everybody. Welcome to our session on behalf of Yale University and Yale Cancer Center. I'm pleased to have you with us as part of the Yale Engage Cancer series. This session is entitled defining Mechanisms and biomarkers of sensitivity and resistance to anti cancer treatments. I'll be your moderator. I'm Barbara burtness. I'm a medical oncologist and have a interest in drug development and head neck cancer. And we have a phenomenal panel of Yale faculty members and Anna corporate guest Susan Galbraith from Etsy.
And hope to have a very very interactive session. I’d like to start with a few housekeeping items. The program format as I said, is going to be each of our panel members giving a brief about 5 minute introduction to the work that they do. What they see is as key questions. We know that to attack cancer we need team science. We need collaborations within our
organization and across different sectors. 

Academic, public and industry and Yale engage was designed to build these connections, particularly between Yale scientists and industry leaders. To keep the discussion lively, we welcome questions. Some have been submitted ahead of time and you’ll have the ability to submit them through the Q&A function. On the Web and R we have an enormous amount of expertise among our panelists and will be. Monitoring those questions as they come up and try to get to as
many of them as possible and I want you to know that this web, nor is being recorded, so now I'm really pleased to be able to introduce Charlie Fuchs. He’s the secular professor of medicine and medical oncology and a professor of chronic disease Epidemiology here at Yale. He’s the director of the Yale Cancer Center and Position in chief at Smilow Cancer Hospital, Charlie.

Forever thank you and thank you for your leadership on this and welcome.
to all the attendees to what is now our third Yale Engage cancer event and it’s really been an exciting and incredibly productive series of forms. So please it could join us for this third one. You know, we all recognize that despite the fact that we’re dealing with a global pandemic, the consistent impact of cancer on public health. And the morbidity and mortality costs on our population. Or considerable an it remains one of the great challenges in medicine. And it also is one of the
NOTE Confidence: 0.871820628643036
00:03:12.409 --> 00:03:13.283 largest investments.
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00:03:13.290 --> 00:03:16.216 I think that goes on and healthcare
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00:03:16.216 --> 00:03:18.321 research and drug development and
NOTE Confidence: 0.871820628643036
00:03:18.321 --> 00:03:21.023 our our our efforts at Yale is
NOTE Confidence: 0.871820628643036
00:03:21.023 --> 00:03:23.777 to really tackle this challenge.
NOTE Confidence: 0.871820628643036
00:03:23.780 --> 00:03:26.629 Yeah Liz had a long legacy in
NOTE Confidence: 0.871820628643036
00:03:26.629 --> 00:03:29.019 Cancer Research and cell biology,
NOTE Confidence: 0.871820628643036
00:03:29.020 --> 00:03:29.896 genetics, pharmacology,
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00:03:29.896 --> 00:03:31.648 immunology, among other elements.
NOTE Confidence: 0.871820628643036
00:03:31.650 --> 00:03:35.880 And I think a lot of the history of success,
NOTE Confidence: 0.871820628643036
00:03:35.880 --> 00:03:37.664 including four Yutema therapies,
NOTE Confidence: 0.871820628643036
00:03:37.664 --> 00:03:40.340 come out of this University were
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00:03:40.414 --> 00:03:42.717 privileged to work at one of the
NOTE Confidence: 0.871820628643036
00:03:42.717 --> 00:03:44.851 national one of the original
NOTE Confidence: 0.871820628643036
00:03:44.851 --> 00:03:46.456 National Cancer Institute,
designated Cancer centers, and has been a really an area that research that is as built a legacy of great innovation as well. Smilow cancer hospital. Our clinical center. Is celebrating its 10th anniversary and is a robust operation that now sees about 48% of every newly diagnosed cancer patient in the state of Connecticut. And really, we view that through the science and through this robust clinical operation we really are committed to moving discovery scientific discovery into the clinic.
NOTE Confidence: 0.871820628643036
00:04:21.530 --> 00:04:23.640 Really pleased with the team
NOTE Confidence: 0.871820628643036
00:04:23.640 --> 00:04:25.328 that’s been assembled today,
NOTE Confidence: 0.871820628643036
00:04:25.330 --> 00:04:28.291 our first and Yale engage cancer was
NOTE Confidence: 0.871820628643036
00:04:28.291 --> 00:04:30.350 focused on immunobiology, our second.
NOTE Confidence: 0.871820628643036
00:04:30.350 --> 00:04:32.325 Was focused on novel therapeutics,
NOTE Confidence: 0.871820628643036
00:04:32.330 --> 00:04:35.386 and the third really ties it all together,
NOTE Confidence: 0.871820628643036
00:04:35.390 --> 00:04:37.300 which is to understand now,
NOTE Confidence: 0.871820628643036
00:04:37.300 --> 00:04:39.988 given these efforts to develop new drugs,
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00:04:39.990 --> 00:04:40.754 new targets,
NOTE Confidence: 0.871820628643036
00:04:40.754 --> 00:04:42.664 how do we understand resistance?
NOTE Confidence: 0.871820628643036
00:04:42.670 --> 00:04:44.580 How do we understand sensitivity?
NOTE Confidence: 0.871820628643036
00:04:44.580 --> 00:04:47.100 And how do we further enhance our
NOTE Confidence: 0.871820628643036
00:04:47.100 --> 00:04:48.790 approaches to cancer therapy?
NOTE Confidence: 0.871820628643036
00:04:48.790 --> 00:04:51.088 Integral to this fight is our
NOTE Confidence: 0.871820628643036
00:04:51.088 --> 00:04:52.237 collaboration with industry,
and we’re so pleased to have Doctor Susan Galbraith join us as our industry partner on the panel, and we realize that. So many of you in the audience come from the biotech and pharma. An really part of this effort. Beyond hearing from these experts in their insights is to really begin a conversation. Because one thing we really welcome here at Yale is to collaborate with you. We want to build strategic partnerships with all of you. Because ultimately this fight against cancer. Yes,
it requires each of these domains on the slide, but it requires a community focused on every aspect, and that includes academia and industry in biotech. So one thing I want to invite you today is to ask questions, but after this form, please reach out to us. And let’s think about ways we can work together. I think we have a lot of resources we can bring here at Yale to
partner with all the great

things you’re all doing and we look forward.

To continuing this conversation

Thank you Charlie. I think that that’s a great introduction to

to what we’re trying to do here I just had a brief opportunity to

to scroll through the list of participants an it’s a formidable group,

including GAIL scientists, industry partners. Alumni are supporters,

so I think that we can anticipate some pretty hard hitting
questions from that group. So we’ve tried to arrange these talks so that.

We’ve tried to arrange these talks so that we hope that there’s a little bit of a natural progression in the scientific questions, and Dan the approaches that are are taken to understanding resistance. As I said, every speakers been asked to sort of reflect a little bit on what’s her, his core expertise.

What questions drive the research and how they hope to, or Yale hopes to work with industry partners. To address cancer cancer
00:07:03.212 --> 00:07:04.938 treatment resistance.
NOTE Confidence: 0.85655349890391
00:07:04.940 --> 00:07:06.974 And what kinds of capabilities and
NOTE Confidence: 0.85655349890391
00:07:06.974 --> 00:07:09.388 resources need to be brought to bear?
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00:07:09.390 --> 00:07:11.679 So each of those speakers has been
NOTE Confidence: 0.85655349890391
00:07:11.679 --> 00:07:14.519 asked to go only for about 5 minutes?
NOTE Confidence: 0.85655349890391
00:07:14.520 --> 00:07:16.970 I’ve been told that I should be
NOTE Confidence: 0.85655349890391
00:07:16.970 --> 00:07:18.968 ruthless and cut you off.
NOTE Confidence: 0.85655349890391
00:07:18.970 --> 00:07:21.539 If you go over and that
NOTE Confidence: 0.85655349890391
00:07:21.539 --> 00:07:23.289 will be hard to do.
NOTE Confidence: 0.85655349890391
00:07:23.290 --> 00:07:25.090 ‘cause I know the talks
NOTE Confidence: 0.85655349890391
00:07:25.090 --> 00:07:26.890 are going to be great,
NOTE Confidence: 0.85655349890391
00:07:26.890 --> 00:07:29.050 but let me start by introducing
NOTE Confidence: 0.85655349890391
00:07:29.050 --> 00:07:30.130 Doctor Katie Palitti.
NOTE Confidence: 0.85655349890391
00:07:30.130 --> 00:07:32.290 She’s an associate professor of pathology
NOTE Confidence: 0.85655349890391
00:07:32.290 --> 00:07:34.809 and Medicine leader in our Cancer Center.
NOTE Confidence: 0.85655349890391
00:07:34.810 --> 00:07:36.250 Through those answering signaling
cancer signaling networks program, as well as a leader of our lung spore program and Katie. Think it away. Thank you very much, Barbara. And I'm really delighted to have the opportunity to speak here today and tell you about some of the things that we're interested in. I have a cancer biology lab here really with a focus on lung cancer and one of the areas that we are really interested in studying is working on resistance and resistance to various cancer therapies including targeted...
Some of the things that we think about a lot and work on. I'm really interested in understanding the relationship between tumor genotype and drug sensitivity. We study the influence of the tumor micro environment on sensitivity to different therapies and also investigate mechanisms of drug tolerance. So why do some cells die when you apply a therapy and instead other cells do not die and stick around and serve as the fertile ground for the emergence of drug resistance?
And then we also investigate new approaches based on the science that we discover to overcome and or to prevent the emergence of drug resistance. And we do these studies by really integrating information from various different systems, various different models and using a variety of different technologies. We use specimens and data from patients, so we have a very robust biopsy program. Here, within the context of the Lung Cancer Group, we can obtain biopsies from patients. Long sort of the spectrum of
their treatment with therapies, and we can generate patient derived models from these biopsies, but also then analyze the data and information to really understand resistance in patients. We use these models to generate or these specimens to generate patient drive Zeno graphs as well, and also 2D or 3D cultures from patient specimens, and we also extensively work with genetically engineered mouse models of lung cancer that we can. I used to study resistance and in that regard I’d like to tell you today.
about some work that we have been doing in the field of EGFR receptor, mutant lung cancer. Next slide, please.

To really use models to study resistance to the EGFR tyrosine kinase inhibitor, also Merton.

If and this is a work that really illustrates a partnership between.

Academia and investigators in academia and work that we’ve done together with Astra Zeneca and also working with Garden Technology and work that was published recently this year and so EGF receptor mutations are found in about 15% of lung cancers and can
be targeted with tyrosine kinase inhibitors and one of the most recent ones. Is this tyrosine kinase inhibitor awesome Merton Eben? So we can take our genetically engineered mouse models and ask the question what happens? If you have mouse models of EGF receptor, mutant lung cancer, and you treat them with awesome Merton, if and so we took my sweet, treated them till the emergence of resistance. And when we looked at resistant tumors to see what was happening, we found that almost 50% of the tumors
that emerged had secondary mutations in EGF receptor that confer resistance to awesome American if and so.

With that information we can actually then go ahead using these models. So we’ve discovered new mechanisms. We can now use these models for preclinical testing and test new therapies. We can also with this information go into human specimens and data and analyze the relevance of the resistance mechanisms there, and so. For example, in this study we found that the mutations that were emerging were particularly relevant to the L.
So at our subset of EGFR mutant tumors, so there was an allele specificity that was revealed through our studies in mouse models and then working with colleagues like Mark Lemon. Here, you’re going to hear from next. We can really then study the biochemical properties in detail of these mutants. Next slide, please. So we also are working extensively to take these models that we have to take these models that we have and sort of take them to the next level to study some of the more complex mechanisms of resistance, and we have modified for example this initial mouse model of EGF receptor,
mutant lung cancer to incorporate additional genetic alterations that are also found in humans in EGFR mutant lung cancer, including, for example, tumor suppressor gene alterations using in vivo CRISPR CAS 9 gene editing and so now. We can study how those additional alterations are impacting tumor progression, sensitivity to therapies, and the phenotypes of tumors. As I mentioned in my first slide, we also have a robust program to generate patient derived models, and here is really an illustration.
of sort of the different.

PDX is that we’ve generated across various different oncogenic subgroups of lung cancer with different oncogenic driver alterations, and so we’re using these models. To really study resistance in human specimens and really use them to study heterogeneity of human tumors, signaling network alterations, and the molecular profiles that you can have in these human who tumors can have in these human who tumors with or without drug treatment. Thank you. Thank you so much Katie. I think that there’s there’s so
much there for the other speakers to riff off of and to set up our questions. Next, let me introduce Mark Lemon, distinguished Professor of pharmacology. You see his leadership roles in the Cancer Biology Institute. There, mark is unique and bringing a wealth of expertise in biology and structural biology to the very interface with drug development and disease based research and so. Looking forward to your comments, mark. Thank you very much, Robert and good afternoon. So a great pleasure to be here.
I look forward very much to hearing discussion later on. As Barbara mentioned, I'm really a basic scientist interested in how molecules work. My core expertise really is in biochemistry and structural biology. The focus of most of our work is detailed understanding of how molecules and networks involved in oncogenic signaling actually do work and do not anatomic detail. Where we can and quantitatively understanding how their properties are changed by oncogenic resistance mutations.
As Katy mentioned, work we’re doing with her and how we can then use that information to guide mechanistically driven personalized medicine or put the biochemistry into personalized medicine. Those kinds of thoughts. So our main focus in general is the class of receptors that Katie discussed. The growth factor receptors that have interested Harrison Chinese have interested Harrison Chinese. As you know, and as key to describe, these are key targets for cancer therapy, particularly lung cancer.
and is clear in general in advancing approaches to controlling their behavior. So the behavior with drugs dealing with resistance really requires us to understand the molecular mechanisms and understanding well enough that we can manipulate them in a predictable way and also manipulate their complex so the networks. And I’ll give a couple of examples of things that are driving have been driving research in my lab. Recently, the first relates to what Katie has been discussing at the level of growth, acquired resistance and primary resistance,
and we’ve actually been working with Katie quite a bit to understand details of how secondary mutations in EGFR cause resistance. As she mentioned, with the automotive resistance mutations and the additional key colon network is to use that understanding as it develops to decide when to use which inhibitor and how to come up with new and indeed repurposed inhibitors in resistance situations. Not going back to two other working in the lab, one of our recent first time
has been to identify and target driver mutations in neuroblastoma, which is one of the most common pediatric cancers. And this is related work we’ve been collaborating with the Children Psychology Group on out another receptor tyrosine kinase, a bit like EGFR, and sequencing out consumers from 1600 patients. That gave us a list with carve out mutations that we analyzed biochemically structure. Real transformation did a full work up on them and show from that that out.
About 14% of neuroblastoma without dependent, and we developed a computational model that you can see in the middle of the left hand part of the slide that we can with which we can predict which mutations are actionable. Mr Working on that and an in refining that to identify out dependent tumors in the clinic and what but importantly this quickly let us understand that some variants are resistant to 1st generation out computers result and it does not work in Europe. Last over and we also learned that the
stable of 1st generation are contributors.  
We’re not that different from one another and impedes.  
In particular, we have one.  
We have to be careful to which drug you choose for the trials,  
because there’s a limited number of patients in pediatric,  
so more monster pick the right one  
and over all those considerations,  
using their biochemistry channel distal mat in it,  
which is now looking promising in neuroblastoma,  
overcomes much of the resistance,  
although of course we are now experiencing
00:17:39.996 --> 00:17:41.500 resistance that we’re working on,
00:17:41.500 --> 00:17:43.318 and I just want to illustrate that as a
00:17:43.318 --> 00:17:45.262 key approach combining biochemistry and
00:17:45.262 --> 00:17:47.377 structural biology and computational aspects.
00:17:47.380 --> 00:17:49.424 But we could use in principle for
00:17:49.424 --> 00:18:00.979 any receptor types in Chinese.
00:18:00.980 --> 00:18:02.799 So next slide please.
00:18:02.800 --> 00:18:04.672 We also very interested in a new
00:18:04.672 --> 00:18:06.979 aspect of getting away from inhibiting
00:18:06.980 --> 00:18:09.140 receptors per say as we tend to do
00:18:09.140 --> 00:18:11.867 instead correcting their signaling.
00:18:11.867 --> 00:18:13.924 So we’re all familiar with biased
00:18:13.924 --> 00:18:16.270 agonists for G protein coupled receptors,
00:18:16.270 --> 00:18:19.068 which can promote different responses to
00:18:19.068 --> 00:18:21.833 the same receptors as strength on the left.
The color of signaling, whether it’s orange, yellow, green or blue. Many common drugs that we take, her bias GPS are agonists, and there’s actually a lot of effort to develop biased agonists of opiate receptors retaining analgesic effects. But without the associated problems of the opiates, we don’t do that for receptor tyrosine kinases. In the light there traditionally thought of as being binary signaling systems, either on or off as an illustrated here, but we recently showed in the
paper a couple of years ago would continue to work on that.

Prices have color in their signaling two and as illustrated on the right, the same receptor EGF receptor. Again in this case can give you can promote self liberation or differentiation depending in the same cell depending on which growth factor is used to activate it, and this reflects you know a different dimer structure, asymmetric or symmetric, for the two ligands with altered dimerization and signaling.
kinetics that define specificity,
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it turns out the mutations in glioblastoma
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shift signaling to the right,
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making it more proliferative.
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That’s one of their.
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At key issues,
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even with small structural changes,
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now that we understand the
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structural basis for this but through
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crystallography and so forth,
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we believe that it’s possible to
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develop biologics that will do the opposite.
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Imagine,
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for example,
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an antibody that could shift EGF
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activated in cancer we mutation
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00:19:31.130 --> 00:19:32.840 allele with living shift signaling to
NOTE Confidence: 0.773119211196899
00:19:32.889 --> 00:19:34.579 the left making it differentiative.
NOTE Confidence: 0.773119211196899
00:19:34.580 --> 00:19:36.428 This could be a really powerful
NOTE Confidence: 0.773119211196899
00:19:36.428 --> 00:19:37.352 approach to signaling,
NOTE Confidence: 0.773119211196899
00:19:37.360 --> 00:19:38.592 switching or correcting signaling
NOTE Confidence: 0.773119211196899
00:19:38.592 --> 00:19:39.208 from preparations.
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00:19:39.210 --> 00:19:40.895 Differentiation is actually 1 proof
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00:19:40.895 --> 00:19:43.192 of principle in that with kit and
NOTE Confidence: 0.773119211196899
00:19:43.192 --> 00:19:44.848 stem cell factor that causes that
NOTE Confidence: 0.773119211196899
00:19:44.848 --> 00:19:46.069 was been working on.
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00:19:46.070 --> 00:19:50.126 At Stanford, so next slide please.
NOTE Confidence: 0.773119211196899
00:19:50.130 --> 00:19:51.297 And so finally.
NOTE Confidence: 0.773119211196899
00:19:51.297 --> 00:19:53.631 We’ve also been focusing on an
NOTE Confidence: 0.773119211196899
00:19:53.631 --> 00:19:55.837 undruggable target the pseudo kinases.
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00:19:55.840 --> 00:19:58.339 About 10% of the kinases in kind
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of is inactive and the blue ones here on the left in history. Many of them don’t even buy native P, and these include regions. Interceptors like Roswick, PK7 involved in wind signaling and involved in several councils, but have been totally ignored as drug targets. For the most part. One hypothesis is that they simply by switching confirmations to bind downstream signaling molecules. We recently determined in this. Paper in 2022, referenced here a bunch of
structures and script screen for small molecule inhibitors to see if we could bring in principle drug these in the middle here in the structure you can see a drug.
It’s actually pronounced enable inhibitor bound to one of these pseudo kinases that doesn’t even bind 80P and M as shown in the top right. We’ve demonstrated using hydrogen determine change studies that put maybe induces conformational changes in role one as it binds and so the idea is that this might inhibit signaling interactions that
00:20:51.912 --> 00:20:53.492 naturally there’s a lot enormous amount
NOTE Confidence: 0.746865034103394
00:20:53.492 --> 00:20:55.620 of work to do with selectivity and.
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00:20:55.620 --> 00:20:56.544 And so forth.
NOTE Confidence: 0.746865034103394
00:20:56.544 --> 00:20:58.392 But early studies of signaling effect
NOTE Confidence: 0.746865034103394
00:20:58.392 --> 00:21:00.081 suggests that banana can inhibit
NOTE Confidence: 0.746865034103394
00:21:00.081 --> 00:21:01.736 went dependent rule one signaling,
NOTE Confidence: 0.746865034103394
00:21:01.740 --> 00:21:03.462 and so the idea of sharing centrally
NOTE Confidence: 0.746865034103394
00:21:03.462 --> 00:21:04.648 here is that confirmational
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00:21:04.648 --> 00:21:06.608 disruptors like this could be
NOTE Confidence: 0.746865034103394
00:21:06.608 --> 00:21:08.176 valuable tools for understanding.
NOTE Confidence: 0.746865034103394
00:21:08.180 --> 00:21:09.158 See Tiffany signaling,
NOTE Confidence: 0.746865034103394
00:21:09.158 --> 00:21:11.440 but also targeting them where they play
NOTE Confidence: 0.746865034103394
00:21:11.494 --> 00:21:13.650 known roles in cancer and other diseases,
NOTE Confidence: 0.746865034103394
00:21:13.650 --> 00:21:15.582 and so far they’re all being
NOTE Confidence: 0.746865034103394
00:21:15.582 --> 00:21:16.870 hit the articaine ones.
NOTE Confidence: 0.746865034103394
00:21:16.870 --> 00:21:18.158 For example, with antibodies.
So that’s about my brief summary. That’s all I wanted to say, so thank you very much for attention, and I look forward to your questions. Thank you very much Mark for that wonderful discussion. Next, I’ll be introducing Meghan King, associate professor of cell biology and molecular, program leader in our Cancer Center and I think notable partly for having been elected by her fellow faculty here at Yale School of Medicine.
As past president of our faculty Senate equivalent, the Faculty Advisory Council where she also showed exceptional leadership. Sort of in that other realm, and she’s going to be talking to us about very impactful work regarding resistance to PARP inhibition. Alright, so thank you. I’m also a basic scientist and my interactions with my colleagues here in the Yale Cancer Center that is driven my group with expertise in genome integrity to really
focus on those aspects that have impacts for cancer therapies.

So I’m going to start with this classic example of synthetic lethality, and that are is specifically PARP inhibitors in the context of Bracco Wanan bracket, two mutations, and although of course these therapies have incredible promise. It’s well established now that the acquired resistance is a major bottleneck for the durability and efficacy of these treatments, and so, how do we tackle this problem and other opportunities that are presented when...
these tumor cells become resistant? So the approach that we've been taking is first to start by really trying to define the genetic basis of resistance in this context, and so we know that there has been real value in crisper screens. But I think increasingly we're very excited about the possibility of circulating tumor DNA sequencing as well as potential for serial biopsies, particularly along this axis. As tumors gain resistance to combine genome sequencing as well as gene expression analysis to provide new insights into therapy resistance.
And we use a range of models, although from model organisms to mouse models to really get the mechanisms, and of course the ultimate goal is always to really be able to leverage the mechanism of resistance, ideally to come up with new therapies and so awhile. Of course we’d like these to be actionable were really particularly would like to go beyond that, would like to go beyond that, and to be sure to consider based on our mechanistic studies, on our mechanistic studies, what can we bring to the table in terms of stratification?
And today I'll talk about an example where we really think that we have to consider Bracco one patient separately from bracket two patients. Of course it would be best if we can develop new biomarkers that will further help us stratify patients based on the mechanisms underlying resistance, and I think one real potential there is for example, circulating tumor DNA may allow us to identify patients who have a so called reversion allele. That'll now will make them insensitive Department of Therapy.
and that baby one cohort, but there may be other patients where resistance is arising through a secondary mechanism that maybe. Therapeutically actionable and so I just wanted to take you through the work that we’ve been doing, just not just my lab, but across our team to look at the genetic basis of resistance. So much of again, these crisper screens have been published. The work that’s been going on here at Yale really has taken advantage of a partnership that we already have
between Astra Zeneca and our team, particularly Ryan Jensen, and Ryan has been modeling reversion alleles that are arising from patient derived DNA sequencing. And testing really is there still an actionable approach that we could use in these contexts or not? By functionally characterizing the reversion alleles? What I’m particularly excited about at the moment is that paleru so has been leading a trial along with Kurt Shopper, who you’ll hear from in a moment where she is and acquiring these serial biopsies. Along this progression to relapse.
And this allows us now to go in and really look not just a genome changes, but gene expression changes. And so these sequencing is ongoing at the moment, and we're really excited about the new targets that it may reveal.

So it's well established that Braca one of its key roles is to promote and some work that my group has done and the possibilities that we can see for this going forward.
what’s called double strand break and

resection through the EXO 1 pathway.

And this is a critical step in

the HR pathway and so it came

out of these screens.

That loss of either 50 BP one or Rev

can drive therapy resistance in

the context of Graco one mutations.

Well, my group discovered is that

these are negative regulators of the

bloom helicase acting with DNA 2,

which is an alternative and

resection mechanism.

So this is a way where these tumor

cells have essentially rewired reception

so they’re no longer dependent on
bracca one and instead can use this
bloom pathway and so as examples
of what that mechanism has brought
about in terms of the way we’re
thinking about future therapeutics,
the first is that identifies
the bloom helicases,
a really novel target that we have
already shown in vitro is also synthetic
lethal with Bracco one on its own.
Particularly if we think in the short term,
maybe more actionable input
ways in which this has changed.
Our thinking is that it highlights
also the potential for combinations
of PARP inhibitors in ATR inhibitors, and that’s because the other thing we discovered is that this blue mediated helicase is driving resection at very high rates and this leads not just to functional reception to do repair. It actually leads to hyper resection, and ATR is an important negative regulator of resection, and so we think that this combination of treatments will push this. Hyper resection even further, and this is a really good rationale for why. Initially patients with RK one mutations may not respond well to a combination with an ATR inhibitor,
but when there is a mechanism that down regulates these particular proteins that will make these tumors very sensitive to the combination, and so along those lines we’re currently just submitting anello I with paleru so where we are proposing to do a trial specifically in Bracco in patients because this is not a mechanism that’s relevant for the bracket, hoping to really test this idea clinically, so thank you and I look forward to the questions.
much of this work as I mentioned was a collaboration with Astra and is also supported very generously by the Great Foundation.

Thank you Megan. That was terrific.

Next, I’d like to introduce Jinyoung he’s an associate professor of pathology and director of our Epigenetics program here at Yale and will be talking about epigenetic mechanisms of resistance.

Thank you, Barbara. On So, uh, my expertise in the menu on cancer genetics, magnet is critical for cancer initiation and progression.
Especially my laptop is interested in understanding how epigenetic regulators, also called reader writer and erasers of being an maceration histone modification. How regulate different steps of cancer progression? My number to your interest in a couple different areas? One is resistant mechanism to anti cancer drugs, which is the main topic today. Cancer metastasis and tumor in valuation, which is one of the areas that I could show but will talk more about later on and next.
My #2 is also very interesting, developing different epigenetic drugs and we have done some work with your Center for molecular discovery, which is our in house training center and I have done some work with the NCI Experimental therapeutics program and right now I'm also collaborating some about tech and pharmaceutical company in this area as well and in the next 2 slides I’m going to tell you some slides of the examples that we have done to look at the resistant mechanisms. One which is targeted therapy,
and in this case the transaction number one called Herceptin for breast cancer, and we can generate those resistant cells in tissue culture. And we found that those resistant cells actually are do not have genetic mutations. They actually resistant mechanism is actually reversible if you take the drug away from the cells for short period time and they are still maintain resistant. But if you take it away for a long period time, for example about months and those cells becomes those so called watch out.
And those cells become sensitive to just over again. To local internal mechanism next piece. We profile the expression of the expression profile of the reason cells compared to the sensitive cells. We can see that those resistant cells have increased oxidative phosphorylation or called off force and remarkable need. Those cells are very sensitive to ox force inhibitor. As you can see the tumor regression if you combine traditional Antonio Massenet you combine traditional Antonio Massenet which is 1 nautical force inhibitor. You can see regression of those. Resistant tumors Next place as I
mentioned that this app is genetic
mechanism that contributes to resistance,
so we are one of the mechanism we
found is that Arcadian 5 histone
demethylase are critical for this
formation of those resistant cells
we can combine with the target
therapy and Kaden 5 inhibitor which
this is one of the early generation
inhibitor and four to prevent the
formation of the recent sales for
both breast cancer which is beating
for some report cells.
And non cancer cells on PC 9 cells.
And next race.
So we are also very interested in understanding how Resistant happens to our email checkpoint blockade and this is our version of the cancer immunity cycle and as you can see, there's actually 2 steps are the critical for email checkpoint to work is the trafficking and infiltration of the immune cells to the tumor and apparently some of the epigenetic modulators have been shown to be critical for those processes, and then I will just show example in our laboratory next please. Where we found the Canadian
00:32:14.990 --> 00:32:17.540 Fire B or history history.
00:32:17.540 --> 00:32:21.959 You must nice file B is critical off for.
00:32:21.960 --> 00:32:27.420 Infiltration and trafficking
00:32:27.420 --> 00:32:29.400 And if not colocating 5B,
00:32:29.400 --> 00:32:32.158 I I in those Yamaha 1.7 cells,
00:32:32.160 --> 00:32:33.740 which is more smaller,
00:32:33.740 --> 00:32:35.320 generated by Markus Persson.
00:32:35.320 --> 00:32:38.664 Book idea we can see that if you
00:32:38.664 --> 00:32:40.894 knockout account info be those
00:32:40.894 --> 00:32:43.510 cells are unable to form tumors.
00:32:43.510 --> 00:32:45.540 And if we re challenge,
00:32:45.540 --> 00:32:48.368 those are two mice with control sales,
00:32:48.370 --> 00:32:50.400 which normally grow very well.
00:32:50.400 --> 00:32:53.046 You can see they cannot grow and
00:32:53.046 --> 00:32:56.710 that is why the tumors cannot grow.
meaning that those might have gained immunity against those younger cells.

If you look at the pony IMo Genic young one point cells down in the policy, you can see those cells are not responsive to PD one blockade at all. And if we do need killing file before those cells, you can see the slowdown of the growth of cells and if you combine with PD one blockade you can significantly extend the lifespan of those miles. To my very mice.

So this suggests that can you invite me is that very good target to overcome resistance to email,
00:33:32.910 --> 00:33:35.535 check one blockade and I would just want to mention that this is done in collaboration with multiple laps and yell, including archical, even sucking and much boersen berg snap. So team science is one of the same idea. We workout together or not. Thank you.

00:33:53.980 --> 00:33:57.164 Thank you that is such a terrific story. Now I’m pleased to introduce Curt Shopper. He’s an assistant professor of pathology and medicine. An recent rooms at the end of an NCI Merit Award. He conducts really cutting edge
immuno profiling studies and

look forward to your talk Kurt.

Thank you, Barbara. Next slide please.

So I trained clinical molecular diagnostics that I've been working in cancer immunology for about 10 years now, and it's unquestionable that immuno oncology has really revolutionized the treatment of cancer.

But there are major challenges still to overcome, so I'll cover a few of the challenges that I think are critical to potentially move the few forward, one of which is that I think there have been conceptual limitations.
of in both in drug development and identification of biomarkers.

Relative to drug development, I think the focus of many people developing targets has been on immuno stimulation, but that doesn’t necessarily consider correcting alterations in the tumor and this is critical because if we’re only stimulating T cells we are and there is not a clear gradient towards activating it more in the tumor. It’s likely that the therapeutic index is smaller and the potential benefit and toxicity balances is affected. So I think the concept is that we shouldn’t
focus only on stimulating T cells everywhere.

We should probably look for.

Signals that have a gradient favoring the tumor in relative to the development of biomarkers for resistance.

I think there have been a little bit of confusion in the field because it mean a therapy has been used so widely that people are calling every patient that don’t respond as a resistance.

And conceptually I think that’s probably not accurate because patients without PD L1 expression tumor mutational burden.

Any biology should not respond to start with, so I think there is a confusion between.

Any patient that Blacks benefit
00:35:55.770 --> 00:35:58.115 versus true resistance, which in my opinion are the patients that should have responded but didn’t.

00:36:00.520 --> 00:36:03.019 I think this is critical to design programs and biomarker plans.

00:36:06.280 --> 00:36:08.030 The second important concept that it’s connected with the previous one is that it’s probably necessary to identify dominant immunization pathways that are well represented. The tumor and this is for the same reason because we need to have this gradient and strong biology in the tumor to be able to achieve a meaningful anti cancer response.
and then another major need in the field is trying to identify potential targets that are beyond the T cells. So to have complementary effort and not have only redundant mechanisms, another important observation is that we as I follow you know when we look at the tumors we realize how difficult and how complex is the tumor micro environment. Where most interactions between tumor and immune cells are happening. And I think the suffering. The tumor micro environment and how different is across tumors and across patients. It’s a major need to really drive better biomarkers and better immunotherapy.
Then also I think we need to do a better work at understanding the interactions between major dominant oncogenic signals and immune evasion pathways. This has been somehow being revealed in EGFR mutant tumors that are less sensitive and less inflamed, but they I think there’s a whole world to discover. What alterations in the tumor, somatic alterations are able to manipulate. It means an immune response. And then finally, I think there are limitations of traditional studies as we just solve from Jane.
Many alterations are not the genomic level.

Which is the favorite way we used to analyze the tumor site of the interaction.

So I think by just doing genomic analysis, we're missing a lot of alterations that the immune system and this.

I think it's something we can overcome and finally think that most of the studies are focusing on both ends on the very early discovery type of work, with crisper screens and other strategies.

And then there is a huge effort on the clinical development.

but I think there is room to improve some studies in more sort of human real context.

Next slide, please.
So this is an example of the approach that we have taken in my group where we generate hypotheses using discovery in biology and then we actually have generated assays to screen for pathways, cell types in tumor cell indicators in the same issue. So we can actually do both genomic analysis to understand the genomic context during drivers, but then we can also look at the immune contexture and pathways that are potentially actionable. We have become pretty good at looking at multiple.
High throughput methods to detect protein level and then we can do single cell analysis, spatial analysis and really try to understand the tumor microenvironment to prioritize what signals are dominant or relevant, we usually use aggressive analysis using outcomes and response to treatment. So that way we can identify which signals are relevant from the ones that are not next slide please. This is important because ultimately those signals are the ones with. Then we can validate in vitro to demonstrate that these are not just
epiphenomenon’s or correlations, but they are mechanistically relevant and ultimately we can go back and then ultimately we can go back and look at this in the context of human clinical trials, and I’ll show you an example of that next slide, please.

So just for to illustrate how this cycle works, this is a story that it’s, uh, have published this year where we identify Interleukin 8 and local neutrophils in the tumor microenvironment as dominant immunization pathway and resistant mechanism.
So the story started a few years ago where we look at inside too.

aren’t expression for Interleukin 8, and we found that it was producing tumor cells and highly associated with resistance to immune checkpoint blockers.

So to advance this further, we look at the relationship between Interleukin 8 and neutral fields as shown in the upper side of the slide, and then we found a fraction of tumors that had up regulation of Interleukin 8 and an unfavorable micro environment characterized by increased deals in fewer T cells.

We also did genomic analysis to
understand that this was independent from tumor mutational burden and major genomic alterations,
and then we finally were able to demonstrate that the production of Interlake in the tumor.
Was actually associated with interleukin 8IN serum in circulation,
so we that we conducted an studying over 1200 cancer patients from three phase three pivotal trials using immune checkpoint blockers and we found that about 1/3 of a patients across tumors have up regulation of interleukin Aiden.
They have low sensitivity to
immune checkpoint blockers.

Next slide, please.

Then to further demonstrate this, we need another study in which we cultured neutrophils and my Lord arise suppressor cells to show the mechanism behind and we were able to demonstrate that formation of Nets was involved in affective response suppression, and then ultimately we’re working with the clinical trial where patients are being treated with an antibody and targeting Interleukin 8, and to understand if this pathway can actually be action in real patients, and hopefully we can use the biology
that we figure out to drive.

The biomarker plant next slide please.

So finally we have gotten a little bit more sophisticated now and generated models or in vitro tumor treatment.

And this is just an example of what we’re doing where we can culture primary tumors, treat them in vitro but intact so that we can then generate preparations and analyze the tumor micro environment.

Change now perturbing these tumors with immunostimulatory or other anti cancer agents and we are incorporating new technologies such as single cell transcriptomics.
Another analysis to do more unbiased studies.

Thank you.

Thank you Kurt. I mean I think probably everybody can see the incredible power of that approach.

Well, we said at the outset, Yale engage is focused on building bridges and collaboration with industry, and in each of these seminars, we’ve invited an industry partner to speak to us, and I’m really thrilled that today it’s Susan Galbreath she’s a senior vice president and head of early oncology R&D and Astra Zeneca.

She’s been there about 10 years and.
In the early development program, there brought 7 compounds into phase three. The story with PARP inhibition, the third generation EGFR inhibitor. Awesome Merton if that our colleague, Roy Herbst, was involved in presenting very impactful angemon trial this year. Megan met inhibitors selective estrogen receptor directed agents. Really phenomenal portfolio and a phenomenal track record of success. So Suzan, we look forward to hearing your thoughts. Thank you, Barbara Ann. It’s a pleasure to be here.
00:43:21.102 --> 00:43:22.950 with you and just a bit introduction.
NOTE Confidence: 0.825893580913544
00:43:22.950 --> 00:43:24.422 I’m a clinical psychologist by
NOTE Confidence: 0.825893580913544
00:43:24.422 --> 00:43:26.186 training MD PhD and I’ve been,
NOTE Confidence: 0.825893580913544
00:43:26.190 --> 00:43:28.276 as Barbara said, Astra Zeneca for 10
NOTE Confidence: 0.825893580913544
00:43:28.276 --> 00:43:30.529 years and before that I was in the
NOTE Confidence: 0.825893580913544
00:43:30.529 --> 00:43:32.198 US with Bristol Myers Squibb also
NOTE Confidence: 0.825893580913544
00:43:32.198 --> 00:43:34.088 in the early Development Group and
NOTE Confidence: 0.825893580913544
00:43:34.088 --> 00:43:36.148 and stayed there for about 9 years.
NOTE Confidence: 0.825893580913544
00:43:36.148 --> 00:43:38.290 Just go on to the next slide.
NOTE Confidence: 0.825893580913544
00:43:38.290 --> 00:43:40.820 I want to talk a little bit to build on
NOTE Confidence: 0.825893580913544
00:43:40.893 --> 00:43:43.294 some of the thoughts we’ve got about,
NOTE Confidence: 0.825893580913544
00:43:44.464 --> 00:43:46.556 and one of the challenges that we’ve
NOTE Confidence: 0.825893580913544
00:43:46.556 --> 00:43:48.056 got about understanding resistance is
NOTE Confidence: 0.825893580913544
00:43:48.056 --> 00:43:49.840 really having access to the samples.
NOTE Confidence: 0.825893580913544
00:43:49.840 --> 00:43:51.496 That would enable us to understand
NOTE Confidence: 0.825893580913544
00:43:51.496 --> 00:43:52.324 the clinical resistance.
NOTE Confidence: 0.825893580913544
00:43:52.330 --> 00:43:54.426 So Katie Elite is already talked to you
NOTE Confidence: 0.825893580913544
00:43:54.426 --> 00:43:56.494 about some of the models that we can
NOTE Confidence: 0.825893580913544
00:43:56.494 --> 00:43:58.430 use pre clinically to model resistance.
NOTE Confidence: 0.825893580913544
00:43:58.430 --> 00:44:00.092 One of the challenges we’ve got
NOTE Confidence: 0.825893580913544
00:44:00.092 --> 00:44:01.200 with those techniques though,
NOTE Confidence: 0.825893580913544
00:44:01.200 --> 00:44:02.904 is that it doesn’t always predict
NOTE Confidence: 0.825893580913544
00:44:02.904 --> 00:44:04.571 what the true prevalence of the
NOTE Confidence: 0.825893580913544
00:44:04.571 --> 00:44:05.771 resistance mechanisms is going to
NOTE Confidence: 0.825893580913544
00:44:05.771 --> 00:44:07.570 be in in the clinical setting.
NOTE Confidence: 0.825893580913544
00:44:07.570 --> 00:44:09.469 So if you start off with a PC 9
NOTE Confidence: 0.825893580913544
00:44:09.469 --> 00:44:11.765 so when you look at the mechanisms
NOTE Confidence: 0.825893580913544
00:44:11.765 --> 00:44:13.109 of resistance to that,
NOTE Confidence: 0.825893580913544
00:44:13.110 --> 00:44:14.342 you don’t necessarily understand
NOTE Confidence: 0.825893580913544
00:44:14.342 --> 00:44:16.513 what the true prevalence of all the
NOTE Confidence: 0.825893580913544
things are when patients are starting
Wiring diagrams in their EGFR mutant lung cancer.
The other challenge that you’ve got is
The other challenge that you’ve got is
tried for number of years to actually get biopsies from patients on at the time of progression in clinical trials,
typically has to be as an optional biopsy. At that time of progression,
we’ve actually heard across the range of clinical trials.
Relatively few of those actually materialized,
and so that means that our mechanisms
00:44:45.543 --> 00:44:46.813 of understanding resistance during
00:44:46.813 --> 00:44:48.278 the development of certain IP,
00:44:48.280 --> 00:44:50.110 you know, have been somewhat limited.
00:44:50.110 --> 00:44:51.976 We started right the beginning by
00:44:51.976 --> 00:44:53.480 looking at circulating tumor DNA,
00:44:53.480 --> 00:44:55.316 it right from the phase one
00:44:55.316 --> 00:44:56.540 trials with awesome antonym,
00:44:56.540 --> 00:44:58.484 and we have some understanding of
00:44:58.484 --> 00:45:00.109 actually published some of the
00:45:00.109 --> 00:45:01.729 data from the first line study
00:45:01.729 --> 00:45:03.534 with a semantic that flora trial
00:45:03.534 --> 00:45:05.406 looking at those CT DNA mechanisms,
00:45:05.410 --> 00:45:07.348 but really actually one of the
00:45:07.348 --> 00:45:09.390 things that comes out of that is,
00:45:09.390 --> 00:45:10.502 we could only explain.
I am just over 1/3 of the patients resistance mechanisms through looking at city DNA and the patterns that we saw there was we saw their city. The emergence of the Sistin 797 S mutation met amplification PSP KEARNEYS pathway mutation. An activation fee 10 losses and in some cases and MEK pathway. The really the majority of patients we still had a question mark over what the resistance mechanisms worth. So that led us to design that this kind of study. It’s called the Orchard and platform study.
This takes patients that we're progressing on. First line automotive, and it offers them something that is potentially of benefit to them, which is to take a biopsy to look at what the data says on next generation sequencing. From that biopsy and then to allocate them to a range of different potential arms and this biomarker matched arms which you can see above depending on the mechanism that is seen with resistance. And then there's also non biomarker match on.
And this has been an important component of many platform trial designs because it means that every patient whose given a consent to have a biopsy gets the offer of something. I can’t guarantee that than what they’re getting offered is necessarily going to work, but it gives them that, and that has driven really quite a good uptake in terms of enrollment and accrual in this. And actually, what one of the things that we’ve already learned now is, we’ve now got, you know, data and over 60 patients. You know,
with tissue available at the time of progression in the Orchard study, and now that we can have an identifiable resistance mechanism now, in nearly 2/3 of patients, as opposed to just a third. We’ve increased the detection and some of the amplification mechanisms which can be underestimated using CT DNA would increase the detection of some of the Fusion mechanisms, which can also be difficult to detect using the CT DNA techniques. And we’ve got a better sense, With the prevalence,
00:47:15.099 --> 00:47:17.470 there’s still some work to be done here,
NOTE Confidence: 0.818565964698792
00:47:17.470 --> 00:47:19.351 and I still think we need to look at
NOTE Confidence: 0.818565964698792
00:47:19.351 --> 00:47:21.148 the epigenetic mechanisms that are
NOTE Confidence: 0.818565964698792
00:47:21.148 --> 00:47:23.063 driving resistance in this setting,
NOTE Confidence: 0.818565964698792
00:47:23.070 --> 00:47:25.009 but I just wanted to illustrate this
NOTE Confidence: 0.818565964698792
00:47:25.009 --> 00:47:27.763 as a as an example of one way that we
NOTE Confidence: 0.818565964698792
00:47:27.763 --> 00:47:30.446 need to look at in terms of understanding,
NOTE Confidence: 0.818565964698792
00:47:30.450 --> 00:47:32.020 documenting resistance and moving on
NOTE Confidence: 0.818565964698792
00:47:32.020 --> 00:47:34.869 from it so we can go to the next slide.
NOTE Confidence: 0.818565964698792
00:47:34.870 --> 00:47:36.370 The similar approach has been
NOTE Confidence: 0.818565964698792
00:47:36.370 --> 00:47:37.570 taken in the understanding.
NOTE Confidence: 0.818565964698792
00:47:37.570 --> 00:47:42.242 Resistance to checkpoint inhibition,
NOTE Confidence: 0.818565964698792
00:47:39.242 --> 00:47:42.270 and I completely agree with shoppers comment,
NOTE Confidence: 0.818565964698792
00:47:42.270 --> 00:47:44.205 but not everybody who progress
NOTE Confidence: 0.818565964698792
00:47:44.205 --> 00:47:46.140 is on a checkpoint inhibitor
NOTE Confidence: 0.818565964698792
00:47:46.213 --> 00:47:48.249 is necessarily truly resistant,
but I think we need to understand some of those mechanisms, and again, this is a mechanism where you can get the biopsies from these patients. Also, some peripheral blood sampling and look at ways in which we can potentially offer them. Treatments that may have the opportunity to make a difference. So again, I just want to share with you a couple of observations from this.
there are some mechanisms that we might anticipate seeing based on, you know, really good data that’s already emerged, and this is about the loss of her Psycho City for HLA or MHC and we are seeing as expected. But after treatment or one of these checkpoints, inhibitors and increased prevalence of loss of HLA or MHC. In the inability of the tumors to be seen by an effective by at the adaptive immune mechanisms of if the antigen can’t be presented effectively, it’s like.
Other things that we’re doing.

We’ve seen a range of different mechanisms that we have.

Wilson mentioned the fact that obviously we’re looking at the ATR combination with a laprobe in terms of part resistance,

but in fact actually one of the observations that we made earlier phase one with our selected slot assertive,

which is, uh, ATI inhibitor,

is that we were seeing some unusual responses in patients that had a prior checkpoints in innovation.
In some other trials, and so that led to some further investigation and so there are certain underbelly maps is one of the arms in the Hudson study and some of the data that we’re seeing is quite interesting in seeing that.

Getting a decrease in exhausted T cells, exhausted NK cells and an increase in antigen presentation in patients that have both got primary resistance to checkpoint inhibition and subsequently had some degree of response and subsequently progressed as well.

And we’re also seeing it not just in the ATM mutant patients that are selected,
but also more broadly, so.

This is just an interesting observation.

There’s a lot more mechanistic data that is required and that will be followed up in order to understand this better.

But I do think that these kinds of trials are really helpful in trying to understand the clinical prevalence of resistance.

Mechanisms get a lot more data that can feedback, and you know, back with the preclinical work that we can do to them to then understand what we might do next. So I’m going to stop there and
I’m very happy to address any questions that you might have. Thank you. That was fabulous. Thank you very much. I am now going to ask that all of the panelists turned on their audio and video and will now go into the full discussion. And I’m going to ask the attendees to please continue to post questions we are monitoring these and the first one, I think. Basically immediately follows that the last slide that we saw and so maybe I’ll ask Susan and Kurt both to address this. How critical is it to overcome the mechanical functional barriers to immune
checkpoint inhibitors and the question relates specifically to HLA loss, although I can think of other mechanisms related to hypoxemia and vascular alterations as well, but can you please comment on? Potential pathways and targets to overcome mechanical and functional barriers to immune checkpoint inhibitors and Susan. Do you want to go first and then kick it to Kurt? Yeah well, the Council you think of when I think of 1st when you’re talking about mechanical barriers potentially is pancreatic cancer.
Cause at the high level of you know

Disney plastic streamer that you see that has been discussed as not just having actually a physical potential barrier to treatment but also the presence of the constituents of that. German may also have a you know, biochemical effects that reduce the likelihood of sensitivity to. Of the tumor cells that are adjacent about two treatment, and I think there are a lot of data suggesting that understanding the components of the micro environment, the distribution and types of you

95
NOTE Confidence: 0.83586585521698
00:52:27.618 --> 00:52:29.070 know cancer associated fibroblasts,
NOTE Confidence: 0.83586585521698
00:52:29.070 --> 00:52:29.798 for example,
NOTE Confidence: 0.83586585521698
00:52:29.798 --> 00:52:31.618 and not in that disease,
NOTE Confidence: 0.83586585521698
00:52:31.620 --> 00:52:33.906 and their feelings that might be
NOTE Confidence: 0.83586585521698
00:52:33.906 --> 00:52:35.430 absolutely critical to understanding
NOTE Confidence: 0.83586585521698
00:52:35.492 --> 00:52:37.757 mechanisms of resistance and sensitivity.
NOTE Confidence: 0.83586585521698
00:52:37.760 --> 00:52:41.158 I think in the context of loss of HLA.
NOTE Confidence: 0.83586585521698
00:52:41.160 --> 00:52:43.552 It it's you know that you know lots
NOTE Confidence: 0.83586585521698
00:52:43.552 --> 00:52:46.333 of HLA may increase the sensitivity
NOTE Confidence: 0.83586585521698
00:52:46.333 --> 00:52:48.968 potentially to other mechanisms like
NOTE Confidence: 0.83586585521698
00:52:48.968 --> 00:52:51.366 inducing the innate immune system
NOTE Confidence: 0.83586585521698
00:52:51.366 --> 00:52:54.060 rather than the adaptive immune system
NOTE Confidence: 0.83586585521698
00:52:54.060 --> 00:52:56.210 to NK cell enhancement potentially.
NOTE Confidence: 0.83586585521698
00:52:56.210 --> 00:52:57.722 Then you know so.
NOTE Confidence: 0.83586585521698
00:52:57.722 --> 00:52:59.990 So there are things that then
NOTE Confidence: 0.83586585521698

96
00:53:00.080 --> 00:53:02.660 creates a formability I suppose.
NOTE Confidence: 0.83586585521698
00:53:02.660 --> 00:53:05.724 I think the issue from my perspective is
NOTE Confidence: 0.83586585521698
00:53:05.724 --> 00:53:09.109 it you know you wouldn’t be expecting.
NOTE Confidence: 0.83586585521698
00:53:09.110 --> 00:53:10.975 No high likelihood of subsequent response to something that requires
NOTE Confidence: 0.83586585521698
00:53:10.975 --> 00:53:12.840 HLA antigen presentation.
NOTE Confidence: 0.83586585521698
00:53:12.898 --> 00:53:14.269 If you’ve got lots of HP laser
NOTE Confidence: 0.83586585521698
00:53:14.270 --> 00:53:17.042 fundamental mechanism,
NOTE Confidence: 0.83586585521698
00:53:17.042 --> 00:53:20.563 so we should be segmenting patients by understanding of these mechanisms
NOTE Confidence: 0.83586585521698
00:53:20.563 --> 00:53:22.661 in order to identify the populations
NOTE Confidence: 0.83586585521698
00:53:22.661 --> 00:53:25.235 that might best be subsequently treated with different kinds of therapies.
NOTE Confidence: 0.83586585521698
00:53:25.235 --> 00:53:28.049 Cut any thoughts from you.
NOTE Confidence: 0.83586585521698
00:53:28.049 --> 00:53:30.399 Yes, I agree with all the comments.
NOTE Confidence: 0.83586585521698
00:53:30.400 --> 00:53:31.930 I think there is more biology emerging
suggesting that the mechanical barriers may not be so mechanical. You know some of these fibroblast basic read inhibitory molecule so it may be also an active immunity victory component to that and that I think is driving. I think they were going to see a lot of new studies showing active mechanism of rejection of immune cells in the tumor bed and relative to the empty in presentation. We have actually a study under review that should see the light soon. When we look at large cohorts of tumor mapping, different parts of the antigen presentation.
pathway in a Long story short where we’ve learned is that when we look at the genomics, we don’t see that. The majority of alterations are non-genomic meaning non-mutation related. In the second interesting lesson is that depending on what molecule is lost in the tumor cell meaning HAHAABCV, A2M or other proteins, the immune contexture changes. Understanding that part will be critical to understand how to treat those patients, we do see upregulation of natural killer service in in certain loss. Eventually molecules,
but not in everyone, and each of them has sort of a certain different balance between T cells, NK cells, and other cells.

So I think it will be critical to do those studies to understand how granular disease and if we can lump the antigen presentation defect into one category. Or maybe it will be more than that. I think that’s to be figured out.

So just continuing on with this theme in a question for Chin can HLA loss be overcome by epigenetic modification? Or what is epigenetic role in HLA loss? So this is not an area I have been
00:55:22.551 --> 00:55:25.230 working on very well having it,
NOTE Confidence: 0.84406441450119
00:55:25.230 --> 00:55:27.636 but I could just mention another
NOTE Confidence: 0.84406441450119
00:55:27.636 --> 00:55:30.151 with those changes are non genetic
NOTE Confidence: 0.84406441450119
00:55:30.151 --> 00:55:32.231 changes so we have different
NOTE Confidence: 0.84406441450119
00:55:32.231 --> 00:55:34.430 tools to execute those jeans.
NOTE Confidence: 0.84406441450119
00:55:34.430 --> 00:55:36.114 Reactivate those jeans and
NOTE Confidence: 0.84406441450119
00:55:36.114 --> 00:55:38.219 to make them successful too.
NOTE Confidence: 0.84406441450119
00:55:38.220 --> 00:55:41.460 Make make them to be sensitive
NOTE Confidence: 0.84406441450119
00:55:41.460 --> 00:55:43.080 to our treatment.
NOTE Confidence: 0.84406441450119
00:55:43.080 --> 00:55:45.735 So email checkpoint blockade will
NOTE Confidence: 0.84406441450119
00:55:45.735 --> 00:55:49.020 work if you re reactivate those.
NOTE Confidence: 0.834680736064911
00:55:50.670 --> 00:55:54.270 Terrific terrific, I have a question
NOTE Confidence: 0.834680736064911
00:55:54.270 --> 00:55:59.640 that was submitted earlier, but I think.
NOTE Confidence: 0.834680736064911
00:55:59.640 --> 00:56:01.926 Could probably be answered extensively or
NOTE Confidence: 0.834680736064911
00:56:01.926 --> 00:56:04.500 exhaustively by each one of the panelists,
NOTE Confidence: 0.834680736064911
00:56:04.500 --> 00:56:06.702 but maybe I'll ask Katie and
How does the mutational landscape of a tumor affect resistance and sensitivity? And I’m interpreting that the questioner means the other mutations besides the one in your target molecule. So now one of the things that we’ve been able to look at,
for example, are in if we think about lung cancers in different oncogenic driver subgroups. We can look at the pattern of co occurring genetic alterations that happened, so I’m thinking about for example, in K Rasputin lung cancers, these can co occur with P53 mutations. They can co occur for example with mutations in STK 11, also known as Elchibey one. And we’re really beginning to learn about what it means. If the tumor has Akira’s mutation and a P53 mutation versus ACARAS mutation. And then Elchibey one mutation for example.
And what and that the LKB one meeting tumors seem to have a different or reduced sensitivity to immunotherapy, for example. In parallel, we're really starting to scratch the surface and really beginning to understand how different occurring alterations also impact response to targeted therapies. For example, some of the work that we've been doing recently looking at different tumor suppressor gene alterations.
in EGFR mutant lung cancer and how they affect sensitivity to tyrosine kinase inhibitors. One of the things that has emerged from our studies in animal models, an also is emerging from studies of patients. Patient specimens is that if you have EGFR mutant tumors that also have mutations in the keep one access, so the keep 1 NRF 2 access that is important for the antioxidant response of a tumor cell. If you have mutations that Co occur in that path where you have a decreased sensitivity to tyrosine kinase inhibitors, so the tumors will shrink.
These targeted therapies, and so that begs the question, is that a subset of patients who you could, for example, select initially for treatment with different therapies, or for combination therapies together with a tyrosine kinase inhibitor so that you could. Improve outcomes in patients with that disease. I think of course, this these types of landscapes also this studying these landscapes.
really requires a lot of mechanistic investigation to understand exactly what is happening in those tumors. Finally, I think one of the other things to think about in terms of the genetic landscape also has to do with the overall mutation burden and the overall tumor mutation burden, which. You know we talk a lot about it in the context of immuno therapies and where you know we’ve. We’ve heard about a lot about it in recent years. I’d say also there’s some evidence that
the overall genetic landscape or the tumor mutation burden can have an effect on the response to targeted therapy. So again in EGFR mutant lung cancer tumors that seem to be in the highest tertile of tumor mutation burden, which is generally lower than most other lung cancers. But in that highest circle seemed to do worse on treatment with targeted therapies with tyrosine kinase inhibitors and the ones with the lower two mutation burden. So there are lots of different
aspects to consider.

The specific mutation.

So qualitatively but also quantitatively.

Yep,

I was just at the office or at a kind of.

Broad conceptual thought to

that which is ultimately,

I think, with all of these,

with all of the therapies.

We’re talking, one is really

I think about the fact that

one is really

trying to correct the signaling network.

However you define network,

whether its intracellular intracellular tissue,

Inter intra Organism.

Once regular network and in a sense

if you think about the fact that
Cancers are really caused by the networks losing robustness and kind of careering out of control to uncontrolled proliferation so far. It’s almost surprising actually. The targeted therapy can work, and indeed, actually, if you create models where you just mutated something, we’re hitting with a targeted therapeutic and nothing else. You don’t actually. But that’s not enough to cause cancer, so the context is key, and the targeted,
the target that we're trying to correct is.

It's really just kind of an Achilles heel in the sense for the rather plastic tour in some sense,

so I think I think that the answer need to think about these things as networks.

We need to get into considering the systems biology of this.

I think there are two ways of thinking about that one,

and you'll be aware of this as the enormous effort put into machine learning,

AI types of approaches,

whereas we collect more and more data.

For the mutational landscape to
01:01:52.440 --> 01:01:54.456 try to understand their with with
01:01:54.456 --> 01:01:56.108 various their principle components,
01:01:56.110 --> 01:01:58.254 analysis and what have you, what.
01:01:58.254 --> 01:02:00.274 How we can correlate combinations
01:02:00.274 --> 01:02:01.890 of mutations with sensitivity
01:02:01.956 --> 01:02:03.066 and so on so forth.
01:02:05.074 --> 01:02:07.544 we have to consider the a variety
01:02:07.544 --> 01:02:09.329 of systems biologists are taking,
01:02:09.330 --> 01:02:11.766 which I think is is really key.
01:02:11.770 --> 01:02:13.822 And actually I think RAF inhibitor
01:02:13.822 --> 01:02:15.600 resistance illustrates this very nicely.
01:02:15.600 --> 01:02:18.345 Is that we we can actually learn an awful
01:02:18.345 --> 01:02:20.818 lot about how the networks operate,
01:02:20.820 --> 01:02:21.410 you know?
A classic example is if you ever ask mutation, then the graph inhibited does the wrong thing, you know, but the bottom line is I think that we really we need to start thinking beyond the targets to the networks and what the effect of the targeted therapeutics is on the networks and that that of course is going to hold in the immune context too because what you actually correcting as as curtain Susan pointed out as you actually dealing with, that is,
01:02:48.802 --> 01:02:50.930 is trying to restore balance in an incredibly complicated interstellar the network.

01:02:50.984 --> 01:02:52.808 So I think there’s a couple of perspectives I would like to.

01:02:55.022 --> 01:02:56.530 Could you could you just answer

01:02:57.060 --> 01:02:59.286 that by introducing people a little bit to what’s going on at the Systems Biology Institute.

01:03:01.132 --> 01:03:04.999 Not all of the audience may may know about the scale of the effort.

01:03:05.000 --> 01:03:06.810 Yeah indeed. So actually at yeah we have a system colleges too that’s headed up by Andra Chanco, who’s the Director of Vietnam.

01:03:12.300 --> 01:03:14.524 Actually headed up by Andra Chanco, who’s the Director of Vietnam.

01:03:21.087 Very is also a Pi on one of the
There's a NCI has a physical Sciences long college center that. Actually, that initiative that you’re involved with one of those at Penn and and also the system cancer systems biology, can sort centers consortia that 100 grand sent, that 100 grand sent, and so the Systems Biology Institute here is really very council focused. It has a lot of interactions with the Cancer Biology Institute on also on West Campus at Yale, and Andre is an integral part of the Cancer Center. Of course, the Council biologist is too,
and so are most members of the Systems Biology Institute and the kinds of things. Being looked at there, which is actually related to this, so that Barbara it’s a good point are for example Andre is very interested in looking at. But it sells from brain tumors in particular and asking. Adam and looking at at migration versus proliferation in those cells, and the epigenetic difference between between those in terms of what’s defining the signaling networks that cause the cells to behave very differently.
And he can do that with some microfabricated devices where you can separate cells based on how rapidly they can migrate and then go in and look with various single cell and other technologies to look at their transcriptome and obviously gentleman and epic transcriptome etc. So that's really very exciting.

There's another element which is really at another #2 elements of City's doing an awful lot of work in terms of it in the system bars Institute. That is one of city channel that many of you will come across. City is doing an awful lot of work in terms of trying to understand
using in vivo CRISPR technologies.

Origins of resistance to terminate therapies and another therapeutic approaches.

And so that’s really very exciting again.

Is is plugged into the network consideration of what’s going on,

and then one other aspect,

which I which I think is really cool.

Actually as a project in our in EU 54

that Andre Valances that Gunter Wagner,

who’s an evolutionary biologist is

is very interested in why certain.

Mammals don’t tend to get meta

static cancer cows in particular.

As an example that caused him
not to die of cancer,

they just carry them around with the carry.

The tumors around with him without metastasize.

and pretty much we don’t see them here because they all killed before they get to that stage for other purposes.

But but and so that’s fascinating.

And so again, it’s looking at the network context.

The network differences between the mammals that do and don’t suffer from metastatic cancer, and actually.

It’s kind of related in some senses to placental invasiveness in some.
In these of these organisms, which kind of makes sense in some ways. And so. So there’s a cost, if any. There was a cost in some ways of having placenta that more interdigitate ihd, which is that you more susceptible to metastatic metastasis in your cancer. So these different perspectives, whether it’s immune. Immunology approaches targeted therapeutics. I think there’s a a burgeoning and is very strong at. Yeah, I’m really very exciting. I think a burgeoning effort and understanding of how to put
this into the quantitative,

and I think it needs to be quantitative in the sense of biochemical networks and pathways contexts.

Wonderful. Oh, it’s perfect.

I have a question here asking the panel to comment on the role of proteomics and studying tumor resistance, and maybe you’ll take that first mark in the market. Only relates exactly to what I was saying. I mean, you know you as a biochemist.

My view is that. Biochemist, but my chemistry is defined by the combination of component.
components that you have and so and a lot of those are proteins.
Of course, it’s not just proteins and that there are lots of other things too, but oh mix of various sorts are crucial for really getting a quantitative handle on an understanding signaling itself.
Response to therapeutic have course therefore resistance, and I think there are two components of it. What is just at and I would just want to stress this one is just the I guess fingerprinting approach that one often sees with pretty and say what proteins are there in the snapshot?
What metabolites are there in Tableau makes sense in the snapshot. That’s one aspect and that can give you a lot of information but looking at changes in the proteome changes in the metabolon with time is really a crucial aspect is really that’s what gives us a picture of the networks that we’re trying to correct and corral. When we’re targeting them in with all of therapeutics that we discuss it and I just point out that there’s a quite a lot of activity on this at Yale, and one of the people recruited into the Cancer Biology Institute, for example, is yeah, Shane Lou,
who has been doing a lot of work looking at, for example. Proteomic Lee, both snapshots and time evolution of protein contents. It is considered an employee, and you know it’s kind of interesting you really. If you look at any point, sells the effects on the protein were really not what you would have predicted based on what you’ve lost in terms of gene copies or gain. And Moreover, it’s important to note that
reaction is really pioneered.

This too that RNA seek data and proteomic
data have substantial discrepancies,
and so and so that means also appreciate the proteomics.

Is really an important thing to add to all of this code.

Yes, so stay think I would like just to comment about the frustration of analyzing tissue without spatial resolution.

This is critical because as a smart pointed, we see a striking difference between our name protein which is becoming the rule more than the exception.

But second, the protein measurements and
any other like really is context dependent. So for example, just to give you a rough example measurement of K protein in any given sample, if it’s in the tumor cell, it means that you know. Tumors are proliferating if it’s in the immune cells means good T cells are expanding, so really I think having the possibility of looking at the proteins in the context of tissue organization, it’s critical for understanding what’s going on, and I think that’s a little bit when I
tried to reflect in my presentation,

we’re still early.

We’re getting more quantitative

It’s coming up to speed,

but but I think it’s a.

It’s an important dimension

of the protein and any

other light data. Absolutely perfect

and Megan. Do you want to just jump

in this one as well? I just wanted

other light data. Absolutely perfect

and Megan. Do you want to just jump

in this one as well? I just wanted

add just also OK, great. You

know, as a first, just to say

I think this is exactly right.

When we asked us why,

we know that just doing the genome
sequencing is not going to be sufficient. We can start with the gene expression analysis because there are these epigenetic changes, but it’s very clear that that’s also in not sufficient. And one thing I just wanted to point out is that as a cell biologist, I think we know understand really well that for example, translational capacity is something highly affected by stress, and so when we think about what’s going on in a particular tumor environment, how that might be affecting the.
Relative efficiencies of translation, which will never be fully reflected in an RNA seek data set, is going to be really important. And you know, one of the things, for example, appeared lasers work is thinking about hypoxia as a good example of this, and then the protein turnover aspects, right? And so these are all the factors that are contributing to what we might see different in a podium data set. And I was going to exactly the same point about,
you know, aneuploidy, because you know, we know, and this is particularly relevant also for DNA repair factors that one of the ideas of why aneuploidy causes such changes in the proteomes that. We have these large protein complexes which are very codependent and they become kind of out of titration with regard to the components and that can you know, most of us are working on complex molecular machines where that’s going to have an impact,
and so that’s going to really require detailed, the kind of mechanistic analysis. But we might get pointed to the fact that we need to do that work only if we go actually looking for proteome wide data instead of just the genomics. Thanks great Katie.

Models actually represent a really useful system to look at signaling...
how signaling changes with treatment. And it's one of the reasons why we engaged in this effort. In developing these models and also allows us to really explore how heterogeneous these samples are across different patient tumors so we can take tumors with a specific alteration or just across the wear resistant to specific therapy, and we can look at specific things in terms of at the protein level in those and we can look if we apply other therapies, what changes and so that really,
I think, is a very valuable system in which to study what’s happening at the protein level and signaling.

Susan, could I just ask you to comment on how the different omics are approached from within an organization like yours and and to what extent leveraging systems biology approaches is practical within your organization? Yeah, sure, and so I mean, I agree with the comments that have been made. First of all that we do need to look at these different mechanisms and it is possible to do that.
Increasingly, you know where we are looking with things like Multiplex immediate fluorescence at the spatial organization of the tumors, and in doing that in patient samples now. So I think the technologies are advancing to enable you to do that single cell sequencing. Is also helping. I think you know what I would say is that you can’t do that intensively on on many child, so you have to choose the trial setting and the context for that. And it does have to be complemented by the kinds of things that Katie was talked about as well,
01:14:04.540 --> 01:14:06.766 so I think you know you can.
NOTE Confidence: 0.838525116443634
01:14:06.770 --> 01:14:09.202 You can see some sense of the overall
NOTE Confidence: 0.838525116443634
01:14:09.202 --> 01:14:11.036 picture emerging from some of the
NOTE Confidence: 0.838525116443634
01:14:11.036 --> 01:14:12.496 clinical trial data you really
NOTE Confidence: 0.838525116443634
01:14:12.496 --> 01:14:14.429 need to understand the mechanism,
NOTE Confidence: 0.838525116443634
01:14:14.430 --> 01:14:16.368 and for that you need a
NOTE Confidence: 0.838525116443634
01:14:16.368 --> 01:14:17.337 different setting and.
NOTE Confidence: 0.838525116443634
01:14:17.340 --> 01:14:19.548 Environment to do that in the
NOTE Confidence: 0.838525116443634
01:14:19.548 --> 01:14:21.379 different techniques and then you
NOTE Confidence: 0.838525116443634
01:14:21.379 --> 01:14:23.388 know the the PDX models have the
NOTE Confidence: 0.838525116443634
01:14:23.388 --> 01:14:25.503 have some challenges the Gen models
NOTE Confidence: 0.838525116443634
01:14:25.503 --> 01:14:27.711 have their own set of challenges.
NOTE Confidence: 0.838525116443634
01:14:27.720 --> 01:14:29.796 The humanized models for IO have
NOTE Confidence: 0.838525116443634
01:14:29.796 --> 01:14:32.212 their own set of challenges and I
NOTE Confidence: 0.838525116443634
01:14:32.212 --> 01:14:34.876 think what we can try and do is
NOTE Confidence: 0.838525116443634
01:14:34.876 --> 01:14:37.054 by looking collectively at at at,
you know the clinical sample data and these range of preclinical models and backwards and forwards across that divide, that’s how you build up the bigger picture of understanding. But you know, I think it’s like trying to sort of workout the overall picture from having several pieces of the jigsaw together, which is great, but you know nothing, that holistic view is absolutely critical to understanding, so I you know my comment would be that I think that the technology
advances are now in place to enable
us to see so much more than we
were able to see 510 years ago.
We need to bring that together,
but have an integrated plan
that goes across preclinical.
Translational and clinical trial environment.
Then I think that’s critical,
so we spend a lot of time in what
is called early stage oncology
without translation of medicine
group actually working with drugs
and programs that are in late phase
development already on the market.
like awesome Internet and you know.
And if I’m out.
The other drugs that we have there because the two reasons one is that I think that’s absolutely critical to understanding how to develop those in and continue that. But Secondly that understanding their feedback into the discovery organization for new opportunities. And I think the final piece I would say is that we can’t do it all internally. Collaborations with organizations like Yale is absolutely critical. You’ve already heard a number of examples of the kinds of collaborations that we have that really helped to.
And to feed and stimulate the work that we're doing internally. So you know really appreciate the work that that Megan, a team of doing that Katie Ability and her team are doing because that sees what we're doing internally and we can’t do all of it. Great good, there’s a question here asking can we share examples of partnership with other academic centers that we may have for precision medicine efforts and adaptive combination treatment to overcome resistance and? And I’ll talk about that maybe a little bit from the medicine side.
Pet Larusso here leads experimental therapeutics clinical trials network U M1 grant that has. Many consortium members and she and her colleagues are leaders in taking molecularly driven questions and actually molecular selection strategies forward in the ETCTN network.

Jeff Sklar, here, runs one of the Lamps that did the precision medicine sequencing for the match trial.

We have investigators here leading match sub trials. We have, I think within our spores collaborations across other cancer.
centers that are molecularly driven clinical trial questions.

So I think from the disease based and clinical arena Ann from the Phase one arena there is quite a rich network of these types of interactions, I don’t know if anybody wants to address more from the preclinical. That’s all guns are long term collaboration with people at Children’s Hospital in Philadelphia and a new pen where much of the computational
modeling is done actually through that.

And then another approach that another aspect that we're working on, which is a collaboration of many.

Out of many academic medical centers actually in the US and abroad,

we actually have through the Alex approach to targeting Myc signaling.

Let me say it's not targeting combination therapies and so forth,

the idea being that multigroup approach.

With the idea that that make aberrations, particularly making neuroblastoma
01:18:48.799 --> 01:18:49.948 affect the network,
NOTE Confidence: 0.786874294281006
01:18:49.950 --> 01:18:52.344 and in principle one could rescue the
NOTE Confidence: 0.786874294281006
01:18:52.344 --> 01:18:54.150 network with appropriate combinations,
NOTE Confidence: 0.786874294281006
01:18:54.150 --> 01:18:56.436 and I think with the technologies,
NOTE Confidence: 0.786874294281006
01:18:56.440 --> 01:18:57.968 as Susan pointed out,
NOTE Confidence: 0.786874294281006
01:18:57.968 --> 01:18:58.350 advancing,
NOTE Confidence: 0.786874294281006
01:18:58.350 --> 01:19:01.455 I think the time is is is is
NOTE Confidence: 0.786874294281006
01:19:01.455 --> 01:19:04.300 right to get to ask that question
NOTE Confidence: 0.786874294281006
01:19:04.300 --> 01:19:06.370 in that type of way.
NOTE Confidence: 0.819485902786255
01:19:09.450 --> 01:19:10.866 Anybody else wanna OK?
NOTE Confidence: 0.819485902786255
01:19:10.866 --> 01:19:12.990 There’s a question here in the
NOTE Confidence: 0.819485902786255
NOTE Confidence: 0.819485902786255
01:19:15.270 --> 01:19:17.115 Can panelists share with their
NOTE Confidence: 0.819485902786255
01:19:17.115 --> 01:19:18.960 most excited about in terms
NOTE Confidence: 0.819485902786255
01:19:19.025 --> 01:19:20.678 of combination modalities?
NOTE Confidence: 0.819485902786255
01:19:20.680 --> 01:19:24.424 And maybe I’ll just ask him to go first?
01:19:28.300 --> 01:19:30.604 But I think everybody probably has their own favorite combination too,
01:19:30.604 --> 01:19:32.440 and you just want to, yeah, so of course I think because I work samples next,
01:19:33.560 --> 01:19:36.192 my opinion might be any bias. Modulation is critical for that and not only the case.
01:19:38.452 --> 01:19:40.708 So one of the example I have showed this Acadian 5B where we can show pretty synergistic effect that you’re going to check my blanket in multiple models.
01:19:41.910 --> 01:19:43.119 So one of the example I have showed this Acadian 5B where we can show pretty synergistic effect that you’re going to check my blanket in multiple models.
01:19:43.120 --> 01:19:45.140 and not only the case.
01:19:45.140 --> 01:19:47.972 I only showed one in breast cancer.
01:19:47.972 --> 01:19:51.330 this Acadian 5B where we can show pretty synergistic effect that you’re going to check my blanket in multiple models.
01:19:51.330 --> 01:19:53.954 and you just want to, yeah, so of course I think because I work samples next,
01:19:53.954 --> 01:19:56.444 my opinion might be any bias. Modulation is critical for that and not only the case.
01:19:56.450 --> 01:19:59.278 So one of the example I have showed this Acadian 5B where we can show pretty synergistic effect that you’re going to check my blanket in multiple models.
01:19:59.278 --> 01:20:02.250 and you just want to, yeah, so of course I think because I work samples next,
Will also see that as well.

In addition, an and there's other modalities that you can actually modulate the tumor micro environment and, for example, someone that can recognize this as we are working on one, then it's called the CCR two, we can by inhibiting that we can change the macrophage population and by that we can change the T cell activity.

So, but basically it’s just moderating the whole tumor micro environment and make it sensitive for email, checkpoint blockade and and this. This works well an intimate asks.
01:20:32.450 --> 01:20:34.598 Setting so I’m quite excited about
01:20:34.598 --> 01:20:37.339 that and that many of you probably
01:20:37.339 --> 01:20:39.399 know in other other institutions
01:20:39.399 --> 01:20:41.650 have studied with DMT inhibitors,
01:20:41.650 --> 01:20:42.450 HVAC inhibitors,
01:20:42.450 --> 01:20:44.450 and is it still inhibitors
01:20:44.450 --> 01:20:45.650 and those actually ,
01:20:45.650 --> 01:20:48.198 I showed him assuming have showed strong
01:20:48.198 --> 01:20:50.450 efficacy in many different models,
01:20:50.450 --> 01:20:52.850 so I’m quite excited about this.
01:20:52.850 --> 01:20:54.450 This kind of combination.
01:20:58.202 --> 01:21:00.730 Anderson and Eli are broken.
01:21:00.730 --> 01:21:02.486 Working on demethylating therapy
01:21:02.486 --> 01:21:04.242 to uncover immune silencing
and virally associated cancers.

And I think there are a lot of examples.

I just wanted to come and I think that’s a very hard question, you know,
because I think ultimately the best combination is not going to be one combination that works every time I think it is so clear now that the tumors evade immunity through different dominant pathways and and more advanced tumors tend to have multiple pathways that I think the question has to do with where in an immunization pathways dominant and where more than one is dominant.
And I think that should drive the combination not think the opposite. Wait and think that one combination will fix tumors with different problems.

Yeah, so I think it’s very interesting that you heard that question as an immune resistance question. It was. It was a very broad resistance question, but that’s an interesting perspective. I think one of the things that I think about sometimes is how some of the same mechanisms that have generated resistance to conventional therapies are now also generating resistance to immunotherapy and...
how you know our relentless focus on target instead of environment, which you know?

I think it’s something I’ve heard. You speak about alot.

Kurt, you know we may have the same Achilles heel over and over again and in head neck cancer. A clear example of this is hypoxia, which leads to resistance to DNA damaging agents. It leads to resistance to. Radiation therapy. Prime example, but is now increasingly linked to resistance, demeanor,
therapy as well. Yeah, and I say even taking it down to the simplest level of talking therapeutics it the answer is it depends because for example, just thinking about RAF inhibitor resistance. Actually David Stern and Marcus Bosenberg and others did a nice study that they published it a few years ago of combination combinations of drugs in a variety of cell lines for Melanoma and elsewhere. And showed that the combination which combinations work in which cells is very valuable and actually one of the things I'm quite excited about.
The moment we’re working as a group with systems biology island and equipment Los Alamos in the group and trying to understand that in terms of the signaling networks around RAF and MEK and rest in different cells, some cells from different cancers, and innocence. Which combinations work depends say on the level of KSR 1. And that’s a key determinant, and so it just depends on so much on how the network is wired, which of course goes back to the question about proteomics, because ultimately that you’re
trying to control the system and the way

the system is set up by a chemically,

it defines on how it will define how

we respond to different combinations.

And so I think we’re going to want

to get into things at that kind of

level to understand where we should

use which combination,

and I think it occurs .2.

That’s that’s exactly.

Got it that the case is going to be

the case in the more complex systems

of intercellular communication too.

And can I just add?

There’s also the kinetic component, right?
So I think when things were still not clear on is are you better off with this combination early on or is this going to be better once you get initial resistance? And actually that’s may seem trivial, but I really don’t think it is and requires modeling to think about just how the kinetics is playing out. Great, related, related to that, one of the things that I was going to say is really what we can learn about the tumor from the get go that can tell us how the kinetics is playing out. But I really don’t think it is and requires modeling to think about just how the kinetics is playing out. Great, related, related to that, one of the things that I was going to say is really what we can learn about the tumor from the get go that can tell us how the kinetics is playing out. Great, related, related to that, one of the things that I was going to say is really what we can learn about the tumor from the get go that can tell us how the kinetics is playing out.
01:25:04.510 --> 01:25:07.327 how we would want to treat it to stave
off certain mechanisms of resistance.

01:25:09.840 --> 01:25:12.164 I think we’re starting to see some
examples also of clinical trials that are starting to subset.

01:25:17.955 --> 01:25:20.179 Patients with certain tumor Gina
types or whether tumors have certain
features and sort of put them and and
into trials with specific combinations,

01:25:28.258 --> 01:25:30.649 interesting approach in the next few years.

01:25:32.070 --> 01:25:33.198 Terrific, thanks, just
a couple comments on this,

01:25:35.090 --> 01:25:37.502 so there’s a few things that
you’ve heard there
that I just like to to build on.

A completely agree that we need to understand what’s the right combination for the set of what the adaptive mechanisms have been in that particular tumor, and I think to that end, looking at the adaptation at an earlier point than we typically do is a key part of this strategy, so there’s some really interesting. Concepts here that you will be working with Gordon Mills from OHSU on and looking at the adaptive rewiring that goes on which really happens quite quickly.
And of course one element of that we need to understand is undoubtedly the epigenetic mechanisms that come in, 'cause they're quite commonly involved in some of the resistance mechanisms, and as I pointed out, we don't really have good techniques for looking for those if we haven't got a biopsy. Early on, so I think that's absolutely key, and then I think that also informs, but the potential for how we do combinations 'cause one of the limiting factors of actually getting these
01:26:44.882 --> 01:26:47.432 to work has been the Taler ability
NOTE Confidence: 0.84442663192749
01:26:47.432 --> 01:26:48.904 of the combinations clinically.
NOTE Confidence: 0.84442663192749
01:26:48.910 --> 01:26:51.798 And for that I think there's a couple
NOTE Confidence: 0.84442663192749
01:26:51.798 --> 01:26:54.668 of chinks of light of what we can do.
NOTE Confidence: 0.84442663192749
01:26:54.670 --> 01:26:55.567 First of all,
NOTE Confidence: 0.84442663192749
01:26:55.567 --> 01:26:57.361 we're starting to develop some better
NOTE Confidence: 0.84442663192749
01:26:57.361 --> 01:26:58.740 tolerated therapies inherently,
NOTE Confidence: 0.84442663192749
01:26:58.740 --> 01:27:01.332 so I think that gives us a bit
NOTE Confidence: 0.84442663192749
01:27:01.332 --> 01:27:03.475 more headroom for some of the
NOTE Confidence: 0.84442663192749
01:27:03.475 --> 01:27:05.599 combinations that we need to do.
NOTE Confidence: 0.84442663192749
01:27:05.600 --> 01:27:06.440 Things like Adcs,
NOTE Confidence: 0.84442663192749
01:27:06.440 --> 01:27:07.840 better ways of you know,
NOTE Confidence: 0.84442663192749
01:27:07.840 --> 01:27:09.328 delivering some of the mechanisms of
NOTE Confidence: 0.84442663192749
01:27:09.328 --> 01:27:11.295 killing give you a bit more headroom
NOTE Confidence: 0.84442663192749
01:27:11.295 --> 01:27:13.155 and understanding what drives total ability,
NOTE Confidence: 0.84442663192749
01:27:13.160 --> 01:27:14.942 and then looking at the sequencing
rather than trying to do it does everything at the same time is another innovation that I think will need to apply all of these tools that we’ve got and the modeling of that too, to reduce down the number of options that we actually bring into the clinic and increase the likelihood of each one of those being. Being successful with in combination therapy is going to keep us occupied for a little while yet before we solve that problem.
Terrific great well this I,

I hope the attendees have enjoyed

this exchange of opinion and

knowledge as much as I have.

I’d like to turn it back now to

Charlie Fuchs and just ask him to

share a couple of concluding remarks.

Well, Barbara,

thank you and all the panelists.

It was a fantastic discussion and

really provided so much insight

in terms of how we continue to

move grade science into the clinic

and frankly how we learn more.

About the tests in clinical

trials that were actively doing
as part of our investigation, this is I mentioned is the third of our Yale engage cancer forms and I hope that our attendees enjoyed it and benefited from it. And as I mentioned, the work continues and we very much want this to be the beginning of the conversation and so hopefully what will what you’ll do and what we’ll do is engage each other in thinking through how we partner, how we work strategically together. To think of these, the ideas that are panels are brought
up an develop new initiatives, 

so people should feel free to 

reach out to me or any of the 

panelists to think about. 

These collaborations will be contacting you 

really appreciate your taking the time. 

You know when I listen to 

discussions like this, 

I think it gives all of us hope 

and excitement about the years 

ahead of cancer investigation. 

So let me just turn it back, 

turn it back to Barbara for 

some final thoughts. 

You know, so I’ve been at Yale about 6 

1/2 years and the conversation today.
Sort of reminds me of the excitement that I felt when I started going to seminars around here. I mean, there’s just unbelievable scale of work of this quality going on at this institution, and a lot of people thinking about how to make cancer treatment better. So thank you all for joining us today. Please stay in touch and I want to thank Susan and curtain, Katie and Mark and Megan Inch in for their wonderful presentation. Thank you very much.