying

NOTE Confidence: 0.8348551

00:42:23.126 --> 00:42:25.850 progression of bladder cancer and.

NOTE Confidence: 0.8348551

00:42:25.850 --> 00:42:27.113 To pursue this,

NOTE Confidence: 0.8348551

00:42:27.113 --> 00:42:28.797 we've actually established patient

NOTE Confidence: 0.8348551

00:42:28.797 --> 00:42:30.710 derived bladder tumor organoids,

NOTE Confidence: 0.8348551

00:42:30.710 --> 00:42:33.038 and these have been established through

NOTE Confidence: 0.8348551

00:42:33.038 --> 00:42:34.590 collaboration with urologists who

NOTE Confidence: 0.8348551

00:42:34.650 --> 00:42:36.459 perform transurethral resection's.

NOTE Confidence: 0.8348551

00:42:36.460 --> 00:42:39.204 So what they do is they sort

NOTE Confidence: 0.8348551

00:42:39.204 --> 00:42:41.760 of go in and extract,

NOTE Confidence: 0.8348551

00:42:41.760 --> 00:42:44.334 sort of like the tops of

NOTE Confidence: 0.8348551

00:42:44.334 --> 00:42:46.620 these of these tumors here.

NOTE Confidence: 0.8348551

00:42:46.620 --> 00:42:48.830 This is what they actually

NOTE Confidence: 0.8348551

00:42:48.830 --> 00:42:50.598 view through the cystoscope.

NOTE Confidence: 0.8348551

00:42:50.600 --> 00:42:53.048 This might look a little uncomfortable

NOTE Confidence: 0.8348551

00:42:53.048 --> 00:42:55.828 for men in the audience, but.

NOTE Confidence: 0.8348551

00:42:55.828 --> 00:42:58.404 This is how it's done and we

NOTE Confidence: 0.8348551

00:42:58.404 --> 00:43:01.279 take these samples and we can

NOTE Confidence: 0.8348551

00:43:01.279 --> 00:43:03.839 establish organoid lines in culture,

NOTE Confidence: 0.8348551

00:43:03.840 --> 00:43:05.820 which we can seriously passage.

NOTE Confidence: 0.8348551

00:43:05.820 --> 00:43:08.190 These organoids can also be grafted.

NOTE Confidence: 0.8348551

00:43:08.190 --> 00:43:09.122 Orthotopic Lee.

NOTE Confidence: 0.8348551

00:43:09.122 --> 00:43:11.452 This orthotopic grafting it uses

NOTE Confidence: 0.8348551

00:43:11.452 --> 00:43:13.236 ultrasound guided implantation into

NOTE Confidence: 0.8348551

00:43:13.236 --> 00:43:15.504 the bladder wall which is a very

NOTE Confidence: 0.8348551

00:43:15.504 --> 00:43:17.737 efficient process so we can readily

NOTE Confidence: 0.8348551

00:43:17.737 --> 00:43:19.637 interconvert organoids into Xena graphs.

NOTE Confidence: 0.80026895

00:43:19.640 --> 00:43:22.970 We can also take the Xeno grafts and convert

NOTE Confidence: 0.80026895

00:43:22.970 --> 00:43:26.784 them back to organoids, so all of these.

NOTE Confidence: 0.80026895

00:43:26.784 --> 00:43:30.537 Together with the parental tumor can be

NOTE Confidence: 0.80026895

00:43:30.537 --> 00:43:34.425 analyzed by sequencing or histopathology etc.

NOTE Confidence: 0.80026895

00:43:34.430 --> 00:43:38.030 So this just shows you some of the organoid

NOTE Confidence: 0.80026895

00:43:38.030 --> 00:43:41.125 lines that we established and what is,

NOTE Confidence: 0.80026895

00:43:41.130 --> 00:43:43.356 I think, evident is that the organoids

NOTE Confidence: 0.80026895

00:43:43.356 --> 00:43:45.918 and the Xeno grafts retained the

NOTE Confidence: 0.80026895

00:43:45.918 --> 00:43:46.942 characteristic characteristic

NOTE Confidence: 0.80026895

00:43:46.942 --> 00:43:49.502 Histology of the parental tumor.

NOTE Confidence: 0.80026895

00:43:49.510 --> 00:43:52.030 We also can establish organoid lines that

NOTE Confidence: 0.80026895

00:43:52.030 --> 00:43:54.540 have less common histological variants,

NOTE Confidence: 0.80026895

00:43:54.540 --> 00:43:57.260 such as squamous cell carcinoma.

NOTE Confidence: 0.80026895

00:43:57.260 --> 00:43:59.092 In recent unpublished work,

NOTE Confidence: 0.80026895

00:43:59.092 --> 00:44:02.459 we've now increased our bio bank to

NOTE Confidence: 0.80026895

00:44:02.459 --> 00:44:04.599 approximately 50 organoid lines.

NOTE Confidence: 0.80026895

00:44:04.600 --> 00:44:07.534 We've been able to establish organized

NOTE Confidence: 0.80026895

00:44:07.534 --> 00:44:09.490 lines from cystectomy samples,

NOTE Confidence: 0.80026895

00:44:09.490 --> 00:44:12.906 as well as from transferring for receptions,

NOTE Confidence: 0.80026895

00:44:12.910 --> 00:44:16.606 and have also a stab Liszt several

NOTE Confidence: 0.80026895

00:44:16.606 --> 00:44:20.289 lines that contain variant histologies.

NOTE Confidence: 0.80026895

00:44:20.290 --> 00:44:22.370 So in collaboration with David

NOTE Confidence: 0.80026895

00:44:22.370 --> 00:44:24.450 Solids Group at Memorial Sloan,

NOTE Confidence: 0.80026895

00:44:24.450 --> 00:44:25.386 Kettering Owen,

NOTE Confidence: 0.80026895

00:44:25.386 --> 00:44:27.726 the previous pathology was in

NOTE Confidence: 0.80026895

00:44:27.726 --> 00:44:29.130 collaborate with collaboration

NOTE Confidence: 0.80026895

00:44:29.198 --> 00:44:31.106 with him at all Media Memorial.

NOTE Confidence: 0.80026895

00:44:31.110 --> 00:44:33.290 We've analyzed these organoid lines

NOTE Confidence: 0.80026895

00:44:33.290 --> 00:44:35.470 molecularly using the targeted sequencing

NOTE Confidence: 0.80026895

00:44:35.535 --> 00:44:37.350 platform at Memorial MSK impact.

NOTE Confidence: 0.80026895

00:44:37.350 --> 00:44:39.725 We sequenced the organoids parental

NOTE Confidence: 0.80026895

00:44:39.725 --> 00:44:43.059 tumor and normal bloods and we can

NOTE Confidence: 0.80026895

00:44:43.059 --> 00:44:45.264 show generally that the organoids.

NOTE Confidence: 0.80026895

00:44:45.270 --> 00:44:47.330 Display mutational profiles that are

NOTE Confidence: 0.80026895

00:44:47.330 --> 00:44:50.420 concordant with that of the parental tumor.

NOTE Confidence: 0.80026895

00:44:50.420 --> 00:44:51.620 We can examine.

NOTE Confidence: 0.80026895

00:44:51.620 --> 00:44:53.620 Sort of the mutational profiles

NOTE Confidence: 0.80026895

00:44:53.620 --> 00:44:55.569 of these organoid lines,

NOTE Confidence: 0.80026895

00:44:55.570 --> 00:44:57.755 which really recapitulates sort of

NOTE Confidence: 0.80026895

00:44:57.755 --> 00:44:59.940 the distribution of of mutations

NOTE Confidence: 0.80026895

00:45:00.005 --> 00:45:01.569 in human bladder cancer.

NOTE Confidence: 0.80026895

00:45:01.570 --> 00:45:04.618 So we can see that among the common

NOTE Confidence: 0.80026895

00:45:04.618 --> 00:45:07.271 mutations we see mutations in a

NOTE Confidence: 0.80026895

00:45:07.271 --> 00:45:09.531 lot of epigenetic regulators which

NOTE Confidence: 0.80026895

00:45:09.531 --> 00:45:11.815 are frequently mutated in bladder

NOTE Confidence: 0.80026895

00:45:11.815 --> 00:45:15.439 cancer such as KDM 6A KMT 2C and 2D.

NOTE Confidence: 0.80026895

00:45:15.439 --> 00:45:17.104 As well as error 1A.

NOTE Confidence: 0.822274

00:45:19.870 --> 00:45:22.733 Interestingly, we also see were also able

NOTE Confidence: 0.822274

00:45:22.733 --> 00:45:25.331 to capture mutations that are relatively

NOTE Confidence: 0.822274

00:45:25.331 --> 00:45:27.929 rare but interesting in bladder cancer,

NOTE Confidence: 0.822274

00:45:27.930 --> 00:45:31.162 such as mutations and ERB B2 and of

NOTE Confidence: 0.822274

00:45:31.162 --> 00:45:34.707 note we have very few nations in RB,

NOTE Confidence: 0.822274

00:45:34.710 --> 00:45:37.636 so many bladder cancer cell lines were

NOTE Confidence: 0.822274

00:45:37.636 --> 00:45:39.377 established from metastatic bladder

NOTE Confidence: 0.822274

00:45:39.377 --> 00:45:41.487 cancer and contain RB mutations,

NOTE Confidence: 0.822274

00:45:41.490 --> 00:45:43.182 whereas are organoids.

NOTE Confidence: 0.822274

00:45:43.182 --> 00:45:46.002 Are generally established from non

NOTE Confidence: 0.822274

00:45:46.002 --> 00:45:48.156 muscle invasive bladder cancer

NOTE Confidence: 0.822274

00:45:48.156 --> 00:45:50.526 or earlier stages of muscle.

NOTE Confidence: 0.822274

00:45:50.530 --> 00:45:54.946 Invasive disease and lack RB mutations.

NOTE Confidence: 0.822274

00:45:54.950 --> 00:45:58.649 So what can we do with these organoid lines?

NOTE Confidence: 0.822274

00:45:58.650 --> 00:46:01.570 One thing we can do is we can

NOTE Confidence: 0.822274

00:46:01.570 --> 00:46:03.580 examine their drug response,

NOTE Confidence: 0.822274

00:46:03.580 --> 00:46:05.986 and of particular interest were able

NOTE Confidence: 0.822274

00:46:05.986 --> 00:46:08.070 to establish organoid lines from

NOTE Confidence: 0.822274

00:46:08.070 --> 00:46:10.155 patients in a longitudinal fashion.

NOTE Confidence: 0.822274

00:46:10.160 --> 00:46:12.210 So patients will often undergo

NOTE Confidence: 0.822274

00:46:12.210 --> 00:46:13.852 transurethral resection, be treated,

NOTE Confidence: 0.822274

00:46:13.852 --> 00:46:15.496 and then sometime thereafter,

NOTE Confidence: 0.822274

00:46:15.500 --> 00:46:17.560 their tumors will unfortunately recur.

NOTE Confidence: 0.822274

00:46:17.560 --> 00:46:20.437 And then we have an opportunity to

NOTE Confidence: 0.822274

00:46:20.437 --> 00:46:22.080 establish another organoid line.

NOTE Confidence: 0.822274

00:46:22.080 --> 00:46:25.475 So here's an example of a patient.

NOTE Confidence: 0.822274

00:46:25.480 --> 00:46:27.783 And a pair of organoid lines where

NOTE Confidence: 0.822274

00:46:27.783 --> 00:46:30.020 patient was not otherwise treated.

NOTE Confidence: 0.822274

00:46:30.020 --> 00:46:31.910 So the tumor was removed,

NOTE Confidence: 0.822274

00:46:31.910 --> 00:46:34.549 but the patient was not otherwise treated,

NOTE Confidence: 0.822274

00:46:34.550 --> 00:46:36.942 and we can see in in terms of

NOTE Confidence: 0.822274

00:46:36.942 --> 00:46:39.539 response to a range of different

NOTE Confidence: 0.822274

00:46:39.539 --> 00:46:40.979 drugs that Interestingly,

NOTE Confidence: 0.822274

00:46:40.980 --> 00:46:43.245 the organoid lines display nearly

NOTE Confidence: 0.822274

00:46:43.245 --> 00:46:45.057 overlapping drug response profiles.

NOTE Confidence: 0.822274

00:46:45.060 --> 00:46:45.543 However,

NOTE Confidence: 0.822274

00:46:45.543 --> 00:46:48.441 in this case the different patient

NOTE Confidence: 0.822274

00:46:48.441 --> 00:46:51.578 was treated with Mitomycin C and BCG.

NOTE Confidence: 0.822274

00:46:51.580 --> 00:46:54.849 The tumor relapsed after over a year,

NOTE Confidence: 0.822274

00:46:54.850 --> 00:46:58.730 and now the recurrent organoid line is much

NOTE Confidence: 0.822274

00:46:58.730 --> 00:47:02.297 more resistant to a range of different drugs.

NOTE Confidence: 0.822274

00:47:02.300 --> 00:47:02.765 However,

NOTE Confidence: 0.822274

00:47:02.765 --> 00:47:05.555 displays similar responses to other drugs,

NOTE Confidence: 0.822274

00:47:05.560 --> 00:47:07.400 so.

NOTE Confidence: 0.822274

00:47:07.400 --> 00:47:12.264 It's of interest to us to understand how.

NOTE Confidence: 0.822274

00:47:12.270 --> 00:47:14.375 Drug response has altered the

NOTE Confidence: 0.822274

00:47:14.375 --> 00:47:16.059 properties of these organoids.

NOTE Confidence: 0.822274

00:47:16.060 --> 00:47:18.601 So one thing we've started to do

NOTE Confidence: 0.822274

00:47:18.601 --> 00:47:21.220 is to perform single cell analysis

NOTE Confidence: 0.822274

00:47:21.220 --> 00:47:23.635 here of this recurrent pair,

NOTE Confidence: 0.822274

00:47:23.640 --> 00:47:24.550 and Interestingly,

NOTE Confidence: 0.822274

00:47:24.550 --> 00:47:26.825 the recurrent organoid line is

NOTE Confidence: 0.822274

00:47:26.825 --> 00:47:28.638 actually much more heterogeneous

NOTE Confidence: 0.822274

00:47:28.638 --> 00:47:31.638 than the sort of the parental of the

NOTE Confidence: 0.822274

00:47:31.638 --> 00:47:34.158 order online from the parental tumor.

NOTE Confidence: 0.822274

00:47:34.160 --> 00:47:37.366 And what is interesting is if you

NOTE Confidence: 0.822274

00:47:37.366 --> 00:47:39.884 re aggregate these together now

NOTE Confidence: 0.822274

00:47:39.884 --> 00:47:41.468 you can identify.

NOTE Confidence: 0.822274

00:47:41.470 --> 00:47:46.174 A cluster that is actually in common

NOTE Confidence: 0.822274

00:47:46.174 --> 00:47:50.267 between both the between the 1st

NOTE Confidence: 0.822274

00:47:50.267 --> 00:47:54.155 and the 2nd organoid lines so.

NOTE Confidence: 0.822274

00:47:54.160 --> 00:47:56.168 This cluster, we believe,

NOTE Confidence: 0.822274

00:47:56.168 --> 00:47:58.176 corresponds to a transitional

NOTE Confidence: 0.822274

00:47:58.176 --> 00:48:00.612 population and we can identify

NOTE Confidence: 0.822274

00:48:00.612 --> 00:48:02.872 markers that are specific for

NOTE Confidence: 0.822274

00:48:02.872 --> 00:48:04.640 this transitional population,

NOTE Confidence: 0.822274

00:48:04.640 --> 00:48:08.465 so our hope here is that we can use

NOTE Confidence: 0.822274

00:48:08.465 --> 00:48:11.831 utilized this pair of organoid lines

NOTE Confidence: 0.822274

00:48:11.831 --> 00:48:14.676 and other examples of recurrent

NOTE Confidence: 0.822274

00:48:14.781 --> 00:48:17.673 disease that we have to sort

NOTE Confidence: 0.822274

00:48:17.673 --> 00:48:20.080 of replay in organoid culture.

NOTE Confidence: 0.822274

00:48:20.080 --> 00:48:22.900 The events that take place during

NOTE Confidence: 0.822274

00:48:22.900 --> 00:48:25.190 the emergence of treatment.

NOTE Confidence: 0.822274

00:48:25.190 --> 00:48:25.860 Resistance.

NOTE Confidence: 0.8480736

00:48:28.340 --> 00:48:30.839 So finally I'd like to address the

NOTE Confidence: 0.8480736

00:48:30.839 --> 00:48:33.738 issue of tumor progression in organoid,

NOTE Confidence: 0.8480736

00:48:33.740 --> 00:48:36.645 so non muscle invasive disease you know

NOTE Confidence: 0.8480736

00:48:36.645 --> 00:48:39.184 can be classified into two lumenal

NOTE Confidence: 0.8480736

00:48:39.184 --> 00:48:42.033 categories as well as a basil category.

NOTE Confidence: 0.8480736

00:48:42.040 --> 00:48:44.248 Muscle invasive disease is more complex

NOTE Confidence: 0.8480736

00:48:44.248 --> 00:48:47.020 and again as I mentioned earlier,

NOTE Confidence: 0.8480736

00:48:47.020 --> 00:48:48.676 the relationship between these

NOTE Confidence: 0.8480736

00:48:48.676 --> 00:48:50.746 entities has been somewhat unclear.

NOTE Confidence: 0.8480736

00:48:50.750 --> 00:48:53.424 However, there is a question of whether

NOTE Confidence: 0.8480736

00:48:53.424 --> 00:48:56.150 you know if we have progression,

NOTE Confidence: 0.8480736

00:48:56.150 --> 00:48:58.808 whether there might be a switch

NOTE Confidence: 0.8480736

00:48:58.808 --> 00:49:00.137 and subtype specifically.

NOTE Confidence: 0.8480736

00:49:00.140 --> 00:49:03.164 From sort of Class 2 luminal tumors to Basel

NOTE Confidence: 0.8480736

00:49:03.164 --> 00:49:06.356 to a basal squamous muscle invasive tumor.

NOTE Confidence: 0.8480736

00:49:06.360 --> 00:49:08.964 So we believe that we can

NOTE Confidence: 0.8480736

00:49:08.964 --> 00:49:11.410 recapitulate this in organoid culture.

NOTE Confidence: 0.8480736

00:49:11.410 --> 00:49:14.350 So many of our organoid lines are

NOTE Confidence: 0.8480736

00:49:14.350 --> 00:49:16.610 phenotypic least able and culture.

NOTE Confidence: 0.8480736

00:49:16.610 --> 00:49:19.627 If you look at different markers there

NOTE Confidence: 0.8480736

00:49:19.627 --> 00:49:22.239 stable and organoids as organoid Xena,

NOTE Confidence: 0.8480736

00:49:22.240 --> 00:49:24.892 graphs ansina graph derived

NOTE Confidence: 0.8480736

00:49:24.892 --> 00:49:26.218 organoids however.

NOTE Confidence: 0.8480736

00:49:26.220 --> 00:49:28.500 Sort of a little over a

NOTE Confidence: 0.8480736

00:49:28.500 --> 00:49:30.490 majority of the organoids from.

NOTE Confidence: 0.8480736

00:49:30.490 --> 00:49:32.590 Non muscle invasive tumors displayed

NOTE Confidence: 0.8480736

00:49:32.590 --> 00:49:34.690 this sort of phenotypic plasticity.

NOTE Confidence: 0.8480736

00:49:34.690 --> 00:49:37.690 This is a they start with the luminal

NOTE Confidence: 0.8480736

00:49:37.690 --> 00:49:39.934 phenotype here and they become

NOTE Confidence: 0.8480736

00:49:39.934 --> 00:49:41.830 basil during organoid culture.

NOTE Confidence: 0.8480736

00:49:41.830 --> 00:49:44.350 But notably this phenotype can be

NOTE Confidence: 0.8480736

00:49:44.350 --> 00:49:46.030 largely reversed by xenografting,

NOTE Confidence: 0.8480736

00:49:46.030 --> 00:49:48.368 so we believe this there's an effect

NOTE Confidence: 0.8480736

00:49:48.368 --> 00:49:50.441 of the tumor micro environment

NOTE Confidence: 0.8480736

00:49:50.441 --> 00:49:53.429 that can repress this basil to

NOTE Confidence: 0.8480736

00:49:53.429 --> 00:49:54.425 luminal differentiation.

NOTE Confidence: 0.8480736

00:49:54.430 --> 00:49:57.542 In fact can reverse it but if we

NOTE Confidence: 0.8480736

00:49:57.542 --> 00:50:00.409 remove the tumors again from the.

NOTE Confidence: 0.8480736

00:50:00.410 --> 00:50:03.406 In a graph and culture miss organoids,

NOTE Confidence: 0.8480736

00:50:03.410 --> 00:50:05.545 they will again undergo the

NOTE Confidence: 0.8480736

00:50:05.545 --> 00:50:06.826 space little differentiation.

NOTE Confidence: 0.8480736

00:50:06.830 --> 00:50:08.850 So John Kristen Terrific Post

NOTE Confidence: 0.8480736

00:50:08.850 --> 00:50:11.456 Document Lab has pursued a small

NOTE Confidence: 0.8480736

00:50:11.456 --> 00:50:14.016 molecule screen to examine organoid

NOTE Confidence: 0.8480736

00:50:14.016 --> 00:50:16.473 lines that display plasticity to

NOTE Confidence: 0.8480736

00:50:16.473 --> 00:50:18.804 see if it's possible to revert it,

NOTE Confidence: 0.8480736

00:50:18.810 --> 00:50:22.234 and he identified one big hit here GSK.

NOTE Confidence: 0.8480736

00:50:22.240 --> 00:50:25.420 Else one, which is a.

NOTE Confidence: 0.8480736

00:50:25.420 --> 00:50:29.564 KTM one inhibitor and it is able to

NOTE Confidence: 0.8480736

00:50:29.564 --> 00:50:32.299 partially revert this plasticity,

NOTE Confidence: 0.8480736

00:50:32.300 --> 00:50:33.440 so the.

NOTE Confidence: 0.81983423

00:50:43.040 --> 00:50:44.520 I'm not showing this here,

NOTE Confidence: 0.81983423

00:50:44.520 --> 00:50:46.888 but if he knocks out KTM one day,

NOTE Confidence: 0.81983423

00:50:46.890 --> 00:50:51.880 he can also see this effect. So.

NOTE Confidence: 0.81983423

00:50:51.880 --> 00:50:53.720 He is currently investigating

NOTE Confidence: 0.81983423

00:50:53.720 --> 00:50:56.020 the mechanisms by which KTM

NOTE Confidence: 0.81983423

00:50:56.020 --> 00:50:58.559 1A regulates this transition.

NOTE Confidence: 0.79841167

00:51:00.730 --> 00:51:03.858 In parallel, he's also been pursuing a taxi.

NOTE Confidence: 0.79841167

00:51:03.860 --> 00:51:06.191 Can Alesis to examine sort of the

NOTE Confidence: 0.79841167

00:51:06.191 --> 00:51:07.697 epigenetic States and eventually

NOTE Confidence: 0.79841167

00:51:07.697 --> 00:51:09.907 the epigenetic marks that are

NOTE Confidence: 0.79841167

00:51:09.907 --> 00:51:11.675 associated with this plasticity.

NOTE Confidence: 0.79841167

00:51:11.680 --> 00:51:14.020 So if you examine, for example,

NOTE Confidence: 0.79841167

00:51:14.020 --> 00:51:15.584 these three organoid lines,

NOTE Confidence: 0.79841167

00:51:15.584 --> 00:51:17.148 this is adluminal line.

NOTE Confidence: 0.79841167

00:51:17.150 --> 00:51:19.663 This is a basil line and this

NOTE Confidence: 0.79841167

00:51:19.663 --> 00:51:22.629 is what we call a plastic line.

NOTE Confidence: 0.79841167

00:51:22.630 --> 00:51:25.750 The plastic line looks like a basil line,

NOTE Confidence: 0.79841167

00:51:25.750 --> 00:51:29.096 although it started with a luminal phenotype.

NOTE Confidence: 0.79841167

00:51:29.100 --> 00:51:31.150 So we've performed a taxi.

NOTE Confidence: 0.79841167

00:51:31.150 --> 00:51:33.178 Can Alesis and we can cluster

NOTE Confidence: 0.79841167

00:51:33.178 --> 00:51:35.632 these so you see that the

NOTE Confidence: 0.79841167

00:51:35.632 --> 00:51:37.688 lumenal lines clustered together.

NOTE Confidence: 0.79841167

00:51:37.690 --> 00:51:39.610 The basil lines clustered together

NOTE Confidence: 0.79841167

00:51:39.610 --> 00:51:42.446 and these are the plastic lines which

NOTE Confidence: 0.79841167

00:51:42.446 --> 00:51:44.561 in the first principle component

NOTE Confidence: 0.79841167

00:51:44.561 --> 00:51:46.280 cluster together with basil.

NOTE Confidence: 0.79841167

00:51:46.280 --> 00:51:47.912 But they're separated along

NOTE Confidence: 0.79841167

00:51:47.912 --> 00:51:49.544 the second principle component.

NOTE Confidence: 0.8060535

00:51:51.990 --> 00:51:55.362 So now if we look at, you know,

NOTE Confidence: 0.8060535

00:51:55.362 --> 00:51:58.766 sort of genomic tracks, you can see that

NOTE Confidence: 0.8060535

00:51:58.766 --> 00:52:01.700 at basil markers such as keratin 14,

NOTE Confidence: 0.8060535

00:52:01.700 --> 00:52:04.070 that the basil lines of course

NOTE Confidence: 0.8060535

00:52:04.070 --> 00:52:06.622 have open chromatin and the plastic

NOTE Confidence: 0.8060535

00:52:06.622 --> 00:52:08.867 lines also have open chromatin,

NOTE Confidence: 0.8060535

00:52:08.870 --> 00:52:11.670 which of course is to be expected

NOTE Confidence: 0.8060535

00:52:11.670 --> 00:52:14.358 because they have a basal phenotype.

NOTE Confidence: 0.8060535

00:52:14.360 --> 00:52:16.355 But what's interesting

NOTE Confidence: 0.8060535

00:52:16.355 --> 00:52:19.015 is that lumenal markers.

NOTE Confidence: 0.8060535

00:52:19.020 --> 00:52:20.576 Such as gotta three.

NOTE Confidence: 0.8060535

00:52:20.576 --> 00:52:24.096 We we see that the plastic organoid lines

NOTE Confidence: 0.8060535

00:52:24.096 --> 00:52:27.390 seem to have partially open chromatin,

NOTE Confidence: 0.8060535

00:52:27.390 --> 00:52:30.200 so they retain an epigenetic

NOTE Confidence: 0.8060535

00:52:30.200 --> 00:52:33.010 memory of their lumenal origin.

NOTE Confidence: 0.8060535

00:52:33.010 --> 00:52:34.985 So we are currently pursuing

NOTE Confidence: 0.8060535

00:52:34.985 --> 00:52:37.477 studies to determine whether we can

NOTE Confidence: 0.8060535

00:52:37.477 --> 00:52:39.269 actually detect this epigenetic

NOTE Confidence: 0.8060535

00:52:39.269 --> 00:52:41.509 memory in human prostate tumors,

NOTE Confidence: 0.8060535

00:52:41.510 --> 00:52:44.228 which might indicate.

NOTE Confidence: 0.8060535

00:52:44.230 --> 00:52:47.350 A specific pacifically base of the

NOTE Confidence: 0.8060535

00:52:47.350 --> 00:52:50.037 basal squamous category to determine

NOTE Confidence: 0.8060535

00:52:50.037 --> 00:52:53.109 whether they may have in fact

NOTE Confidence: 0.8060535

00:52:53.109 --> 00:52:55.930 originated from more lumenal tumor.

NOTE Confidence: 0.83516306

00:52:58.500 --> 00:53:01.295 Finally, we're also pursuing motif

NOTE Confidence: 0.83516306

00:53:01.295 --> 00:53:03.531 discovery approaches to identify

NOTE Confidence: 0.83516306

00:53:03.531 --> 00:53:05.804 candidate transcription factors that

NOTE Confidence: 0.83516306

00:53:05.804 --> 00:53:08.529 might be driving this transition,

NOTE Confidence: 0.83516306

00:53:08.530 --> 00:53:12.020 and we're coupling this with

NOTE Confidence: 0.83516306

00:53:12.020 --> 00:53:14.114 other computational approaches.

NOTE Confidence: 0.83516306

00:53:14.120 --> 00:53:17.529 We think that this really is modeling

NOTE Confidence: 0.83516306

00:53:17.529 --> 00:53:20.728 something that's happening during, you know.

NOTE Confidence: 0.83516306

00:53:20.728 --> 00:53:23.548 Sort of transition to muscle

NOTE Confidence: 0.83516306

00:53:23.548 --> 00:53:25.240 invasive disease because.

NOTE Confidence: 0.83516306

00:53:25.240 --> 00:53:27.520 As has been noted in breast

NOTE Confidence: 0.83516306

00:53:27.520 --> 00:53:29.040 cancer for Andy Walt,

NOTE Confidence: 0.83516306

00:53:29.040 --> 00:53:31.952 what we've found is at the at the

NOTE Confidence: 0.83516306

00:53:31.952 --> 00:53:33.979 invasive front of these tumors.

NOTE Confidence: 0.83516306

00:53:33.980 --> 00:53:37.463 Now we see the expression of a basal marker

NOTE Confidence: 0.83516306

00:53:37.463 --> 00:53:39.676 cytokeratin 14 at the invasive front,

NOTE Confidence: 0.83516306

00:53:39.680 --> 00:53:42.890 but this is not expressed within

NOTE Confidence: 0.83516306

00:53:42.890 --> 00:53:44.495 the tumor body.

NOTE Confidence: 0.83516306

00:53:44.500 --> 00:53:45.544 So in closing,

NOTE Confidence: 0.83516306

00:53:45.544 --> 00:53:48.504 then I'd like to underscore that we think

NOTE Confidence: 0.83516306

00:53:48.504 --> 00:53:51.180 that these organoids represent a model

NOTE Confidence: 0.83516306

00:53:51.180 --> 00:53:53.780 system for studying tumor plasticity.

NOTE Confidence: 0.83516306

00:53:53.780 --> 00:53:55.780 So we can identify transitional

NOTE Confidence: 0.83516306

00:53:55.780 --> 00:53:58.297 populations in patients in order rates

NOTE Confidence: 0.83516306

00:53:58.297 --> 00:54:00.537 from patients with recurrent disease,

NOTE Confidence: 0.83516306

00:54:00.540 --> 00:54:03.500 and we think that the sort of plasticity

NOTE Confidence: 0.83516306

00:54:03.500 --> 00:54:05.722 we're studying culture can reflect

NOTE Confidence: 0.83516306

00:54:05.722 --> 00:54:08.548 processings of disease progression in vivo,

NOTE Confidence: 0.83516306

00:54:08.550 --> 00:54:10.306 and we're using computational

NOTE Confidence: 0.83516306

00:54:10.306 --> 00:54:12.501 systems approach is to identify

NOTE Confidence: 0.83516306

00:54:12.501 --> 00:54:14.500 the drivers of plasticity.

NOTE Confidence: 0.83516306

00:54:14.500 --> 00:54:16.261 And more generally,

NOTE Confidence: 0.83516306

00:54:16.261 --> 00:54:19.196 we believe that organoid models.

NOTE Confidence: 0.83516306

00:54:19.200 --> 00:54:21.880 Are incredibly useful because they

NOTE Confidence: 0.83516306

00:54:21.880 --> 00:54:24.024 will allow mechanistic studies

NOTE Confidence: 0.83516306

00:54:24.024 --> 00:54:26.782 of complex questions in cancer

NOTE Confidence: 0.83516306

00:54:26.782 --> 00:54:29.452 biology that may be inaccessible,

NOTE Confidence: 0.83516306

00:54:29.460 --> 00:54:33.108 used using other approaches.

NOTE Confidence: 0.83516306

00:54:33.110 --> 00:54:34.002 Of course,

NOTE Confidence: 0.83516306

00:54:34.002 --> 00:54:36.232 the work that I've described

NOTE Confidence: 0.83516306

00:54:36.232 --> 00:54:38.540 involved large team of terrific

NOTE Confidence: 0.83516306

00:54:38.540 --> 00:54:41.204 scientists really did all the work.

NOTE Confidence: 0.83516306

00:54:41.210 --> 00:54:42.110 So notably,

NOTE Confidence: 0.83516306

00:54:42.110 --> 00:54:44.810 Laura Crowley is a graduate student.

NOTE Confidence: 0.83516306

00:54:44.810 --> 00:54:47.197 My lap who led the single cell

NOTE Confidence: 0.83516306

00:54:47.197 --> 00:54:49.535 analysis of the prostate epithelium

NOTE Confidence: 0.83516306

00:54:49.535 --> 00:54:52.007 together with Francesco Comma,

NOTE Confidence: 0.83516306

00:54:52.010 --> 00:54:54.260 Boolean, former postdoc Moshe Botton,

NOTE Confidence: 0.83516306

00:54:54.260 --> 00:54:56.510 now at George Washington University.

NOTE Confidence: 0.83516306

00:54:56.510 --> 00:54:59.285 The work on normal neuroendocrine

NOTE Confidence: 0.83516306

00:54:59.285 --> 00:55:00.950 differentiation was performed

NOTE Confidence: 0.83516306

00:55:00.950 --> 00:55:03.549 by graduate student gave alone.

NOTE Confidence: 0.83516306

00:55:03.550 --> 00:55:07.378 And the prostate ***** organized by

NOTE Confidence: 0.83516306

00:55:07.378 --> 00:55:11.210 Jolly a terrific postdoc in the lab.

NOTE Confidence: 0.83516306

00:55:11.210 --> 00:55:13.904 Then former lab members soup soup

NOTE Confidence: 0.83516306

00:55:13.904 --> 00:55:16.243 Lee started the bladder organized

NOTE Confidence: 0.83516306

00:55:16.243 --> 00:55:19.027 project and I mentioned John Kristen

NOTE Confidence: 0.83516306

00:55:19.027 --> 00:55:22.590 is a current post Doc who's played a

NOTE Confidence: 0.83516306

00:55:22.590 --> 00:55:25.130 major role in continuing this project.

NOTE Confidence: 0.83516306

00:55:25.130 --> 00:55:26.930 We've had terrific collaborators.

NOTE Confidence: 0.83516306

00:55:26.930 --> 00:55:29.170 Roll rabadan Andrea Califano for

NOTE Confidence: 0.83516306

00:55:29.170 --> 00:55:30.514 computational systems biology.

NOTE Confidence: 0.83516306

00:55:30.520 --> 00:55:31.418 Jim Mckiernan,

NOTE Confidence: 0.83516306

00:55:31.418 --> 00:55:33.663 whole team of talented urologists

NOTE Confidence: 0.83516306

00:55:33.663 --> 00:55:35.010 who provided samples.

NOTE Confidence: 0.83516306

00:55:35.010 --> 00:55:37.698 We've collaborated with Korea Body Shen,

NOTE Confidence: 0.83516306

00:55:37.700 --> 00:55:39.950 in analysis of Mouse models,

NOTE Confidence: 0.83516306

00:55:39.950 --> 00:55:42.260 which how Lewin, epigenetic analysis.

NOTE Confidence: 0.83516306

00:55:42.260 --> 00:55:45.374 Need help search for pathology as

NOTE Confidence: 0.83516306

00:55:45.374 --> 00:55:49.298 as well as Max load at Cornell.

NOTE Confidence: 0.83516306

00:55:49.300 --> 00:55:51.052 For pathological analysis and

NOTE Confidence: 0.83516306

00:55:51.052 --> 00:55:53.242 a great group of collaborators

NOTE Confidence: 0.83516306

00:55:53.242 --> 00:55:55.498 at Memorial Sloan Kettering,

NOTE Confidence: 0.83516306

00:55:55.500 --> 00:55:58.250 David Solid Hickman to Marty

NOTE Confidence: 0.83516306

00:55:58.250 --> 00:55:59.900 and Barry Taylor.

NOTE Confidence: 0.83516306

00:55:59.900 --> 00:56:01.846 So thank you very much and I'll

NOTE Confidence: 0.83516306

00:56:01.846 --> 00:56:03.980 be happy to take any questions.

NOTE Confidence: 0.91066235

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 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

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

NOTE Confidence: 0.8553434

00:57:24.462 --> 00:57:26.190 question regarding media so.

NOTE Confidence: 0.8553434

00:57:26.190 --> 00:57:29.060 One of the things that I forgot

NOTE Confidence: 0.8553434

00:57:29.060 --> 00:57:32.527 to mention is that we use our own

NOTE Confidence: 0.8553434

00:57:32.527 --> 00:57:35.387 sort of homegrown media for all

NOTE Confidence: 0.8553434

00:57:35.387 --> 00:57:37.867 of these organoid experiments.

NOTE Confidence: 0.8553434

00:57:37.870 --> 00:57:41.662 This is a complex medium containing

NOTE Confidence: 0.8553434

00:57:41.662 --> 00:57:44.190 hepatocyte media and serum.

NOTE Confidence: 0.8553434

00:57:44.190 --> 00:57:46.578 You know we.

NOTE Confidence: 0.8553434

00:57:46.580 --> 00:57:50.132 Develop this years ago to grow

NOTE Confidence: 0.8553434

00:57:50.132 --> 00:57:53.169 mouse prostate organoids so it's

NOTE Confidence: 0.8553434

00:57:53.169 --> 00:57:55.974 quite different from the ENR

NOTE Confidence: 0.8553434

00:57:55.974 --> 00:57:58.960 based media that many groups

NOTE Confidence: 0.8553434

00:57:58.960 --> 00:58:02.110 use to pursue organoid assays.

NOTE Confidence: 0.8553434

00:58:02.110 --> 00:58:05.170 There are although.

NOTE Confidence: 0.8553434

00:58:05.170 --> 00:58:07.900 You might imagine that some of the

NOTE Confidence: 0.8553434

00:58:07.900 --> 00:58:10.080 growth factors involved are in common.

NOTE Confidence: 0.8553434

00:58:10.080 --> 00:58:12.028 There are undoubtedly differences

NOTE Confidence: 0.8553434

00:58:12.028 --> 00:58:14.463 between the media compositions in

NOTE Confidence: 0.8553434

00:58:14.463 --> 00:58:16.886 terms of what's actually going on.

NOTE Confidence: 0.8553434

00:58:16.890 --> 00:58:18.722 We know that, anecdotally,

NOTE Confidence: 0.8553434

00:58:18.722 --> 00:58:21.012 for bladder tumor organoids that

NOTE Confidence: 0.8553434

00:58:21.012 --> 00:58:24.025 it is probably easier to establish

NOTE Confidence: 0.8553434

00:58:24.025 --> 00:58:26.005 patient derived organoids using

NOTE Confidence: 0.8553434

00:58:26.005 --> 00:58:28.795 our media than in our based media.

NOTE Confidence: 0.88473046

00:58:31.010 --> 00:58:33.994 And we also know that you can transition

NOTE Confidence: 0.88473046

00:58:33.994 --> 00:58:36.706 organoid lines from one media to the other,

NOTE Confidence: 0.88473046

00:58:36.710 --> 00:58:40.084 but it may not be that straightforward.

NOTE Confidence: 0.88473046

00:58:40.090 --> 00:58:42.960 So we have some experience with DNR

NOTE Confidence: 0.88473046

00:58:42.960 --> 00:58:45.764 based media, but all the analysis

NOTE Confidence: 0.88473046

00:58:45.764 --> 00:58:49.326 that I've showed you today were done

NOTE Confidence: 0.88473046

00:58:49.326 --> 00:58:52.266 in our sort of homegrown media.

NOTE Confidence: 0.88473046

00:58:52.270 --> 00:58:55.444 So do we observe shifts in

NOTE Confidence: 0.88473046

00:58:55.444 --> 00:58:57.560 composition in different media?

NOTE Confidence: 0.88473046

00:58:57.560 --> 00:59:02.030 We have not really examined that.

NOTE Confidence: 0.88473046

00:59:02.030 --> 00:59:04.578 In part because it can be different,

NOTE Confidence: 0.88473046

00:59:04.580 --> 00:59:07.148 it can be difficult to transition

NOTE Confidence: 0.88473046

00:59:07.148 --> 00:59:10.370 organ lines from one medium to another.

NOTE Confidence: 0.88473046

00:59:10.370 --> 00:59:12.680 Be a composition to another.

NOTE Confidence: 0.88473046

00:59:12.680 --> 00:59:14.940 In terms of drug treatment,

NOTE Confidence: 0.88473046

00:59:14.940 --> 00:59:18.588 we have only started to do this with

NOTE Confidence: 0.88473046

00:59:18.588 --> 00:59:22.219 respect to the prostate organoids the.

NOTE Confidence: 0.88473046

00:59:22.220 --> 00:59:24.340 Bladder organizer, something that

NOTE Confidence: 0.88473046

00:59:24.340 --> 00:59:27.520 we've been examining in more detail.

NOTE Confidence: 0.88473046

00:59:27.520 --> 00:59:30.170 We've been particularly interested in

NOTE Confidence: 0.88473046

00:59:30.170 --> 00:59:32.290 mechanisms of cisplatin resistance,

NOTE Confidence: 0.88473046

00:59:32.290 --> 00:59:35.470 which, of course is of considerable

NOTE Confidence: 0.88473046

00:59:35.470 --> 00:59:36.530 translational interest.

NOTE Confidence: 0.88473046

00:59:36.530 --> 00:59:40.770 So those are studies that are that are,

NOTE Confidence: 0.88473046

00:59:40.770 --> 00:59:42.094 you know,

NOTE Confidence: 0.88473046

00:59:42.094 --> 00:59:45.404 currently being pursued to examine

NOTE Confidence: 0.88473046

00:59:45.404 --> 00:59:48.170 how cisplatin treatment alters.

NOTE Confidence: 0.88473046

00:59:48.170 --> 00:59:49.268 Or the phenotype,

NOTE Confidence: 0.88473046

00:59:49.268 --> 00:59:50.732 and perhaps the heterogeneity

NOTE Confidence: 0.88473046

00:59:50.732 --> 00:59:51.830 of the organized,

NOTE Confidence: 0.88473046

00:59:51.830 --> 00:59:55.470 but I don't have any results yet.

NOTE Confidence: 0.88473046

00:59:55.470 --> 00:59:56.040 To show you.

NOTE Confidence: 0.7797154

00:59:56.820 --> 00:59:58.200 Great, thank you.

NOTE Confidence: 0.7797154

00:59:58.200 --> 01:00:00.500 There's a question from Gefsky.

NOTE Confidence: 0.7797154

01:00:00.500 --> 01:00:04.020 Are have you been able to analyze human

NOTE Confidence: 0.7797154

01:00:04.020 --> 01:00:06.738 lumenal bladder tumors for plasticity,

NOTE Confidence: 0.7797154

01:00:06.740 --> 01:00:08.608 markers and correlate those

NOTE Confidence: 0.7797154

01:00:08.608 --> 01:00:10.476 results with subsequent development

NOTE Confidence: 0.7797154

01:00:10.476 --> 01:00:12.500 of muscle invasive tumors?

NOTE Confidence: 0.84377086

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

NOTE Confidence: 0.84377086

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

NOTE Confidence: 0.84377086

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

NOTE Confidence: 0.84377086

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

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

NOTE Confidence: 0.9077339

01:01:39.706 --> 01:01:42.368 to gather together the.

NOTE Confidence: 0.9077339

01:01:42.370 --> 01:01:44.220 Cohorts that are essential to

NOTE Confidence: 0.9077339

01:01:44.220 --> 01:01:46.070 address this type of question

NOTE Confidence: 0.9077339

01:01:46.134 --> 01:01:48.329 because they don't currently exist,

NOTE Confidence: 0.9077339

01:01:48.330 --> 01:01:51.095 and these types of samples are rare.

NOTE Confidence: 0.8201053

01:01:52.640 --> 01:01:55.070 Thank you we have another question

NOTE Confidence: 0.8201053

01:01:55.070 --> 01:01:58.228 from Mike Hurwitz who says great talk

NOTE Confidence: 0.8201053

01:01:58.228 --> 01:02:00.668 within the different luminal subtypes.

NOTE Confidence: 0.8201053

01:02:00.670 --> 01:02:03.196 Do you think some are more

NOTE Confidence: 0.8201053

01:02:03.196 --> 01:02:05.570 likely to develop into cancer?

NOTE Confidence: 0.8201053

01:02:05.570 --> 01:02:07.800 Any correlate in human prostates?

NOTE Confidence: 0.86231977

01:02:08.910 --> 01:02:11.024 OK, so this is a question about

NOTE Confidence: 0.86231977

01:02:11.024 --> 01:02:13.136 prostate and of course we're very

NOTE Confidence: 0.86231977

01:02:13.136 --> 01:02:15.026 interested in cell of origin.

NOTE Confidence: 0.86231977

01:02:15.030 --> 01:02:17.375 You know, we've always been sort of

NOTE Confidence: 0.86231977

01:02:17.375 --> 01:02:19.108 dissatisfied with our previous analysis

NOTE Confidence: 0.86231977

01:02:19.108 --> 01:02:21.748 of Cell of Origin because you know you

NOTE Confidence: 0.86231977

01:02:21.807 --> 01:02:23.865 have luminal cells and basil cells.

NOTE Confidence: 0.86231977

01:02:23.870 --> 01:02:26.250 There's only so much you can say,

NOTE Confidence: 0.86231977

01:02:26.250 --> 01:02:29.456 but we we think that there's still

NOTE Confidence: 0.86231977

01:02:29.456 --> 01:02:31.999 something to explore here because.

NOTE Confidence: 0.86231977

01:02:32.000 --> 01:02:37.747 This is well known phenomenon in which.

NOTE Confidence: 0.86231977

01:02:37.750 --> 01:02:41.000 You know 85 to 90% of prostate

NOTE Confidence: 0.86231977

01:02:41.000 --> 01:02:41.930 cancer patients.

NOTE Confidence: 0.7963109

01:02:44.550 --> 01:02:47.718 With sort of intermediate risk disease,

NOTE Confidence: 0.7963109

01:02:47.720 --> 01:02:53.187 you know a will actually have indolent.

NOTE Confidence: 0.7963109

01:02:53.190 --> 01:02:55.740 Prostate cancer, whereas the remaining

NOTE Confidence: 0.7963109

01:02:55.740 --> 01:02:58.764 10 to 15% of patients actually

NOTE Confidence: 0.7963109

01:02:58.764 --> 01:03:01.254 have aggressive disease and it's

NOTE Confidence: 0.7963109

01:03:01.254 --> 01:03:03.871 difficult to distinguish between the

NOTE Confidence: 0.7963109

01:03:03.871 --> 01:03:06.436 indolent and aggressive tumors and

NOTE Confidence: 0.7963109

01:03:06.436 --> 01:03:09.510 despite a lot of molecular analysis,

NOTE Confidence: 0.7963109

01:03:09.510 --> 01:03:12.060 they haven't tremendously improved over.

NOTE Confidence: 0.7963109

01:03:12.060 --> 01:03:15.120 Just simple histological police and grading.

NOTE Confidence: 0.7963109

01:03:15.120 --> 01:03:17.916 So we think that it remains

NOTE Confidence: 0.7963109

01:03:17.916 --> 01:03:21.144 possible that cell of origin could

NOTE Confidence: 0.7963109

01:03:21.144 --> 01:03:23.680 explain at least partially.

NOTE Confidence: 0.7963109

01:03:23.680 --> 01:03:25.848 The difference between indolent

NOTE Confidence: 0.7963109

01:03:25.848 --> 01:03:27.474 and aggressive disease.

NOTE Confidence: 0.7963109

01:03:27.480 --> 01:03:29.652 And so that's something we're very

NOTE Confidence: 0.7963109

01:03:29.652 --> 01:03:31.234 interested in pursuing. The.

NOTE Confidence: 0.7963109

01:03:31.234 --> 01:03:35.186 We we know already that you know from

NOTE Confidence: 0.7963109

01:03:35.186 --> 01:03:38.413 the literature that both proximal

NOTE Confidence: 0.7963109

01:03:38.413 --> 01:03:42.343 and distal luminal cells can be

NOTE Confidence: 0.7963109

01:03:42.459 --> 01:03:45.897 cells of origin in mouse models.

NOTE Confidence: 0.7963109

01:03:45.900 --> 01:03:49.374 But that does not necessarily answer

NOTE Confidence: 0.7963109

01:03:49.374 --> 01:03:52.818 the question because you know they

NOTE Confidence: 0.7963109

01:03:52.818 --> 01:03:56.409 may be different in terms of their

NOTE Confidence: 0.7963109

01:03:56.409 --> 01:03:59.679 phenotype or response to treatment or.

NOTE Confidence: 0.7963109

01:03:59.680 --> 01:04:03.960 Ultimate outcomes so you know we're in the

NOTE Confidence: 0.7963109

01:04:03.960 --> 01:04:08.367 process of pursuing these types of studies.

NOTE Confidence: 0.7963109

01:04:08.370 --> 01:04:11.090 It's not really clear what's

NOTE Confidence: 0.7963109

01:04:11.090 --> 01:04:14.900 going on in the human prostate.

NOTE Confidence: 0.7963109

01:04:14.900 --> 01:04:15.536 And again,

NOTE Confidence: 0.7963109

01:04:15.536 --> 01:04:17.444 I think we're just scratching the

NOTE Confidence: 0.7963109

01:04:17.444 --> 01:04:19.428 surface in terms of understanding

NOTE Confidence: 0.7963109

01:04:19.428 --> 01:04:21.140 the relationship between the

NOTE Confidence: 0.7963109

01:04:21.140 --> 01:04:23.111 lumenal populations in the mouse

NOTE Confidence: 0.7963109

01:04:23.111 --> 01:04:24.977 and the populations of the human.

NOTE Confidence: 0.7963109

01:04:24.980 --> 01:04:27.032 There's a lot more work that

NOTE Confidence: 0.7963109

01:04:27.032 --> 01:04:28.940 needs to be done there.

NOTE Confidence: 0.88329786

01:04:31.310 --> 01:04:33.599 Well, thank you very much Michael for

NOTE Confidence: 0.88329786

01:04:33.599 --> 01:04:36.039 this visit for this fascinating talk.

NOTE Confidence: 0.88329786

01:04:36.040 --> 01:04:38.830 I I know I it made me think of a

NOTE Confidence: 0.88329786

01:04:38.917 --> 01:04:41.371 lot of things or some parallels

NOTE Confidence: 0.88329786

01:04:41.371 --> 01:04:44.410 in in the world of lung cancer.

NOTE Confidence: 0.88329786

01:04:44.410 --> 01:04:46.755 So it was really great to think

NOTE Confidence: 0.88329786

01:04:46.755 --> 01:04:49.204 about this this so thank you very

NOTE Confidence: 0.88329786

01:04:49.204 --> 01:04:51.256 much for visiting us today and

NOTE Confidence: 0.88329786

01:04:51.333 --> 01:04:53.727 thank you everybody also who joined

NOTE Confidence: 0.88329786

01:04:53.727 --> 01:04:55.700 and have a wonderful afternoon.

NOTE Confidence: 0.7524229

01:04:56.440 --> 01:04:58.155 Well, thank you Katie. Thank you every.