WEBVTT

NOTE duration:"00:21:14.4130000"

NOTE language:en-us

NOTE Confidence: 0.916019380092621

00:00:00.020 --> 00:00:30.650 A biology at the School of Medicine. She received her PhD from Boston University. Ann has been the recipient of a prestigious NIH directores. New Innovator Award, where her work has been focused akin to the title on understanding Self Aiden and cancer cell of origin and I think among other things are laboratory work is really understand what are the rules of of cell fate the decision process important to understand how to?

NOTE Confidence: 0.880777418613434

00:00:30.650 --> 00:00:36.360 Avoid Harmon as well understand how cells ultimately become cancerous or Darkwa. Thank you.

NOTE Confidence: 0.937739849090576

00:00:41.210 --> 00:00:47.200 I'm grateful for this opportunity to share with your work and uh.

NOTE Confidence: 0.928109586238861

00:00:48.100 --> 00:00:54.670 And this is the vast expanse of what we're talking today, so on one hand, we just heard.

NOTE Confidence: 0.93992954492569

00:00:55.480 --> 00:01:06.870 At doctors take care of cancer patients, but now I would like to bring you to the very, very beginning. Before this normal cell has crossed over to the dark side to become cancer.

NOTE Confidence: 0.479911088943481

00:01:07.500 --> 00:01:08.450 So.

NOTE Confidence: 0.923952758312225

00:01:09.940 --> 00:01:17.960 The question that ultimately I'm asking is what kind of normal cells give rise to cancer.

NOTE Confidence: 0.906324982643127

00:01:18.620 --> 00:01:41.820 So the way that I was taught a cancer biology is very similar to this that put together by Bert Vogelstein. I'm particularly within colleagues so during the cancer development. These normal cells sequentially acquire more and more and worse and worse mutations.

NOTE Confidence: 0.883616030216217

00:01:42.320 --> 00:01:47.260 Such that I don't know whether I can have the arrow here.

NOTE Confidence: 0.795204758644104

00:01:48.390 --> 00:01:52.520 OK, I don't think I can.

NOTE Confidence: 0.887329578399658

00:01:53.030 --> 00:02:24.160 OK, OK, so one of these blue bars, indicating the normal cells would sequentially successively acquire worse mutations and become bad eventually gives rise to some kind of malignancy so in normal cases in in most cases that the malignancy is a protracted and rare event. It's so it could be so rare that as long as 1 cell goes through this process, we will see clinical.

NOTE Confidence: 0.644050896167755

00:02:24.160 --> 00:02:24.780 Cancer.

NOTE Confidence: 0.893675267696381

00:02:25.310 --> 00:02:37.170 But because it is rare and a protracted event that identity and behavior of the cancer cell of origin has only been largely detection lives in our head.

NOTE Confidence: 0.908550798892975

00:02:38.060 --> 00:02:47.630 And this sometimes is also called the multiple hit model where the full transformation requires accumulation of many genetic abnormalities.

NOTE Confidence: 0.902007579803467

00:02:48.880 --> 00:03:19.190 We still advent of genome sequencing. We do know now that the number of mutations observed in a wide variety of human cancers are not always equal on the right hand side. We can see that cancers like skin cancer Melanoma or lung cancers. They are known to be particularly overladen with cancer mutations. But we also see cases of cancers cancer types on the left hand side.

NOTE Confidence: 0.915938198566437

00:03:19.190 --> 00:03:29.070 In particular, I draw your attention to acute lymphoblastic leukemia and acute my Lloyd leukemia. These are all malignancy of the hematopoietic linkage or our blood.

NOTE Confidence: 0.9347243309021

00:03:29.770 --> 00:03:41.970 Where the mutations are consistently see to be very low in particular the acute lymphoblastic leukemia. We know that most of these cases are actually observed in pediatric patients.

NOTE Confidence: 0.886623680591583

00:03:42.530 --> 00:04:04.900 So here in particular in the mix, linear leukemia rearranged malignancy's the recurrent Genomic Optimality is on average. Only

about 1.3 so that really says in these kinds of human appointed malignancy's perhaps the success of accumulation of mutations.

NOTE Confidence: 0.857246935367584

00:04:05.430 --> 00:04:08.290 That theory itself cannot explain or?

NOTE Confidence: 0.897591829299927

00:04:10.400 --> 00:04:24.140 Of course, being in the stem cell center. We also have to consider this hit in this stem cell model that it, which postulates if the stem cells instead of one of these.

NOTE Confidence: 0.916798055171967

00:04:24.660 --> 00:04:42.300 Differentiated progenies when they acquire mutations because they live for a long time and they are the ones that give rise to cancer. But it my personal opinion is that this is a somewhat not really a meaningful argument because if we?

NOTE Confidence: 0.895594835281372

00:04:43.020 --> 00:05:13.330 Imagine the stem cells. This is depicting the hematopoietic stem cells. If you step move. Many bags steps behind. That's going to be the germ cell mutation, but we do know even in patients with germline predisposition. Most of their soma end up being normal, So what we are considering really is which somatic cells give rise to certain rare sulfate? Why are we even bothered with this crazy question?

NOTE Confidence: 0.91976135969162

00:05:13.550 --> 00:05:45.660 Is because we are believers that mutations themselves or combination of mutations are not sufficient to drive certain rare self bait? This is mostly a well known in the somatic cell reprogramming into induced pluripotent stem cells or I PS cell experiments. We know now. The remarkable combination of those for transcription factors. Several of them are known uncle jeans when you introduce these 4 jeans.

NOTE Confidence: 0.886941373348236

00:05:45.660 --> 00:05:51.040 Or for transcription factors even in every single cell of a mouse still.

NOTE Confidence: 0.901558995246887

00:05:51.630 --> 00:06:20.010 Only a minute percentage of these somatic cells can ever become I PCs. So we consider somewhat dissimilar analogy is it possible that the uncle genic mutations. One even when they're accumulated inside the somatic cells. They have to follow. Some rules or selectivities that the soul of origin. The initial somatic cells may be somewhat restrictive.

NOTE Confidence: 0.892447352409363

00:06:21.050 --> 00:06:51.710 So our approach in the study of the induced pluripotency case has been a live so long term lifestyle image in the tracking so I don't know whether we can see but this yellow arrows were tracking a hematopoietic progenitor of blood forming progenitor. And when they're in the beginning. There were blood cells. They under go rounds of division and I'll just Fast forward and to show you by tracking these fate now at the end, we can.

NOTE Confidence: 0.855118155479431

00:06:51.710 --> 00:07:04.250 Endued generate induced pluripotent stem cells. We know these ris CS because the their morphology because they're pretty stereotypic Reporter gene activation.

NOTE Confidence: 0.890653073787689

00:07:04.820 --> 00:07:15.400 And we are formulating this hypothesis is also because malignancy and pro potency initiation. They share many commonality's I List A couple here.

NOTE Confidence: 0.881223678588867

00:07:16.150 --> 00:07:40.970 Uh, which compares the similarities between malignancy induction and proteins induction on the left under the malignancy induction. Many features were put forward by example for Bob Weinberg and colleagues classically. They transformed the normal cells. Both mouse and human with uncle jeans like SV40 large T antigen so on, and so forth.

NOTE Confidence: 0.870303809642792

00:07:41.520 --> 00:08:12.330 Importantly, for example, P 53 and loss of function or CD key gain of function. They both they promote both of these kind of sulfate and a variety of somatic cells can be converted into the target cells, which both in this case are highly productive and it's pro. It's a protracted rare event. So then our question becomes simplified doesn't latency actually initiate from these normally.

NOTE Confidence: 0.806717932224274

00:08:12.330 --> 00:08:14.760 Already faster cycling cells.

NOTE Confidence: 0.929138898849487

00:08:16.070 --> 00:08:28.250 To address that question, we have to create a few tools first first. We have to make sure that all the cells can share the same necessary uncle genic mutations.

NOTE Confidence: 0.840500056743622

00:08:28.840 --> 00:08:42.970 And then they can drive cancer development. So to do this we first derived knocking on Koji model in this uncle gene in this model, we directed Murph 9 mutation.

NOTE Confidence: 0.838155925273895

00:08:43.670 --> 00:09:14.300 In humans, it's created by chromosome translocation and we knocked this into the endogenous HP art. Lucas under the control over that Tetra cycling tetracycline. Inducible promoter and in the same construct following internal ribosomal entry site following the same M RNA. There's this S surface Reporter Nonfunctional NGFR.

NOTE Confidence: 0.828220725059509

00:09:14.300 --> 00:09:31.840 And when this is crossed with a Rosa 26 R GTA and when cells or mice are given. Doc see cycling. All cells could similarly induce this angle G and this is confirmed by flow cytometry, staining for this oncogenic a construct.

NOTE Confidence: 0.867837250232697

00:09:32.740 --> 00:10:03.790 And we can also confirm this construct or this uncle gene allele can drive bona fide acute myeloid leukemia. AML development in mice and this is dependent on its genome type, so if you don't have the RTT even if you feed them eyes with dogs. There's no development of cancer and in this case. If you give the right to Geno type, but don't feed the mice with docs in the control line.

NOTE Confidence: 0.835374712944031

00:10:03.810 --> 00:10:11.460 Oh my eyes are not are viable and the red lines indicate those mice developer these acute myeloid leukemia.

NOTE Confidence: 0.888734340667725

00:10:12.020 --> 00:10:42.790 So we are validated our cassette works and but these little leukemia could have happened as long as one normal cell has crossed over to the dark side right so our question now OK. So we know now all cells can be made to express' this uncle gene leading to AML the question next is do also transform. I don't have the time to show you but I can tell you the results here is actually very few cells.

NOTE Confidence: 0.881838083267212

00:10:42.790 --> 00:11:12.900 Even in this model can be transformed key questions who is what kind of cells transform so we start doing we attempted to them to image malignancy initiation from normal hematopoietic progenitor's from when we are not so we took the cells from the mouse bone marrow carrying our uncle Gene Cassette and put them into these micro Wells and started our microscopy to follow their division.

NOTE Confidence: 0.895920813083649

00:11:12.900 --> 00:11:23.940 So this is one particular well but in reality, we imaged simultaneously hundreds of these single cells so in this 1st.

NOTE Confidence: 0.886304616928101

00:11:24.480 --> 00:11:55.140 You can see when we started the image Ng. There's one cell after awhile. There's 4 progeny after a week. These transforming cells gives rise to this highly compacted, dense Colonie because they're confined in the individual wells. What we can do is we can pluck them out and grow give them another round of Colonie plating so in this cereal, Colonie, replacing I say that is our definition of the Noble transformation and some of these cells when you plug out.

NOTE Confidence: 0.857831835746765

00:11:55.140 --> 00:12:23.830 And to inject into the mice you can indeed induced leukemia in the mice. So now we get to ask we can watch hundreds of single hematopoietic progenitor. Zahl expressing the same uncle gene who transforms and what which cells are transformed so walk you through how to read these graphs, so out of hundreds of these hematopoietic progenitor's specifically were tracking GPS or short for granular site Mackovic Progenitors.

NOTE Confidence: 0.905481398105621

00:12:24.420 --> 00:12:54.610 About 20% of them You see look at the black Gray bars about 20% of them within the first 24 hours of imaging never divided about 40% of them divided once 20% of the divided 20 twice and about 1% of them divided 3 times, so and within this timeframe. Whether you give them doxycycline or not. It does not change their cycling behaviors or whatever you were measuring here.

NOTE Confidence: 0.920230746269226

00:12:54.610 --> 00:13:17.080 Is their intrinsic inherent behavior now? This is their transformation potential so clearly. This is showing with the cells that can normally divide 3 times within the first 24 hours were looking at them. Essentially, 100 of them 100% of them all of them can give rise to.

NOTE Confidence: 0.665983915328979

00:13:17.590 --> 00:13:21.590 Untransformed growth.

NOTE Confidence: 0.870931625366211

00:13:22.150 --> 00:13:52.180 So that's a nice correlation so if under conditions when we accelerate the GNP cycle without the uncle gene can, we alter the possibility of of malignancy. So here we use the emergency. Milo Poesis model is under a challenge or stressed condition. The hematopoietic progenitor's have to produce a vast number of cells to fight.

NOTE Confidence: 0.90667051076889

00:13:52.180 --> 00:14:23.110 Infection for example, that we can see that our treatment induced the increase in the category. The 1% of the GMPS that can normal divide about 3 times or more and also remarkably now we see a subcategory of cells that can divide even 4 times within the first 24 hours. I'm not going to show you. The current account. But this is for the cells that

are going into the mice. Indeed, we generate a much more aggressive kind of leukemia.

NOTE Confidence: 0.867176532745361

00:14:23.110 --> 00:14:51.480 Conversely, it's also true is that if we pre incubate. These cells with the CDK 46 inhibitor in this case power circuit. Only one treatment or short those of treatment in the beginning of the talks induction. We can slow the development of leukemia in the sub coordinate these never developed looking at.

NOTE Confidence: 0.904391467571259

00:14:52.500 --> 00:15:00.160 So with this we started wondering how does this uncle gene transform the rapidly cycling normal cells?

NOTE Confidence: 0.872752547264099

00:15:01.510 --> 00:15:19.180 So this again is a hematopoietic progenitor stem on the progenitor. Trian here we see the stem. Stem cells on Top in the middle are the rapidly cycling progenitor cells and dance here? Is there circulating post mitotic cells.

NOTE Confidence: 0.880105435848236

00:15:19.740 --> 00:15:51.190 So we thought if if we can understand what target jeans are being driven by this uncle gene. Perhaps we can get to some understanding what's surprising, however, is that so wait? What we did is we do it. We took out these 3 kinds of cells by and large and induced at them by dogs treatment. Just simply by doing RNA seek to ask whether or which kind of what gene expression signature is overlapping.

NOTE Confidence: 0.89506858587265

00:15:51.190 --> 00:16:07.460 Uh what's surprising is that there's barely any overlapping driven by the same uncle gene so in this in this plot. It's showing that the there are only 5 overlapping jeans and one of them being uncle gene itself.

NOTE Confidence: 0.902534127235413

00:16:08.000 --> 00:16:16.430 So this is puzzling until we did the single cell RNA sequencing experiments again we're comparing the minus dogs.

NOTE Confidence: 0.908404648303986

00:16:16.960 --> 00:16:39.880 With the Plus Docs and these 3 are the classic while recognizer or well accepted M. LF9 target gene what you can see is that there are small subset of cells normal cells have never seen uncle gene they already started expressing their already expressing all of these.

NOTE Confidence: 0.856020867824554

00:16:40.530 --> 00:16:56.380 Classic target jeans and it's not just that these 3 jeans. We hand picked. It's entirely their their entire transcript. So this is in collaboration with Dan Burkhart in Smithville Smith's lab.

NOTE Confidence: 0.898996651172638

00:16:56.940 --> 00:17:28.270 You can see that the Plus Docs minus docs condition. The data structure is essentially overlapping so at least at this time point. This uncle gene has really not ordered the cellular state. So now that becomes a bit funny, OK, so I will come back to this so then we were wondering whether this phenomenon. We're seeing these rapidly dividing cells to be supportive or to be responsible for initiating cancer means anything for human cancer.

NOTE Confidence: 0.872464120388031

00:17:28.270 --> 00:17:59.540 And the answer is yes, so in the Target data set which annotated there. Merle Fusion status. We can see that this is a cycling D1CC N. D1 expression specifically predicts the pores prognosis for MLL Fusion based leukemia, but not for all the other kind of underlying leukemia, so this work is just impressed now furniture communication, so to summarize what I'm proposing.

NOTE Confidence: 0.882124125957489

00:17:59.540 --> 00:18:33.610 As an alternative way of seeing what cancer really is or how it is coming to Bing is that rapidly cycling cells existed normally but ordinarily they only are in existence briefly in transient and what this kind of uncle gene does is that preserves these naturally existing fast cycling progenitor state So what I'm suggesting is this uncle gene this kind. At least the MLL Fusion uncle gene when it is expressed or when it needs these normally rapidly cycling.

NOTE Confidence: 0.86564964056015

00:18:33.610 --> 00:19:05.560 Dividing cells it perpetuates this state and that creates cancer zero what I'm the overall model is that hit in the transiently faster cycling model. So we know in the hematopoietic progenitor hierarchy. The particular one in this case, we studied is the GMP they normally cycle fast and when this sees the uncle Jean Murphy Ocean, based leukemia. This is what happens is naturally existing cell state.

NOTE Confidence: 0.87634688615799

00:19:05.560 --> 00:19:09.630 Being preserved and perpetuate it by this uncle gene.

NOTE Confidence: 0.872557580471039

00:19:10.490 --> 00:19:31.800 And Lastly I would like to thank my lab. The this work is done by a very talented. Graduate students image and and our collaborator. Doctors Middle Krishnaswamy and her student Daniel Burkhardt and thanks for our funding support. Thank you very much.

NOTE Confidence: 0.488274872303009

00:19:38.920 --> 00:19:46.870 Yes, it sells.

NOTE Confidence: 0.203961998224258

00:19:47.860 --> 00:19:49.060 Wander.

NOTE Confidence: 0.643242597579956

00:19:50.040 --> 00:19:54.510 Getting out of time lapse experiment.

NOTE Confidence: 0.788697898387909

00:19:55.570 --> 00:20:14.150 Can you show that those are preferentially remerge form so in our assay for transformation is almost binary you either get a hugely compactor, Colonie or no Colonie at all, there's no in between.

NOTE Confidence: 0.674892127513886

00:20:14.990 --> 00:20:20.620 So again in your original assets, we have this recent wells.

NOTE Confidence: 0.662202656269073

00:20:25.650 --> 00:20:26.770 Right.

NOTE Confidence: 0.50418347120285

00:20:29.700 --> 00:20:30.780 And then

NOTE Confidence: 0.242017135024071

00:20:32.130 --> 00:20:32.600 Hum.

NOTE Confidence: 0.643410444259644

00:20:33.770 --> 00:20:35.090 Can you show me?

NOTE Confidence: 0.86845201253891

00:20:36.010 --> 00:21:06.460 Fashion that those are those in subset that are already at the time when we're doing those experiments. We were not able to prospec tively pick out whoever that's about to do that. So to address that question, we actually took the time to create a fluorescent lifestyle Reporter of cell cycle speed just by looking at the on going. South cycle rate. Yes, so we do have a tool like that now but at the time we did not.

NOTE Confidence: 0.800814747810364

00:21:08.620 --> 00:21:11.310 Haven't yet I'm going yes.

NOTE Confidence: 0.672122538089752

00:21:13.790 --> 00:21:14.420 Any other