WEBVTT

NOTE duration:"00:30:04.6530000"

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NOTE Confidence: 0.813314139842987

00:00:14.040 --> 00:00:35.650 At 12:25 twenty five two.

NOTE Confidence: 0.923283219337463

00:00:36.330 --> 00:00:48.050 Professor professor.

NOTE Confidence: 0.783004462718964

00:00:48.830 --> 00:00:51.190 Thank you.

NOTE Confidence: 0.889304637908936

00:00:51.770 --> 00:01:22.640 Thank you. David can everyone hear me OK OK. It's a pleasure to be here. This is my first trip to Cancer Center. Grand rounds and it stems from a collaboration that Nick Joe Sheehan. I have established Nick of course, is a leader and genetically engineered mouse models of cancer and I think about how immune response develops to antigens in this case. Tumor engines and I'll tell you more about that as we go along I have no disclosures so.

NOTE Confidence: 0.883191645145416

00:01:22.640 --> 00:01:53.630 The goals of the work from Nick in my lab is shown for you here and it's really to try to understand how B cells and T cells interact and how their critical presumably to prevent growth lung. Cantlin Edna Carcinoma, but applicable to other tumors as well, and to eventually elucidate the potential for BCL targeting Therapeutics. Now the first step. Of course, is to set up a model in which we can track cells because there a lot of B cells are 10 to the 13th.

NOTE Confidence: 0.907114028930664

00:01:53.630 --> 00:02:25.360 A lot of T cells tend to 15. Ten 16, so it's important to have a system in which we can track tumor specific or antigen specific cell so that's really the first step and Fortunately. This is a challenging project is really been made. Much much easier by the engineered mouse models. I'll tell you about but the work is applicable to human tumors, then because it's a challenging project. We need a wizard to help with this and The Wizard is Sunsweet, who is 1/3 year.

NOTE Confidence: 0.87388014793396

00:02:25.360 --> 00:02:56.490 Emitter biology graduate student this is sign in her Harry Potter outfit standing from the Castle. But she is a wizard in the lab, she's a trained physician who elected to come back to Graduate School to get training in immunology and to understand tumor immunology, so immunologist

or Fonda paradigms? What's a paradigm? How does a TLC in anagen? How does a bee celsian, antigen paradigmatic examples, the example of the innate immune system stimulating the adaptive immune response.

NOTE Confidence: 0.918554425239563

00:02:56.490 --> 00:03:26.830 There's a paradigm to be studied in this project as well. And this is the paradigm and to relatively old experiment, but it's really critical to think about this experiment as we think about how tumors are recognized by the immune system and in this case in this experiment was done, 50 years ago, now and it was taking Guinea pigs. Of course, Guinea pigs are out bread. They're not inbred like mice are there out bread like us and so the idea was to determine the basis of aloe transplantation to take?

NOTE Confidence: 0.90413898229599

00:03:26.830 --> 00:03:59.220 Skin graph from one Guinea pig and put it on another Guinea pig and of course, the closer out bread just like humans. You will reject the skin graft, OK that makes sense. But the question is what are the mechanisms of rejection So what these investigators did was to take a vascular eyes skin flap and then put the allograft into the vascular eyes skin flap and now you can manipulate the skin flap and what they did was they let it remain Bachelor eyes. The skin flap has to stay alive, but they either maintain the lymphatics or cut the lymphatics, which you can dissect bye.

NOTE Confidence: 0.896936237812042

00:03:59.220 --> 00:04:29.390 Using a dye like methylene blue so in essence, you have a skin flap with that foreign antigen. In it that either has lymphatics or not connected to the rest of the animal and the outcome of the experiment was pretty clear cut if you have in fully intact skin graft, a fully intact skin flap. The graft is rejected relatively quickly as you would anticipate however. If you cut the lymphatics. The graphs are no longer rejected what that says, is there has to be in a ferret loop.

NOTE Confidence: 0.9051393866539

00:04:30.180 --> 00:04:46.100 That connects the skin flap to the animal and it's mediated by the lymphatics. It says there's some structure within the intact animal, which is critical for the immune response here to foreign antigen so in essence, there is an A ferret loop.

NOTE Confidence: 0.891145288944244

00:04:46.630 --> 00:05:16.920 Through the lymphatic Sinani Farrant Loop and that's mediated by the blood bubbles where the immune response after it's activated by the A Farrant loop can now reject the graph now. You could pick many different problems with this experiment is not a Cliff a rating Antigen. It's a skin graph. So you might argue that rules might not apply to that system. But it's very similar to what you might see with the tumor. But it does says

you need organized structures in the organized structure is a lymph node what it tells us I think.

NOTE Confidence: 0.91090977191925

00:05:16.920 --> 00:05:49.090 As we think about immune responses to tumors those immune responses one would argue have to initiate in a structure. They don't. They're not initiated the immune system is not primed in the tumor. It's primed somewhere else where B cells and T cells are activated in this case, a limp node and then the cells can now traffic to the tumor in initiate the immune response and further activation of the immune system comes downstream, so this is what a lymph node looks like I'm going to go through this in detail because it's a little bit complicated the next slide.

NOTE Confidence: 0.913188874721527

00:05:49.090 --> 00:06:20.040 Will be a little bit more detailed. I'll spend a little time on, but this is what a secondary lymphoid structure. Looks like a lymph node and this is very analogous to tertiary. Linford structures that form at the side of tumors and we believe are quite important in tumor elimination that you need that structure to get an immune response to the tumor you probably also need that structure for regulatory mechanisms that block the immune system from removing the tumor. So both were going on in essence. It's the same structure. I've told you about already.

NOTE Confidence: 0.879963278770447

00:06:20.040 --> 00:06:50.090 You need an A Farrant Loop in this case, the lymphatic duck that brings Anagen and sells Berry management into the lymph node. You need a lift nodes with T cells and B cells. B cells shown for you here and T cells shown for you here that need to come together to be activated. You can also activate CD 8 cells as well as CD4 cells where the T cells are after Anagen is delivered through the A Farrant limp, and then those activated cells, either T cells are B cells that need to migrate out to the skin graft migrate out to the.

NOTE Confidence: 0.881604135036469

00:06:50.090 --> 00:07:20.510 Viruses replicating or migrate out to the tumor can now lead through the E farrant through the E farrant vein and artery now, what this looks like in real time is a little bit more complicated. But this becomes important becaus show. This slide to highlight the multiple roles that T&B Cells have when they're activated all of which one would argue or relevant to tumor responsiveness. So imagine the same scenario of already outlined.

NOTE Confidence: 0.917012453079224

00:07:20.510 --> 00:07:50.530 Or you already in which an agent either from a skin graft or from a tumor or virus is transported into the lymph node is transported by the A Farrant limp, and it can be transported alone or with cells that can also be delivered by the blood in certain circumstances. It comes

in contact with an antigen presenting cell and dendritic cell, which has the capability of activating a whole plethora of T cells cells that we know are very important for example in.

NOTE Confidence: 0.8862344622612

00:07:50.530 --> 00:08:22.700 Post protection but also in tumor rejection for example, CD 8 cells and TH one cells. These are killers. These are helpers that make interferon gamma that activate innate cells. You also can get TH 17 cells and TH 2 cells have shown this is one dendritic cell. There's probably multiple populations of dendritic cells that do different things. They drink cells can also activate a population of cells. You may not be so familiar with called follicular helper or TFH cells. These are the primary cells in the lymph node and I'll show you in the tertiary Linford structures.

NOTE Confidence: 0.891353964805603

00:08:22.700 --> 00:08:52.860 Analogous to a lymph node that helped B cells and of course, B cells or the topic today and how B cells are critical and what their role is in mediating protection against tumors so once these cells are activated then. These cells CD. HTH ones TH twos TH 17 leave the T zone in the lymph node and now they can migrate out migrate to the tumor. For example, or migrate to the site of viral replication and interact with other cells to help eliminate tumors.

NOTE Confidence: 0.908214211463928

00:08:52.860 --> 00:09:24.250 Or help eliminate viruses for example. By contrast, the follicular help yourself stay home and they interact with B cells. B cells are initially localized in a different part of the lymph node there in the B cell follicle as I showed your only earlier slide. They have to be activated by engine as well. And when they are, they can move and this is the initial step of TB collaboration. This is how B cells get their signals to mature into antibody producing cells. Another effector cells and I say that because B cells do multiple things.

NOTE Confidence: 0.912669062614441

00:09:24.250 --> 00:09:56.460 We tend to think of them as antibody producers, but they also make cytokinins their robust affect ourselves and as this implies. They also interact with T cell so they're very good at activating T cells are maintaining their activation so they're doing 3 different things. They're serving to activate cells. There serving to produce antibodies and their serving to produce pro inflammatory and anti inflammatory cytokine so potentially then in a tumor environment. B cells could be doing any of these things and we have to parse those individual roles.

NOTE Confidence: 0.917549967765808

00:09:56.460 --> 00:10:29.430 I think of what B cells are doing in terms of tumor rejection for example, OK now. After this initial interaction form over the first 2 to 3 days of the immune response after your flu shot this fall. For example,

which is coming up so it's important to think about it, biologically uniform. Shortliffe plasma cells PC and short lived. B cell memory, meaning these are cells that can be reactivated when you come in contact with the flu. But these are shortly of cells, but there are very important in protecting us against viral challenge. We don't know their role.

NOTE Confidence: 0.911729216575623

00:10:29.450 --> 00:11:02.100 I into more responsiveness what we do know, though, is over the course of the next several days after you get an immune challenge and a flu shot is a perfect example because you know that I'm in which you get the shot. It's not like a tumor when you don't know it develops you don't know when the immune system is being primed and a priore that's a very important lesson, here with our genetically engineered mouse models because we can look at and delivery to the immune system in a timely manner, so we know when the immune system gets the antigen so.

NOTE Confidence: 0.907973945140839

00:11:02.100 --> 00:11:33.680 After this initial few days over the course of time. B cells now migrate deeper into the follicle along with their helper cells. TFH cells and this is called the germinal center and I'm telling you about this because this is where B cells mature and they undergo a process called somatic hypermutation in which random mutations are inserted into immunoglobulin jeans and those are random. But if the B cell makes the right mutation that allows for selection of Antigen, it can appropriately mature.

NOTE Confidence: 0.886542022228241

00:11:33.680 --> 00:12:06.350 In the setting of T cell so B cells will proliferate they will undergo these random mutations and something called the dark zone. It's dark because there's a lot of Cliff Oracion. This is also parenthetically the source of where many be so lymphomas arise because of all the mutations that occur. It makes sense. For example, like Mick driven lymphomas. For example, a mic translocations. But B cells can now move from that area into the lights own where they come in contact with antigen presenting by this antigen presenting cell and T cells in the T cell select B cells?

NOTE Confidence: 0.905514538288116

00:12:06.350 --> 00:12:37.180 And those that have the appropriate mutation that can bind Antigen and bind it well will present that an original class 22AT cell and a repetitive cycle of TB interactions will incur and this can go on and on for days so you can get higher and higher affinity of the McLaughlin jeans now again. It's important to note that B cells are not only receiving T cell help. There also serving his antigen presenting cells for T cells. Here B cells are doing more than one thing now over the course of several days.

NOTE Confidence: 0.915507376194

00:12:37.180 --> 00:13:08.950 Or even longer along lift memory B cells developed as shown for you here of different different infinities and Long live plasma cells, which end up in the bone marrow. So when you got your tetanus shot when you were a kid. You still have tetanus, producing plasma cells. Even if you have not been revaccinated and these are in the bone marrow and they sort of protect you against tetanus. Likewise, when you get your flu shot the same thing happens. We don't know necessarily the role of these and tumor immunity so this model is important, but it's also important to recognize as well.

NOTE Confidence: 0.903918206691742

00:13:08.950 --> 00:13:39.520 That their regulatory pathways to their operative regulatory cells can modulate these interactions and regulatory cells can modulate these interactions. And while we tend to think of CTL A4 and PD1 as molecules that regulate T cells within the tumor. Both those molecules are highly expressed in the lymph nodes so arguably when you're used blockade of CTL A4 or when you use blockade of PD1, not only your modulating affect your capability of cells within the tumor.

NOTE Confidence: 0.900300741195679

00:13:39.520 --> 00:14:10.170 You're also modulating the effector capability of cells within the limp node as well and some data would suggest although it's not proof positive because we really don't know the answers. Yet that the immune related adverse events. We see with nuvola mab ripple. Emma mab or also partly engendered by the effect of those drugs not necessarily in the two more. Most certainly that is happening, but also by the effect in the in the secondary lymphoid structures and that has to be parsed and it hasn't been parsed at least to my knowledge.

NOTE Confidence: 0.817250967025757

00:14:10.170 --> 00:14:12.810 Now I have no slides.

NOTE Confidence: 0.937181770801544

00:14:13.560 --> 00:14:15.010 So I did something wrong.

NOTE Confidence: 0.789122700691223

00:14:16.860 --> 00:14:28.240 Uh so somebody's got to rescue me how about that. It was not bad for have a trivia question I am a Luddite.

NOTE Confidence: 0.867549598217011

00:14:28.830 --> 00:14:58.900 Blood I'd buy know what a lot ideas, OK question and answers think about it. I'm definitely a lot when it comes to technology so this is what a TLS looks like and again the same structures apply that I've already talked to about as well. There's T cell Service B cells. There is also a place where the T cells and B cells can enter through the vascular system. The high endothelial venules and they're also conduits limp structures were antigens can enter so this looks very much like.

NOTE Confidence: 0.851738154888153

00:14:58.900 --> 00:15:02.150 What you would see with a limp node OK now?

NOTE Confidence: 0.884633719921112

00:15:02.660 --> 00:15:33.890 These things form in human blowing adenocarcinomas as well as in the mouse's I'll show you. This is a slide. That song put together along with the other slides. I'll show you parenthetically and this is a this is a tertiary allenport structure around a long tumor here and it has. It's hard to know where the T cells and B. Cells are here because they are not really staying for that or the Germinal Center for that matter. But you can see it's a well organized structure now are B cells important. I'll show you 2 slides to get at that point this is.

NOTE Confidence: 0.8763427734375

00:15:33.890 --> 00:15:54.680 Individuals with non small cell lung cancer, either stage one or stage to treatment, naive are individuals. More and more advanced disease that have gotten neoadjuvant chemotherapy and in those tumors. There are tertiary. Linford structures there. B cells of all different maturation. B cells that are plasma cells, making antibodies B cells that are Maturin Germinal Center B cells.

NOTE Confidence: 0.881869375705719

00:15:55.180 --> 00:16:25.770 The some of it is, is that the presence of Follicular B cells mean B cells within the follicle or within the germinal center are associated with a better response. That's the some of the data. B cells are good. These data show the same thing in which another group of investigators. This is a group from Vienna. The first slide was from a group in France, but the data analogous in which tumor induced plasma blast like B cell so these are B cells that are maturing to antibody formation, they have not.

NOTE Confidence: 0.898578226566315

00:16:25.770 --> 00:16:56.720 Fully matured, yet and they can still interact with other cells that can have the capacity to make antibodies. They have the capacity to serve as antigen presenting cells and they can also make inflammatory molecules. They can do all 3 things of B cell can do so it doesn't tell you what they're doing, but just tells you they're important, but cause individuals in this Melanoma study that had more of these plasma blast like structures had a better overall outcome. So B cells. At least we would argue op ryori or good, the question now is.

NOTE Confidence: 0.89952290058136

00:16:56.720 --> 00:17:26.890 What are the B cell seen? What are they doing and what are they doing and so that's what's on has really set out to answer in the lab and the way she's done this again. Remember this temporal response had mentioned that in a tumor or a chronic viral infection. You don't know when

things began. This is a member of trained as a clinical rheumatologist. It's a major problem in rheumatology like in rheumatoid arthritis. What's driving the disease. We have no idea because we see patients months or even years after onset of disease.

NOTE Confidence: 0.874317705631256

00:17:26.890 --> 00:17:58.050 In this case using these models that Nick Joshi initially developed when he was a postdoc in Tyler Jacks layout. She's now refined those with sons help as I'll show you we can look at Antigen delivery own set and that's really critical in thinking about the steps that lead to the role of B cells in mediating tumor tumor regression, presumably So what Nick made was an animal with an oncogene. That's not expressed so it's only expressed after you clip out locks P sites.

NOTE Confidence: 0.885031640529633

00:17:58.050 --> 00:18:11.410 In the oncogene so once they're clipped out it can now be expressed and cross that to a mouse that has a P53 Mutation OP 53 lack of P53A tumor suppressor so in the baseline.

NOTE Confidence: 0.862009108066559

00:18:12.220 --> 00:18:43.330 At baseline these guys are not expressed and you can see that in the rest. Corey epithelium no tumor. However, if you now insert down the airway a lentivirus expressing Cree Recombinase Creek and now clip out. These stop sites. So K races expressed they can phlox this gene so now we get a mutant P 53. You get no tumor suppressor. At least know P 53. So now you get an driven tumor without P 53.

NOTE Confidence: 0.896124303340912

00:18:43.330 --> 00:19:14.110 And what you see and that's what the Cree is due in Fluxing. These out you get a transform cell in the respiratory epithelium and what that looks like over the course of time and this has been well worked out in Nexlab is that you get low grade maligna sees that advance over the course of time with metastatic disease. Now, if you just look at the Cree only just put in the lentivirus down the respiratory epithelium. You just see background cells. Now, if you insert the creep and in this case what has been done.

NOTE Confidence: 0.867660641670227

00:19:14.110 --> 00:19:44.840 Is to put in neoantigens so these are antigens that are recognized by T cells and that allow us to look at Antigen specific T cells. So you can track the T cells again. You need to know the anagen you need to know when it's delivered you can now track the immune response and in that case, the neo antigens are peptide of ovalbumin or 2 peptides of albumen here. CD4 and CD8 and with and if this is.

NOTE Confidence: 0.891021907329559

00:19:44.840 --> 00:20:15.910 Express' with a luciferase you can track these cells have shown here, so this is what luciferase looks like and their T cells and B cells and T cells in here as well, and you can now identify those with the luciferase expressing construct here. So now there is a system in which you can look at own set of antigen delivery in the setting of a genetically engineered tumor. So we can have natural own set, presumably natural instead of a tumor and track antigen specificity aids very much.

NOTE Confidence: 0.898730158805847

00:20:15.910 --> 00:20:47.860 And thinking about how the kinetics of the tumor of developed now. This is from a paper that was published by Nick when he was still a postdoc and what it shows is using the system. You can see the tertiary. Linford structures on the left and won't go through the staining but in particular, but you can see CD. 3T cells and B20B cells. T cells and B cells were both there. You can also see something called follicular dendritic cells. I talked about those on earlier slide. But there are essential for activating B cells so their present here as well.

NOTE Confidence: 0.892883956432343

00:20:47.880 --> 00:21:06.740 There's a structure of fibroblastic reticular cells that provides structure to the tertiary. Linford structure and there are also blood vessels as determined by a standing of CD 31 and lymph node address and is shown for you here, so T cells B cells antigen presenting cells.

NOTE Confidence: 0.879757463932037

00:21:07.460 --> 00:21:38.690 Structure and blood vessels all are present in TLJ. LS is in this model. This looks like a lymph node in essence. So it sets up a structure in which you can get antigen activation of specific T cells and B cells and that's what it looks like here? When we have Luke OS expressing both T cell antigens. K SP53 negative tumor. And this is what it looks like now because we can also see within B cells here.

NOTE Confidence: 0.874068439006805

00:21:38.690 --> 00:22:10.140 In the mediastinal lymph node you can see that flicker helper cells. Those cells that help B cells because they expressed a specific transcription. Factor called BCL 6, so the cells that are Blue Blue. CD4 cells and red purple cells have shown for you. Here are CD4 cells. B cells within their activated in the germinal center also expressed BCL 6 are there here so this is a germinal center.

NOTE Confidence: 0.889525532722473

00:22:10.140 --> 00:22:42.470 This is exactly what you see after viral infection. This is the tertiary. Linford structure in the long and again, you can see TFH cells here shown here and a lot of B cells. So it's re capitulating what we've seen a limp node and this is what we're trying to model now cause. We know in normal circumstances in tertiary. Linford structures with the tumor and Brown,

an with a T cells in green and B cells in blue with their antigen presenting cells. This is the intimate molecular structure that's going on.

NOTE Confidence: 0.911076366901398

00:22:42.470 --> 00:23:14.580 And we can begin to manipulate the molecules that that are necessary for T cell B cell interactions. B cell maturation, presumably necessary for their factor capability and tumors. We can begin to now take this apart. Now I'm going to show you one last set of experiments in the last couple of slides and then I'll begin the one issue with this model is I've shown you T cell epitopes. So we can activate antigen specific T cells. But we don't have a tool yet to activate antigen specific B cells. We need both.

NOTE Confidence: 0.879435837268829

00:23:14.580 --> 00:23:45.660 And this was an innovation from son what she developed which was to take the same vector of the vector in which we insert into the lawn to activate the grass. Mutation is shown for you here in essence? What she did was to insert a B cell epitope called Hell and this is the same episodes. These are slightly different T cell epitopes. These are viral epitopes, but regardless we can now track the Antigen specific cells.

NOTE Confidence: 0.862869560718536

00:23:45.660 --> 00:24:16.070 Get react with both the B cell antigen. the CD 8, Antigen and the CD 4 engine so now we have a system in which we can track Tanager Pacific B cells. Anisha specific CD. 4 cells and specific CD. 8 cells and we can determine the individual roles of what those cells were doing in terms of tumor modulation because it's also colored with him. Scarlet we can identify the Cree expressing cells and it's called hello that stands for held which is the B cell antigen.

NOTE Confidence: 0.853606164455414

00:24:16.070 --> 00:24:25.170 The LC MB antigen and the code on optimized in Scarlet. This was sons name Hello. It's pretty cool and we can remember.

NOTE Confidence: 0.850799381732941

00:24:26.870 --> 00:24:57.260 And now we can do lentiviral infection with a Cree only the KP only sorry and I won't go through this in detail but we can now generate with injecting of this vector. This Cree expressing vector into the K SP53 mutant mice. We can now generate tumors. But the tumors are expressing these specific B&T. Cell antigens and now we can track the tumor allows us to.

NOTE Confidence: 0.885162949562073

00:24:57.260 --> 00:25:27.410 Measure that owns head of timing of when the antigens are expressed in the context of the tumor and what's On is going on to show in the last 2 slides is that the B cells and these are the transgenic B cells. We can use to measure the B cell antigen expression is shown for you in

the hello. The Gray very robustly respond to the Antigen and when she does, that using this system and this is really the critical experiment do antigens.

NOTE Confidence: 0.864048659801483

00:25:27.410 --> 00:25:58.360 Pacific diesels matter and the way that experiment is done is to look at wild type mice. The KP wildtype mice and you can see that after she transplants tumors expressing the K Race Mutation and again with a lentivirus vector injected into the mouse. You can see robust tumor progression. However, if you have an antigen specific system that KP hello. So B cells now have a new antigen they can see.

NOTE Confidence: 0.893860578536987

00:25:58.360 --> 00:26:29.000 As shown in the Orange. You really markedly delay in almost halt in this case over the course of 20 days after a transplant of the tumor halt progression of the tumor. So it suggests very strongly that it be cell. Antigen expressed within the tumor is critical for regression of the tumor or prevention of its progression. So the question now is next steps an what's On is trying to address is? What are the mechanisms of B cell dependent?

NOTE Confidence: 0.893261849880219

00:26:29.000 --> 00:26:59.670 Anti tumor immunity is it's accreted antibodies is the engine presenting function of the B cells is it their location. Their presents in lymph node. The TLS or in the tumor and what's the role of CD8 cells. We can now parse all these individual questions using the system that son has developed and we can also look at the B cell response to immune checkpoint inhibitors so I think we have a very nice system, which has been shown at least in this transplant tumor model to be beneficial to bowl of B cells.

NOTE Confidence: 0.880029916763306

00:26:59.670 --> 00:27:26.070 Management specific B cells appear to be important in preventing tumor progression. At least over a short term and now we have a system to address these questions, thanks to sign so these are this on this is the rest of my lab. We work on secondary lymphoid organs. There's a pass. People lab and Nick Joshi. His really important collaborator and we've had support from the Yale sporran lung cancer. Thank you very much.

NOTE Confidence: 0.865710377693176

00:27:28.710 --> 00:27:36.570 I'm looking into the sun is a member of the cancer training grant they yell cancer biology training program.

NOTE Confidence: 0.867609322071075

00:27:37.210 --> 00:27:45.320 We have time for a couple of questions. Obviously, we're going to have to have son back here in 2 years.

NOTE Confidence: 0.884527742862701

00:27:46.200 --> 00:28:19.190 I can hang around afterwards. It's a lot of data. I realized but I'm happy answer questions. So one kind of beginner questions from Maine is so do these structures do you need all these cellular interactions 1st to form the structures or are there specific cells that nucleate formation of these if I understand the question correctly the kinetics of forming a structure it's a very important question, we know I actually a fair amount about that. That B cells are really critical to form lymph nodes.

NOTE Confidence: 0.825053989887238

00:28:19.190 --> 00:28:50.110 They are also critical to form tertiary Linford structures, naive B cells, but cause they have lymph a toxin on their surface and lymph a toxin is an important it was first identified by Nancy Rodelin Barn. Axman Here back in the 70s. It's really the first side ocon but lympha talks. A nancies continue to work on that. She really has done similar work in that in this area, but lympha talks and expressed on B cells is important interact with lymph a toxin receptors on other cells flickered and Rick cells and so forth to initiate.

NOTE Confidence: 0.888567984104156

00:28:50.110 --> 00:29:20.350 The structure that's ongoing so one would argue that the inflammatory response might be sufficient to recruit naive B cells to form TLS is but it's still activation assume within the mesentery Lymph Tour. Mesenteric lymph nodes in lung cancer. For example, that serves to do the initial priming an adult in the inflammation. At least to the TLS structure. That's the kinetic so I would think about. I think it's On is shaking her head yes.

NOTE Confidence: 0.844760239124298

00:29:20.350 --> 00:29:21.240 And she's the expert.

NOTE Confidence: 0.82671993970871

00:29:23.010 --> 00:29:26.540 OK, thank you guys.

NOTE Confidence: 0.2171381264925

00:29:28.760 --> 00:29:33.350 OK.

NOTE Confidence: 0.803381562232971

00:29:33.980 --> 00:29:49.520 Today is actually trained.

NOTE Confidence: 0.722140431404114

00:29:50.030 --> 00:30:04.660 Yeah, and he's now.