

WEBVTT

NOTE duration:"01:16:51.3300000"

NOTE language:en-us

NOTE Confidence: 0.908539116382599

00:00:00.070 --> 00:00:05.020 Welcome everybody to the inaugural George are Henninger lecture.

NOTE Confidence: 0.906725764274597

00:00:05.590 --> 00:00:36.700 And this is about as good as it gets in science because we have the opportunity to both celebrate a beloved member of our faculty and 2:00 and then here from an extraordinary son of our Department before I get into that. Let me just let you know about the upcoming grand round lectures next week. We have Simon icon from the University of Dusseldorf will be talking about some very exciting.

NOTE Confidence: 0.913380980491638

00:00:36.700 --> 00:01:07.670 Brain imaging findings where artificial intelligence techniques are applied to the analysis of functional brain imaging scans so that should be in exciting grand rounds and then the following week, the 24th of January. We have Justin Baker from Harvard Medical School in McLean, Hospital, who's going to be talking about digital or computational phenotypes of psychosis. The use of passive data collection to try to identify people who are.

NOTE Confidence: 0.896832585334778

00:01:07.670 --> 00:01:20.900 At risk for psychosis and then and then at the end of the month. We have Darren Lattimore, who's our deputy Dean for diversity who's going to be talking about microaggressions in the health learning environment.

NOTE Confidence: 0.930087268352509

00:01:22.110 --> 00:01:24.700 So I'm going to make a few comments.

NOTE Confidence: 0.893201768398285

00:01:25.320 --> 00:01:56.030 About George Henegar, who needs no words to recognize his contributions to the Department and then introduce Eric Nestler, who needs no introduction in order to to celebrate the work that he's going to tell us about in his career. So I just wanted to say a few words about George for those of you who may not know know him as as well as as we all do I see people in the back of the room.

NOTE Confidence: 0.854273796081543

00:01:56.590 --> 00:02:30.620 We have, I would call them aisle seats available up here. There are certainly uh maybe a stairwells stare seat or or 2 we should. Look up in the right front. If you'd like to to make use of them You know this.

Eric was reminding me that that when we renovated the CMHC Auditorium years ago. George was one of the people who bemoan the fact that we were going to lose seats.

NOTE Confidence: 0.815847992897034

00:02:30.620 --> 00:02:36.010 For grand rounds, but I would say that that there is.

NOTE Confidence: 0.900938153266907

00:02:36.940 --> 00:02:52.800 We should have anticipated this and had it in a bigger setting, but there's something about the communality of being altogether. In this very this room, which is meant so much for the Department in its history that that that makes the setting seemed very appropriate.

NOTE Confidence: 0.861044049263

00:02:54.330 --> 00:03:24.960 But so not too long ago as you know, we had the celebration for the 2 George is George Henry Jerin George Agaj Anian. The two of them are seminal figures in our Department who have mentored so many people and equally important set the kind of scientific vision that everybody since then has followed in terms of the values of.

NOTE Confidence: 0.892198264598846

00:03:24.960 --> 00:03:34.860 Of Science and the possibilities of Science and the need for rigor in both thinking an end in experimental design.

NOTE Confidence: 0.916593194007874

00:03:35.390 --> 00:03:40.990 That that we had this wonderful celebration to celebrate both of their careers.

NOTE Confidence: 0.885008156299591

00:03:41.520 --> 00:03:53.610 Subsequent to that Eric and Dennis Charney had the idea that we should really do something more that we should.

NOTE Confidence: 0.903431415557861

00:03:54.340 --> 00:04:02.250 That we should create an Dau Electro ship that recognizes the contributions of these 2 incredible people for the Department.

NOTE Confidence: 0.886685132980347

00:04:02.930 --> 00:04:33.540 And once we heard about it once they share the idea with me the the IT was such an obvious thing for us to do and it took all of about 10 minutes to find all of the donors who wanted to participate to endow this lectureship, so this lectureship is really the work of a whole group of people who contributed to to endowing this lectureship. The other part of the lectureship. They agaj anian lectureship will be taking place.

NOTE Confidence: 0.845877289772034

00:04:33.540 --> 00:04:39.730 A little bit later this year and Doctor Charney will be the agagianian lectureship.

NOTE Confidence: 0.689432382583618

00:04:40.590 --> 00:04:43.500 Eric nestler the Henegar lecture.

NOTE Confidence: 0.509686052799225

00:04:44.370 --> 00:04:45.680 So uhm.

NOTE Confidence: 0.919996976852417

00:04:46.270 --> 00:04:51.420 So let me tell you a little bit about George in case in case you don't know him all that well.

NOTE Confidence: 0.904415428638458

00:04:52.080 --> 00:05:17.040 So so this is where George grew up Utah State Hospital. The mental hospital in Provo. UT he was not. It wasn't a patient in the in the in the hospital actually his father was the psychiatrist. The Superintendent of the state hospital and his brother also became a psychiatrist.

NOTE Confidence: 0.684482872486115

00:05:17.610 --> 00:05:18.580 And uh.

NOTE Confidence: 0.869518160820007

00:05:19.550 --> 00:05:29.440 George George, his who's been an athlete is his entire life tells the story of being one of the early people who?

NOTE Confidence: 0.891423404216766

00:05:30.030 --> 00:06:00.240 Discovered jogging or discovered running you know was running around in the farmers would shout at him as he was running by if you've got so much enerji you can help me on the farm here, but but he he came from this background. He developed a lifelong appreciation of the suffering of people with mental illness and it profoundly shaped his decision to pursue occur in psychiatry and 2.

NOTE Confidence: 0.819957256317139

00:06:00.240 --> 00:06:01.280 Conduct research.

NOTE Confidence: 0.899178326129913

00:06:02.120 --> 00:06:34.890 George was born in 1934 and attended the University of Utah and then had a seminal experience at Mass. Mental Health Center, which was probably one of the very Premier places to train in psychiatry in that era and then went to do a research Fellowship at NIH with Dick quiet on the biology of schizophrenia and came to Yale in 1966 with the opening of the Connecticut mental Health Center.

NOTE Confidence: 0.923057198524475

00:06:34.890 --> 00:06:38.000 And the creation of the clinical research unit.

NOTE Confidence: 0.922596514225006

00:06:39.120 --> 00:06:48.140 The establishment of that clinical research unit was really a partnership between George and the late Malcolm Bowers, who was the inpatient unit chief.

NOTE Confidence: 0.870693504810333

00:06:48.670 --> 00:07:14.120 Uh and they work together on that unit for a long time. Malcolm ultimately became the chief of psychiatry at Yale, New Haven Hospital and for a period of time head of the psychiatry residency program here. George ran the research enterprise, becoming first head of the research unit, then director of the Ribicoff research facilities.

NOTE Confidence: 0.877193152904511

00:07:14.660 --> 00:07:21.330 Then associate chair for research and ultimately professor emeritus.

NOTE Confidence: 0.680222988128662

00:07:21.950 --> 00:07:23.180 George.

NOTE Confidence: 0.901810586452484

00:07:24.220 --> 00:07:55.090 Throughout this period of leadership was the most fierce and the most generous advocate for research in the Department of protecting the research enterprise from from all sorts of challenges at over over the period of time of his leadership and more importantly, inspiring creative innovation in research in the Department of psychiatry and fostering their development.

NOTE Confidence: 0.823646485805511

00:07:55.090 --> 00:08:02.000 Of the careers of young psychiatrist who have gone on to to be seminal leaders.

NOTE Confidence: 0.895812451839447

00:08:03.270 --> 00:08:19.580 Probably uh the one of the very exciting, most important collaborations in the history of this Department was the collaboration between George and Dennis Charney.

NOTE Confidence: 0.87391072511673

00:08:20.180 --> 00:08:53.690 George the reflective introspective force and Dennis the volcanic creative energetic in the merger of that, too was of those two was extraordinarily creative in terms of research and but also incredibly creative in terms of mentor ship.

NOTE Confidence: 0.800186038017273

00:08:53.690 --> 00:08:55.590 I can say for myself.

NOTE Confidence: 0.892717182636261

00:08:56.320 --> 00:09:08.130 There was no better place to train in the world than on the clinical neuroscience research in the era. When Dennis and George were leading the enterprise.

NOTE Confidence: 0.708036005496979

00:09:08.720 --> 00:09:10.890 Um their work.

NOTE Confidence: 0.901323974132538

00:09:11.450 --> 00:09:22.720 Uh set the tone for psychiatry at Yale of being a serious neuroscience enterprise and that sounds almost obvious like how could it be.

NOTE Confidence: 0.924134254455566

00:09:23.370 --> 00:09:34.580 Not a serious enterprise and how could it not be a scientific enterprise, but but clinical research in the error that this was that this work was going on.

NOTE Confidence: 0.897404491901398

00:09:35.870 --> 00:10:07.220 Um was not well founded in neuroscience and in fact, Yale was one of the very few very few places in the world where the clinical psychiatry research and the basic neuroscience research. People got together and wrestled with common scientific problems, so that that we felt very much that we were in a common enterprise and and and had common values.

NOTE Confidence: 0.723924577236176

00:10:07.280 --> 00:10:09.110 And common names.

NOTE Confidence: 0.90974748134613

00:10:09.690 --> 00:10:19.940 And that was extraordinarily energizing extraordinarily inspiring both for the basic and the research communities here here at yeah.

NOTE Confidence: 0.841496765613556

00:10:22.080 --> 00:10:24.690 The other innovation where these 2 kids.

NOTE Confidence: 0.943016171455383

00:10:26.750 --> 00:10:30.260 Really that the foundation of molecular psychiatry.

NOTE Confidence: 0.0375711247324944

00:10:30.850 --> 00:10:31.470 Um.

NOTE Confidence: 0.897715210914612

00:10:31.970 --> 00:10:44.350 Again, hard to believe but there was an era where neuroscience research in psychiatry meant measuring whether the dopamine level was up or the dopamine level was down.

NOTE Confidence: 0.926301956176758

00:10:45.270 --> 00:10:58.670 In the clinical research enterprise, we got to the level of trying to understand how receptors were regulated. It wasn't until the advent of molecular psychiatry at Yale that psychiatry as an enterprise.

NOTE Confidence: 0.880019843578339

00:10:59.270 --> 00:11:29.860 Seriously wrestled with what happened once a neurotransmitter bound to its receptor target and that was made possible really through the work of Eric, who brought the signal transduction focus from his work with Paul Greengard. I'll talk about that. A little bit later as well as Ron's work ultimately on many complementary aspects of signal transduction and.

NOTE Confidence: 0.712176442146301

00:11:29.860 --> 00:11:33.990 Neurobiology but this this.

NOTE Confidence: 0.953872442245483

00:11:35.100 --> 00:11:38.080 Enterprise was so inspiring.

NOTE Confidence: 0.838790953159332

00:11:38.750 --> 00:11:47.890 That, it inspired Julio Licinio to steal that title and create a Journal called molecular psychiatry.

NOTE Confidence: 0.79101824760437

00:11:50.210 --> 00:12:14.450 OK, so George George George honors do not are great and there are many fold, the animatic apprised one of the highest most valued prizes and depression. Steven Fleck Award in the LPR a best teacher award. The Axelrod Julius Axelrod Mentorship Award from from a CNP.

NOTE Confidence: 0.0350188463926315

00:12:15.010 --> 00:12:16.550 Um.

NOTE Confidence: 0.877818942070007

00:12:17.070 --> 00:12:44.850 In some ways, they don't, they don't adequately capture. Georges impact on science is much better way to get that feeling are the many famous productive scientists around the world. Some of whom are here in the room today. They have a car. I see and others. Eric myself, but Nelson many others.

NOTE Confidence: 0.814306139945984

00:12:45.640 --> 00:12:52.810 Um, who have been inspired by George and Ann.

NOTE Confidence: 0.911686599254608

00:12:54.570 --> 00:13:07.400 It's hard to capture what it is about George that is so inspiring. But maybe you'll get a feel for it. If I read to, you, the holiday card that I got this year from George.

NOTE Confidence: 0.870620489120483

00:13:07.990 --> 00:13:14.280 You know, let us welcome a new year blah blah blah and then.

NOTE Confidence: 0.829879343509674

00:13:14.800 --> 00:13:18.070 Dear John this is the holiday card right.

NOTE Confidence: 0.857743859291077

00:13:18.940 --> 00:13:45.120 One possibility is to measure oxidative stress in molecular changes in brain derived exosomes in schizophrenia in order to guide treatment. I will stop by to explain our plan now. Maybe that's not the kind of holiday card, usually right, but it says a lot about about Georges.

NOTE Confidence: 0.858016550540924

00:13:46.560 --> 00:13:53.790 Georges embrace how George embraces the science at the at the edge.

NOTE Confidence: 0.91010046005249

00:13:54.500 --> 00:14:05.210 At the at the forefront and is always thinking about how to bring that Horizon of neuroscience into clinical research and that.

NOTE Confidence: 0.872985243797302

00:14:05.750 --> 00:14:21.570 His unchanging throughout his life so George on behalf of everybody here today. We salute you and we express our gratitude and I hope everyone will stand and join join us in the round of class.

NOTE Confidence: 0.892100870609283

00:14:43.240 --> 00:14:46.990 Georges is reserving his comments until after Eric speaks.

NOTE Confidence: 0.145765170454979

00:14:48.250 --> 00:14:48.610 So.

NOTE Confidence: 0.285612553358078

00:14:51.600 --> 00:14:52.390 So.

NOTE Confidence: 0.669390201568604

00:14:54.320 --> 00:14:55.860 Eric Nestler.

NOTE Confidence: 0.904824793338776

00:14:57.100 --> 00:15:01.150 Eric is and is a person who has improved.

NOTE Confidence: 0.880089640617371

00:15:01.930 --> 00:15:08.100 Every group, he has been in probably since kindergarten.

NOTE Confidence: 0.750904083251953

00:15:09.080 --> 00:15:14.600 That's what his mother told me on the way in today.

NOTE Confidence: 0.901713013648987

00:15:15.370 --> 00:15:24.620 He is the Nash family professor of neuroscience director of the Freedmen Brain Institute. Dean for academic affairs at the Icahn School of Medicine at Mount Sinai.

NOTE Confidence: 0.717711389064789

00:15:26.340 --> 00:15:32.570 Um so, so Eric's roots go very deep here at Yale.

NOTE Confidence: 0.823654115200043

00:15:33.110 --> 00:15:41.360 This in the back of the room, you probably can't see this, this is a tattoo of the Yale sign.

NOTE Confidence: 0.824585020542145

00:15:42.090 --> 00:15:49.420 I'm not saying that Eric has a tattoo of Yale sign logo on him.

NOTE Confidence: 0.805846631526947

00:15:50.250 --> 00:15:56.480 But I'm not saying he doesn't have it have a tattoo the tattoo.

NOTE Confidence: 0.90176659822464

00:15:57.270 --> 00:16:28.640 Yell was Eric was a Phi Beta Kappa graduate of Yale College, publisher of the Yale Daily News. He stayed in New Haven for medical school and for pursuing his PhD with Paul Greengard, who I think in many ways, certainly scientifically and perhaps more broadly was a spiritual father for Eric. In some ways. He was class president of Yale Medical school I didn't even know we had a class president, but that's how accomplishment.

NOTE Confidence: 0.862675487995148

00:16:28.640 --> 00:16:50.840 They created a role for Eric to be class president. He was Alpha Omega Alpha, which is the honors. Medical Honor Society and stayed here for psychiatry residency after a brief trip to Boston and received the Lessman toward the highest honor for psychiatry resident research.

NOTE Confidence: 0.883749544620514

00:16:53.260 --> 00:17:10.520 He has had by any standard a meteoric career with with Ron Doom and they established the laboratory of molecular psychiatry very soon. He was the Elizabeth mirrors in-house Jameson first assistant professor then associate professor then professor.

NOTE Confidence: 0.898523688316345

00:17:11.150 --> 00:17:31.650 He went on to lead the Abraham Ribicoff research facilities here and in so doing really transformed the science, bringing many new investigators into the labs inspiring new directions in molecular cellular in translation or research.

NOTE Confidence: 0.876471042633057

00:17:32.510 --> 00:18:04.260 And then he ran around 1999, two thousand he left for become chair of psychiatry at Utah, southwestern he had a transformative effect on on that Department and its research mission, and then was in a stroke of inspiration and brilliance was recruited by Dennis Charney to become chair of neuroscience and head of the Freeman Brain Institute at the Icahn School of Madison.

NOTE Confidence: 0.0374072790145874

00:18:04.840 --> 00:18:05.520 Um.

NOTE Confidence: 0.865395486354828

00:18:06.020 --> 00:18:27.070 Along the way he became president of a CMP president of the Society for neuroscience and spine off company. Psycho genic's and has been an advisor to all sorts of groups and is now Dean for academic affairs.

NOTE Confidence: 0.903684735298157

00:18:29.540 --> 00:18:47.440 Eric has had a transformative impact on science, beginning with his work with Paul Green Garden. Synaptic fossil proteins, continuing with establishing his own line of research initially around signal transduction than transcriptional mechanisms around substance abuse stress an antidepressant.

NOTE Confidence: 0.894418776035309

00:18:48.310 --> 00:19:10.750 And and overtime essentially pushing the boundaries of what could be explored using animal models to study the biology of these kinds of approaches leading him to study aspects of synaptic construct brain structural Ramada Ling Epigenetic regulation.

NOTE Confidence: 0.887561857700348

00:19:11.400 --> 00:19:41.930 With and more recently, including the pathophysiology of psychiatric disorders using things like postmortem brain tissue in other

other relevant paradigms. An Eric has had an inspired sense of where the important questions lies so for example, in studying the biology of depression. In a really groundbreaking paper to find out that the biology of depression.

NOTE Confidence: 0.897351682186127

00:19:41.930 --> 00:20:05.960 In in women and men as well as in male and female animals is really quite different a profound profound insight that has yet to be translated into a novel sex specific Therapeutics, but but is an example of the kind of of of really seminal work that he has done.

NOTE Confidence: 0.896799981594086

00:20:07.840 --> 00:20:31.990 Again, uh Eric is replete with honors member of the National Academy of Madison, a fellow in the American Academy of Arts and Sciences are recipient of the highest prize in neuroscience from the National Academy of Medicine called the Sarnak Prize recipient of the mood disorders, and cognitive neuroscience prizes from the brain and behavior research foundations.

NOTE Confidence: 0.593127548694611

00:20:32.590 --> 00:20:34.510 Um Deanna Monica Prize.

NOTE Confidence: 0.398761689662933

00:20:35.070 --> 00:20:36.220 Uh uh.

NOTE Confidence: 0.876089870929718

00:20:36.770 --> 00:21:06.980 The Society of biological psychiatry got a large gift and created a prize, which is only given every several years to people who have made really extraordinary indistinctive contributions to science and psychiatry called the Red Alzheimer Rentals Heimer Award in Eric was the first recipient of that award is received awards both for his science, Efron toward an mentorship the Axelrod Award from a CMP.

NOTE Confidence: 0.888348758220673

00:21:06.980 --> 00:21:19.200 And recently received something called the Wilbur Cross metal from Yale University, which is the highest honor given to a graduate of the graduate an alumnus or of the graduate department's so.

NOTE Confidence: 0.879071652889252

00:21:19.990 --> 00:21:36.740 Uh these these awards are signposts of Eric's extraordinary impact on science is extraordinary impact on people. His extraordinary impact on the institutions.

NOTE Confidence: 0.87968248128891

00:21:37.330 --> 00:21:51.580 And groups within an organizations within which he works. These impacts are lasting and meaningful so we are honored pleased to welcome my dear friend.

NOTE Confidence: 0.470093965530396

00:21:52.860 --> 00:21:54.350 Eric Nestler.

NOTE Confidence: 0.921708345413208

00:22:04.900 --> 00:22:10.480 Thank you so much John just give me a second while I set up my PowerPoint here. It's a blast to be back.

NOTE Confidence: 0.87326318025589

00:22:11.740 --> 00:22:20.340 And a tremendous honor to be here today to give the inaugural George Henninger Lecture John gave you.

NOTE Confidence: 0.934137284755707

00:22:21.080 --> 00:22:29.340 Background of Mycareer, but in looking back, I've been very fortunate to have so many senior faculty. Help me along the way.

NOTE Confidence: 0.890243887901306

00:22:30.510 --> 00:22:40.930 But I can identify 2 primary mentors. John mentioned Paul Greengard, who was my scientific mentor. He taught me how to do science had to run a lab.

NOTE Confidence: 0.892801463603973

00:22:41.840 --> 00:22:45.200 And George Henninger, who was my administrative mentor.

NOTE Confidence: 0.932245850563049

00:22:46.350 --> 00:22:53.590 More than anyone else, George taught me how to navigate the political intrigue of life in academia.

NOTE Confidence: 0.949823796749115

00:22:54.610 --> 00:22:59.130 But more importantly than that George helped me grow beyond.

NOTE Confidence: 0.894247055053711

00:22:59.740 --> 00:23:03.460 The inherent selfishness of running ones own lab.

NOTE Confidence: 0.931259036064148

00:23:04.260 --> 00:23:12.440 To build and manage a group of people help helping each to thrive and flourish. I'm going to come back to that in just a few minutes.

NOTE Confidence: 0.931351125240326

00:23:14.220 --> 00:23:23.190 George also influenced me and many other sitting in the audience here enormously through his truly unique way.

NOTE Confidence: 0.908496737480164

00:23:23.820 --> 00:23:27.900 Of framing a problem with provocative metaphors.

NOTE Confidence: 0.926328122615814

00:23:29.740 --> 00:23:40.130 I first met George Henninger formally in July 1984. I had just returned to Yale to start my PG 2 year in psychiatry had an appointment with George.

NOTE Confidence: 0.934244334697723

00:23:40.650 --> 00:23:49.490 The next week and a paper from National Geographic appeared in my mailbox focused on smelting copper and iron.

NOTE Confidence: 0.89165860414505

00:23:50.060 --> 00:23:59.830 In Preindustrial Africa with a note for discussion with Doctor Henninger next week and I remember my fellow PG 2 resident and I looking at one another saying.

NOTE Confidence: 0.911490857601166

00:24:00.380 --> 00:24:04.660 OK, who we had no clue what to expect.

NOTE Confidence: 0.953319072723389

00:24:05.540 --> 00:24:12.580 We read the article, which basically described a weeks long process involving dancing singing religious rituals.

NOTE Confidence: 0.91815322637558

00:24:13.130 --> 00:24:20.610 And ultimately heating the ore to thousands of degrees when we met with George, he made the point that this is just like psychotherapy.

NOTE Confidence: 0.93907755613327

00:24:22.640 --> 00:24:29.670 We know it works, but most of it is a series of superstitious rituals without knowledge of the active required step.

NOTE Confidence: 0.918349981307983

00:24:30.660 --> 00:24:34.880 Amazing insight and you know, I still use this metaphor with our residents today.

NOTE Confidence: 0.912555515766144

00:24:36.170 --> 00:24:46.050 2 years later in this auditorium, George gave grand rounds to psychiatry and he began in my own memory with I think a 10 minute exposition.

NOTE Confidence: 0.939704298973084

00:24:46.930 --> 00:24:51.280 Of a storybook character called Flat Stanley, a children's book series.

NOTE Confidence: 0.870302140712738

00:24:52.070 --> 00:24:57.110 Flat Stanley is flat 2 dimensional, he can slip under a door.

NOTE Confidence: 0.939178466796875

00:24:58.010 --> 00:25:03.120 He can put himself in an envelope and Mail himself across country and all sorts of cool things.

NOTE Confidence: 0.921279489994049

00:25:03.840 --> 00:25:09.540 And I remember sitting where you are today thinking to myself, Oh Lord Where is this going.

NOTE Confidence: 0.916400671005249

00:25:11.010 --> 00:25:18.120 What were George brought it was to the bio cycle social theory of psychiatry? Which was

NOTE Confidence: 0.935116529464722

00:25:19.040 --> 00:25:21.920 Dominant in the field in those days.

NOTE Confidence: 0.911998927593231

00:25:22.770 --> 00:25:31.060 And Georges Point was is that it's the flat Stanley view of psychiatry flat 2 dimensional obvious trivial.

NOTE Confidence: 0.926388561725616

00:25:31.610 --> 00:25:36.640 Ultimately, unhelpful and explicating mechanisms of psychiatric disease.

NOTE Confidence: 0.897102653980255

00:25:37.380 --> 00:25:49.860 What was all the more remarkable to me is a PG for resident was that one of the major proponents of this theory was more riser who is chair of the Department at the time, meaning Georges Boss.

NOTE Confidence: 0.882792174816132

00:25:52.250 --> 00:25:54.300 As I said George was provocative.

NOTE Confidence: 0.898938119411469

00:25:55.780 --> 00:25:57.400 Then there are what we all.

NOTE Confidence: 0.752137124538422

00:25:57.990 --> 00:26:00.120 Lovingly call Henninger isms.

NOTE Confidence: 0.862635910511017

00:26:00.980 --> 00:26:08.000 Decorum prevents me from sharing these with you today lest I be cancelled.

NOTE Confidence: 0.91111958026886

00:26:09.600 --> 00:26:11.020 But I will share one.

NOTE Confidence: 0.915439486503601

00:26:12.220 --> 00:26:17.870 Being an administrator is like walking behind people and picking up their shit as it falls from them.

NOTE Confidence: 0.93817526102066

00:26:21.620 --> 00:26:27.060 I can tell you the number of times that I think of this to this very day and smile.

NOTE Confidence: 0.949551641941071

00:26:29.760 --> 00:26:36.250 In the mid 1990s, we held a 60th birthday party for George where we celebrated and roasted him.

NOTE Confidence: 0.885235905647278

00:26:36.950 --> 00:26:51.660 A week later in my mailbox appear to photograph of that from that party with Georges scribbles on the Top so there's Georgian Julie at the right. Denison in the middle Larry Price, Chris McDougall, myself in the foreground.

NOTE Confidence: 0.943696856498718

00:26:53.020 --> 00:26:54.990 About a week later.

NOTE Confidence: 0.889088332653046

00:26:55.500 --> 00:26:57.590 This appeared in my homes Mail.

NOTE Confidence: 0.906524538993835

00:27:00.430 --> 00:27:05.740 You know you may not recognize me with her, but that's me upside down in a 2 two I guess.

NOTE Confidence: 0.922119319438934

00:27:06.370 --> 00:27:10.830 This is a picture of what George showed at the party to roast Maine.

NOTE Confidence: 0.900535881519318

00:27:11.440 --> 00:27:41.940 And similar pictures of everyone else here roasting them certainly out roasting us compared to what we did with him, but was particularly remarkable is this was not addressed to me, this was dressed to our son, David, who had unbeknownst to us had sent. Georgia picture of me that he could use in this picture along with this note, which I'll read dear. David thanks for the note in picture for the party. I thought you might like it picture of what goes on. In these parties. These are the kind of adult ideas that get passed around.

NOTE Confidence: 0.900828719139099

00:27:41.940 --> 00:28:02.530 Sometimes dad's or not as big as they seem at least with trick pictures. You can make them smaller George George, new

David because he would take David and my other son. Madden me on an annual fishing trip canoe trip and the like and really wonderful times, that we still reminisce about to this day.

NOTE Confidence: 0.876143574714661

00:28:04.550 --> 00:28:08.300 I loved Georges Irreverence.

NOTE Confidence: 0.908494651317596

00:28:09.240 --> 00:28:12.640 It gave me license to embrace my own.

NOTE Confidence: 0.915076315402985

00:28:13.920 --> 00:28:20.440 Along the way I learned from George that the worst kind of person in academia probably every.

NOTE Confidence: 0.875683307647705

00:28:21.190 --> 00:28:24.750 Path of life are those who kiss up and kick down.

NOTE Confidence: 0.935236573219299

00:28:25.920 --> 00:28:30.050 George of course was always the exact inverse.

NOTE Confidence: 0.921811401844025

00:28:30.580 --> 00:28:41.340 Providing maximal support to junior people, while challenging authority that resonated with me very much and helped shape the way I've tried to lead.

NOTE Confidence: 0.943896174430847

00:28:43.440 --> 00:28:46.490 According to George Fighting Convention.

NOTE Confidence: 0.945011794567108

00:28:47.020 --> 00:28:52.210 And bureaucracy in the interest of innovation and driving scientific and medical discoveries.

NOTE Confidence: 0.881918132305145

00:28:53.220 --> 00:28:55.640 Today we call that type of person, a disruptor.

NOTE Confidence: 0.886750161647797

00:28:56.390 --> 00:28:59.750 George was the consummate disruptor.

NOTE Confidence: 0.926873445510864

00:29:03.040 --> 00:29:18.480 In the early 1990s, George stepped down from his two administrative posts. Vice chair of research in psychiatry and director of the Ribicoff research facilities, so that Dennis Charney and I could have those career opportunities.

NOTE Confidence: 0.951418340206146

00:29:19.430 --> 00:29:24.660 What incredible an unprecedented generosity?

NOTE Confidence: 0.949345409870148

00:29:25.720 --> 00:29:30.210 I have worked very hard to pay forward that generosity.

NOTE Confidence: 0.943641722202301

00:29:30.730 --> 00:29:36.780 Ever since George thank you so much for being such a wonderful mentor to Maine.

NOTE Confidence: 0.949182152748108

00:29:37.300 --> 00:29:41.660 And to so many other people who have passed through this great Department of psychiatry.

NOTE Confidence: 0.916286468505859

00:29:42.510 --> 00:29:50.990 And congratulations on establishment of the George hanging or lecture at Yale University in perpetuity, let's give George another round of applause.

NOTE Confidence: 0.915980100631714

00:30:02.620 --> 00:30:05.100 So now from the sublime to the ridiculous.

NOTE Confidence: 0.944983899593353

00:30:05.700 --> 00:30:12.370 I'll spend the rest of the time that we have telling you a little bit about the work that we've done in the area of drug addiction.

NOTE Confidence: 0.926492512226105

00:30:14.050 --> 00:30:32.890 Back when I was still at Yale couple of decades ago. We proposed along with many other groups that addiction could be seen as a form of drug induced neural plasticity mediated in large part through changes in gene expression as depicted in this cartoon so we know that drugs of abuse.

NOTE Confidence: 0.905289113521576

00:30:33.640 --> 00:30:39.980 Find initially to proteins at the extracellular level of synapses receptors transporters channels.

NOTE Confidence: 0.894338011741638

00:30:40.820 --> 00:30:43.840 But the diction requires repeated exposure to a drug.

NOTE Confidence: 0.925098896026611

00:30:44.660 --> 00:31:11.820 And that ultimately produces changes in a wide array of intracellular signaling pathways, which ultimately lead, according to this notion to regulation of transcription factors proteins that bind to DNA in a sequence specific fashion to regulate expression of Target Jeans, so the hypothesis was that drugs of abuse over repeated exposures with cause induced

neural plasticity associated with addiction by producing long lasting changes in gene expression.

NOTE Confidence: 0.915955483913422

00:31:13.150 --> 00:31:28.520 Now parents erikli all current treatments and all currently research treatments for addiction still remain focused on extracellular proteins without taking advantage of thousands of intracellular signaling proteins. I'll come back to that toward the end of the talk.

NOTE Confidence: 0.918989419937134

00:31:30.120 --> 00:31:42.710 In order to explore these drug induced changes in transcriptional mechanism. We had to know where in the brain to look for that. We've relied on a large literature over several decades, identifying so-called brain reward regions.

NOTE Confidence: 0.903161108493805

00:31:43.330 --> 00:31:59.180 Beginning with dopamine containing nerve cells in the ventral tegmental area of the midbrain and the many for brain regions to which those neurons project. Most importantly, the nucleus accumbens but also amygdala hippocampus regions of prefrontal cortex among others.

NOTE Confidence: 0.903400838375092

00:32:02.010 --> 00:32:08.160 And in the early days for Maine when I was still back at Yale and will work focused on 2 transcription factors.

NOTE Confidence: 0.861672520637512

00:32:08.670 --> 00:32:16.700 We identified Delta Fosby because it was a unique Foss June. EPI one family protein induced after chronic drug exposure.

NOTE Confidence: 0.853592157363892

00:32:17.230 --> 00:32:31.410 And we focused on crib because it's a downstream effector of the cycle campy pathway and we had shown along with George Agagianian colleagues that the cycle game. P pathway was very important in the actions of drugs of abuse on the brain.

NOTE Confidence: 0.879319727420807

00:32:34.010 --> 00:33:05.170 The panels to the right show the very different temporal properties of these 2 proteins and highlighting the unique temporal properties of Delta Fosby, which one modified by phosphorylation at specific residues becomes very stable, so that even though it is induced for a slightly in response to an initial drug exposure. These small amounts of Delta Fosby gradually accumulate feedback suppress these other Foss proteins. And so that faucet Delta Fosby becomes the dominant. AP one transcription factor present in nucleus comments after chronic drug exposure.

NOTE Confidence: 0.899715602397919

00:33:06.580 --> 00:33:21.380 And over the years at Yale in Dallas. More recently at Mount Sinai. We've learned a great deal about these 2 proteins. We believe that Delta Fosby, which is induced mostly in D1. Type medium spiny neurons. I'll come back and define that in just a moment.

NOTE Confidence: 0.924827516078949

00:33:22.880 --> 00:33:30.430 Increases an animals sensitivity to drugs and natural rewards represents a form of positive reinforcement.

NOTE Confidence: 0.882649779319763

00:33:30.980 --> 00:33:40.320 Crab does the opposite it's really a classical mediator of drug tolerance and dependance induced in both major subtypes of striatal medium spiny neurons.

NOTE Confidence: 0.91373199224472

00:33:40.930 --> 00:33:49.020 Opposes drug and natural reward mechanisms, but it to drive self administration through negative reinforcement and I want to credit.

NOTE Confidence: 0.861153662204742

00:33:49.520 --> 00:33:57.000 Bill Carl's on and David Self, 2, former postdocs of mine here at Yale. Bill is now at Harvard and David is at Utah southwestern.

NOTE Confidence: 0.911395788192749

00:33:58.600 --> 00:34:04.750 When we moved to Dallas. We decided to move beyond transcription per se to epigenetics Chrome and in biology.

NOTE Confidence: 0.907326459884644

00:34:05.550 --> 00:34:37.280 Let me just first define what I mean by that. We know that a mailing an Organism has about 3 billion nucleotides in its genome is stretched out linearly those nucleotides would be about 2 meters in length. That is compacted in every cell into a microscopic cell nucleus. One of the extraordinary achievements of evolution. We've learned a lot about the biological basis of that compaction over the last couple of decades. We know that the DNA double. Helix is wrapped around Oct rumors of histone proteins to form the unit of chromatin called a nucleosome.

NOTE Confidence: 0.907002925872803

00:34:37.580 --> 00:34:44.190 Which is then further organized in many ways in the most condensed form? What would be recognizable as a chromosome?

NOTE Confidence: 0.912879168987274

00:34:44.700 --> 00:35:03.110 In this organization is very important because spans of DNA that are in compacted regions of chromatin or can cannot be used to transcribe RNA or serve other functions, whereas DNA and open regions

are biologically active, which means that we can use this information to help identify the jeans that are affected by drugs.

NOTE Confidence: 0.908709406852722

00:35:04.010 --> 00:35:05.510 Really providing the 1st.

NOTE Confidence: 0.919669091701508

00:35:06.520 --> 00:35:10.340 Insight into transcriptional mechanisms in the brain in Vivo.

NOTE Confidence: 0.923536956310272

00:35:11.300 --> 00:35:24.560 And then by analogy with the developmental biology and cancer biology fields, where certain types of epigenetic modifications that control. This opening and closing a chromatin once they occur permanent. We hypothesize that perhaps the same occurs.

NOTE Confidence: 0.918696165084839

00:35:25.060 --> 00:35:35.900 With behavioral experience that life experience produces similar types of permanent epigenetic changes in certain cells in the brain that drive these forms of emotional learning and memory.

NOTE Confidence: 0.909600138664246

00:35:36.500 --> 00:36:09.390 Let me tell you a little bit more about these mechanisms looking at this level of organization. Now the DNA or these gold stripes wrapped around these fibers the histone octamer's forming a nucleosome looking at one end of the spectrum where Chromatin is open or active. The other end, where it's condensed and inactive and we've learned a great deal about the biological mechanisms, controlling that opening and closing histones proteins themselves or modified in hundreds of ways. I'll give you examples a bit later through acetylation phosphorylation methylation and many others.

NOTE Confidence: 0.88328343629837

00:36:10.780 --> 00:36:19.400 Transcription factors like Delta Fosby and crab combine 2 areas of DNA that are relatively open where nucleosomes are not deposited.

NOTE Confidence: 0.888446390628815

00:36:20.200 --> 00:36:28.050 Where they then recruit other ends other proteins to form the transcriptional complex mediating transcription of RNA?

NOTE Confidence: 0.911813139915466

00:36:29.200 --> 00:36:37.690 Mechanisms of repression are equally complicated and all told, and simpler systems where it's been studied in stem cells and yeast cells for example.

NOTE Confidence: 0.916979551315308

00:36:38.210 --> 00:36:46.090 Hundreds of proteins are involved in coming together to activate 1 gene or to suppress a different Genomic region.

NOTE Confidence: 0.893657565116882

00:36:46.830 --> 00:37:17.860 So we decided little over a decade now to take advantage of open ended next. Generation sequencing technologies to back up and take a more open ended view of the molecular changes that drugs induce in the reward circuitry with the idea that we pluck Delta Fosb, Ian crib based on reasonable hypothesis. But they were candidate jeans. They were not based on truly open ended unbiased data and we felt it was essential to do the latter.

NOTE Confidence: 0.883534610271454

00:37:18.440 --> 00:37:23.340 So we've used RNA sequencing for example, to identify rnas that are up or downregulated.

NOTE Confidence: 0.905638873577118

00:37:23.980 --> 00:37:33.280 We would overlay that with Chrome and and measures by chip sequencing. Another approach is that I'll discuss looking at different types of histone another modifications.

NOTE Confidence: 0.909397661685944

00:37:33.860 --> 00:37:56.650 Doing chip sequencing or related approaches to measure binding sites of Crab Delta Fosby. Other transcription factors and so on. This is an enormous bioinformatic challenge generating terabytes of data but we feel that it's absolutely essential to have biology teach us? What jeans are the most important to study and I'll give you some examples of how we've used this approach.

NOTE Confidence: 0.884158611297607

00:37:57.690 --> 00:38:13.260 So about a year ago, a little over a year ago. Idina Walker, who's on her way to Oregon, an error in Calipari, who's at Vanderbilt were in my lab and published. This study where they had my self administer cocaine or Saline for a period of time.

NOTE Confidence: 0.879236876964569

00:38:13.950 --> 00:38:18.110 We took one cohort of animals the day after this last self administration session.

NOTE Confidence: 0.913491427898407

00:38:18.820 --> 00:38:23.360 We left the other animals sit in their home cages and live normally for 30 days.

NOTE Confidence: 0.874484479427338

00:38:24.050 --> 00:38:31.630 At that 30 daytime point we then gave animals in acute dose of cocaine or Saline and analyze the animals an hour later.

NOTE Confidence: 0.898352265357971

00:38:32.230 --> 00:38:42.590 I said there were 6 experimental conditions and we isolated six brain regions. All the major brain reward all the major components of the brain's reward circuitry.

NOTE Confidence: 0.912717819213867

00:38:43.180 --> 00:38:49.540 This 30 day withdrawal point is an important one because we know and animals and to a certain extent. It's been shown in humans.

NOTE Confidence: 0.882897436618805

00:38:50.210 --> 00:39:15.800 That incubation of craving occurs during this type of withdrawal so if one takes a mouse and puts it back in the Self Administration Cage. At that 24 hour. Timepoint turns off the Lever. My mouse compressed the lever, but it no longer gives cocaine the mouse still presses. The lever in presumably anthropomorphizing searching for the cocaine, but after 30 days, putting that mouse back in the chamber.

NOTE Confidence: 0.899520039558411

00:39:16.610 --> 00:39:20.450 There is a much greater response called incubation of cocaine Cravings.

NOTE Confidence: 0.903513312339783

00:39:21.210 --> 00:39:38.170 So this is an enormous data set RNA sequencing of six time points across six brain regions. I'm just going to show you a very small sliver of the data focusing only on nucleus incumbents where we've used machine learning to identify genes, particularly regulated at that 30 day withdrawal time point.

NOTE Confidence: 0.877774298191071

00:39:39.030 --> 00:39:45.800 So we ask the computer to tell us what genes are uniquely regulated up or down up as in yellow blue is.

NOTE Confidence: 0.886912941932678

00:39:46.300 --> 00:40:04.060 Down at the 30 daytime point withdrawal cocaine Self Administration Saline Challenge or cocaine self administration with an acute cocaine challenge for those of you who are not used to looking at these heat Maps each vertical line represents a single RNA.

NOTE Confidence: 0.897888422012329

00:40:05.560 --> 00:40:15.780 So here at the left, I can show you genes that are similarly uniquely altered up or down at either of these 230 day withdrawal conditions.

NOTE Confidence: 0.906416177749634

00:40:16.320 --> 00:40:21.890 And on the right those jeans in particular that are uniquely induced or suppressed by that.

NOTE Confidence: 0.891067564487457

00:40:22.940 --> 00:40:34.790 Challenge dose of cocaine, we would call these jeans that are in yellow to be primed. Most of them You see are not regulated by the first dose of cocaine the acute dose of cocaine that the animal receives.

NOTE Confidence: 0.90526157617569

00:40:35.420 --> 00:40:38.040 Or desensitized with the opposite phenomenon.

NOTE Confidence: 0.898351550102234

00:40:39.660 --> 00:41:06.190 Then we dug in to look at the behavior of individual mice and now in this heat map. I'm not showing you jeans. I'm showing you behaviors. We took on animals different aspects of pressing a lever and taking and seeking cocaine. Many dozens of behavioral measures an came up with what we call the addiction index with a big caveat that we don't know when a mouse is addicted, but it is showing a range of addiction related behaviors.

NOTE Confidence: 0.86206465959549

00:41:06.940 --> 00:41:23.010 And then we plotted here, then the behavior index diction index of the individual animals that self administered Saline or self administered cocaine. You could see the self animals itself administered sailing show low addiction index, which is what one would expect.

NOTE Confidence: 0.916676342487335

00:41:23.720 --> 00:41:42.400 And you see that the animals that self administered cocaine all meeting criteria for significantly self administering the drug showing actually a wide variation in that addiction response, even though these are genetically inbred mice. So this is looking at non genetic based differences, which we could talk about during the question period if you're interested.

NOTE Confidence: 0.749939441680908

00:41:42.920 --> 00:41:45.210 So Idina did next is then to ask.

NOTE Confidence: 0.869842708110809

00:41:46.460 --> 00:41:49.850 What jeans at that 30 day withdrawal time point?

NOTE Confidence: 0.864656627178192

00:41:50.790 --> 00:41:58.420 Or related to the addiction index, and I'm showing you examples here for 2 brain regions nucleus comments and ventral hippocampus.

NOTE Confidence: 0.888709843158722

00:41:59.020 --> 00:42:29.550 Showing jeans that are up regulated or down regulated by in these 30 day withdrawal time points that are significantly positively

regulated in red or negatively regulated in correlated in Gray with the addiction index. Let me just highlight 1 high level conclusion or hypothesis that we made from these data note? How a large portion of the jeans that are primed or desensitized at that 30 daytime point by a challenge dose of cocaine.

NOTE Confidence: 0.801557004451752

00:42:29.550 --> 00:42:31.370 We're regulated oppositely.

NOTE Confidence: 0.915199816226959

00:42:31.930 --> 00:42:36.430 In response to an animal's first ever exposure to cocaine.

NOTE Confidence: 0.892758011817932

00:42:37.220 --> 00:43:08.140 Very highly significantly regulated, too, and animals inherent addictiveness Interestingly, suggesting that an individual's addictiveness actually could be derived from their response to initial drug exposure, even though the changes that are induced by chronic drug exposure are very different opposite in some brain regions to what's seen acutely this pattern, it was most apparent in nucleus accumbens for example, not seen in Hippocampus and then we can go into these data and ask what transcription factors are.

NOTE Confidence: 0.899183034896851

00:43:08.140 --> 00:43:11.610 Would be expected to regulate these subsets of jeans?

NOTE Confidence: 0.891759157180786

00:43:12.290 --> 00:43:29.130 And you know, sometimes one is lucky in life because among the highest rank transcription. Factors are crab and AP one representing Fosby's family that was reassuring for our older older data but we also found many transcription factors.

NOTE Confidence: 0.909188151359558

00:43:30.440 --> 00:43:37.610 Most of which have never been studied in addiction models previously and if I have time I'll come back to one called the E2F family.

NOTE Confidence: 0.917351484298706

00:43:39.760 --> 00:44:04.650 Now everything that I've been talking to you about so far is showing you heat Maps of jeans that are significantly up or downregulated so-called differential gene expression analysis, but because of the magnitude of these datasets. We've been able to do much more complicated. Bioinformatics for example, different forms of Co expression network analysis working very closely with bin Zhang at Mount Sinai and one of his postdoc John show.

NOTE Confidence: 0.902862191200256

00:44:05.750 --> 00:44:07.940 This is depicting the entire.

NOTE Confidence: 0.90019303560257

00:44:08.580 --> 00:44:33.910 Transcriptome all rnas within the nucleus accumbens under control conditions how each RNA is related to one another just by correlations within our data set notice how cocaine dramatically alters the structure of that transcriptome really driving the genes to be much more tightly correlated. One can use cercos plots as shown here to look at different segments or branches of these trees called gene modules.

NOTE Confidence: 0.909555733203888

00:44:34.410 --> 00:45:04.230 To identify the modules that are most significantly altered by cocaine treatments and it provides ways to begin to digest enormous experiment so for example, Dina Walker in the lab is has a data set where she analyzed animals responses to acute and chronic cocaine, but comparing males and females. With those responses and also comparing normal animals to animals that have been stressed earlier in life.

NOTE Confidence: 0.876260101795197

00:45:05.380 --> 00:45:13.710 An enormous data set and I'm illustrating one aspect of that here showing that the ability of chronic cocaine to alter rnas.

NOTE Confidence: 0.924140572547913

00:45:14.410 --> 00:45:18.740 In the nucleus of comments of a male and female mouse under control conditions.

NOTE Confidence: 0.910028457641602

00:45:19.250 --> 00:45:36.010 Is quite different between the sexes notice the very different effects of cocaine under control conditions. But if one does this experiment in animals exposed to stress earlier in life. It obliterates most of these sex differences just to give you 1 example that we're now pursuing to understand.

NOTE Confidence: 0.906944870948792

00:45:39.420 --> 00:45:50.060 Now all the work that I've talked about thus far has been taking both dissections of nucleus accumbens and doing these molecular analysis, which is good as a start but we know that the nucleus accumbens.

NOTE Confidence: 0.870981931686401

00:45:50.680 --> 00:46:22.040 Contains about half neurons half glia of the neurons. Maybe 95% are called medium spiny neurons. The major projection neurons and there are 2 main types of projection neurons based on named by the dopamine receptor that they predominantly expressed. The D1 medium spiny neurons in the D2 Dopamine D2 medium spiny neurons and they've been shown to exert opposite effects on reward so for example, activation of D1 medium spiny neurons.

NOTE Confidence: 0.831379055976868

00:46:22.520 --> 00:46:28.260 Medically, or chemo genetically promotes drug reward activation of the two cells does the opposite.

NOTE Confidence: 0.862542152404785

00:46:29.140 --> 00:46:44.050 And using methods like fiber photometry. It's been possible to have an animal in. That's awake and behaving and responding to drug and be able to show that acute drug exposure activates D1 MSN's does the opposite to D2 MSN's?

NOTE Confidence: 0.873304843902588

00:46:44.730 --> 00:46:58.840 And that chronic drug exposure exaggerates these responses that are cell type different. These are just two of the papers done by Mary Kay Lobo and Aaron called party. My lab this work represents work by the field, many laboratories.

NOTE Confidence: 0.907480359077454

00:47:00.350 --> 00:47:15.350 So it becomes crucial to replicate these transcriptomic and molecular analysis on a more cell type specific basis. So more recently, Phillip Muse in the lab has begun to do this and this is an example of the data, he's accumulated.

NOTE Confidence: 0.902611613273621

00:47:17.000 --> 00:47:33.120 1st I'll show you data that's called a tax sequencing. I'm not going to define it. It basically reflects a way to identify regions of the genome that are open that don't have nucleosomes deposited so these are presumed active regions of chromatin.

NOTE Confidence: 0.872221529483795

00:47:33.840 --> 00:47:54.770 And one can identify that in control animals. The pink lines that the D2 mediums, finding neurons have many more open regions of chromatin than D1 neurons. That's consistent with the fact by the way that there are many more transcripts. Rnas expressed in D2 neurons and D1 neurons at rest.

NOTE Confidence: 0.861752152442932

00:47:55.560 --> 00:48:00.040 On centering these plots around this transcription start site and then looking genome wide.

NOTE Confidence: 0.858198404312134

00:48:00.590 --> 00:48:19.680 One can see then in the D1 medium spiny neurons in acute dose of cocaine really causes dramatic opening of chromatin within the genome wide that is maintained through 30 days of withdrawal and opened still further in response to that priming dose of cocaine.

NOTE Confidence: 0.877992212772369

00:48:20.240 --> 00:48:24.380 Notice the responses in D2 mediums, finding neurons are much smaller.

NOTE Confidence: 0.893542587757111

00:48:25.690 --> 00:48:55.980 This is showing the data the same exact data. But in a different way. Each horizontal line is now a different Genomic region showing you. The dramatic opening a chromatin that occurs in D1 medium spiny neurons across these acute and chronic conditions. Much smaller responses seen in D2 medium spiny neurons and it's possible to validate these data in the following way, so for example, I can show that we can show that the gene encoding. The D1 Receptor is active open has a lot of a taxi peaks.

NOTE Confidence: 0.814779579639435

00:48:55.980 --> 00:48:57.850 In D1 medium spiny neurons.

NOTE Confidence: 0.891195833683014

00:48:58.430 --> 00:49:07.360 Whereas the gene encoding the D2 Dopamine Receptor shows evidence of being active in D2 medium spiny neurons and not vice versa.

NOTE Confidence: 0.819860279560089

00:49:08.120 --> 00:49:15.820 These are genome wide data so one can go in and take a look at what any gene is how any gene is behaving so let's look at Fosby.

NOTE Confidence: 0.875283539295197

00:49:16.610 --> 00:49:33.610 Not surprisingly, fosby is induced it shows an opening by a taxi can response to acute cocaine. This opening persists. After 30 days of withdrawal consistent with the fact that Fosby is drive is one of these primed jeans.

NOTE Confidence: 0.879615664482117

00:49:35.120 --> 00:50:08.660 More recently, we've obtained RNA sequencing data separately for D1 and D2 mediums, finding neurons and consistent with the attack seek data showing that it is the D1 meaning spiny neurons that show a truly dramatic number of prime jeans in the chronic cocaine state that 30 day withdrawal followed by a cocaine challenge much weaker response is seen in the D2 medium spiny neurons. And when we ask? What are the upstream regulators of these prime jeans in D1 medium spiny neurons?

NOTE Confidence: 0.883398592472076

00:50:08.660 --> 00:50:13.110 Again, the E2F family of transcription factors comes up as highly regulated.

NOTE Confidence: 0.878773808479309

00:50:15.110 --> 00:50:20.270 The Top most prime gene the gene that's prime to the greatest magnitude.

NOTE Confidence: 0.73468291759491

00:50:20.780 --> 00:50:21.730 Is phosphate?

NOTE Confidence: 0.878637969493866

00:50:22.460 --> 00:50:25.290 As I said sometimes one is just lucky.

NOTE Confidence: 0.921616554260254

00:50:27.950 --> 00:50:39.080 And one can even go beyond doing these analysis on single types of cells to doing the analysis on single cells. So so called single cell RNA sequencing.

NOTE Confidence: 0.885148465633392

00:50:39.910 --> 00:51:00.180 The interesting Lee one can take dissection of nucleus accumbens sequence every cell that you isolate a nucleus accumbens have a computer identify the different clusters of cells color coded and then based on the genes that are expressed in those cells we can label them neurons.

NOTE Confidence: 0.869064450263977

00:51:00.680 --> 00:51:03.010 Astrocytes microglia and so on.

NOTE Confidence: 0.929799139499664

00:51:03.720 --> 00:51:09.390 But notice how the computer cannot differentiate D1 and D2 neurons.

NOTE Confidence: 0.896251142024994

00:51:10.080 --> 00:51:35.830 So the whole literature on striatum has focused on differences between D1 and D2 medium spiny neurons, which is not evident based on their transcriptomes. In fact, if one looks at expression levels of D1 and D2 receptors across these mediums, finding neurons. You can see rather broad distributions, suggesting that the main difference in this cell type is due to their circuitry, not inherent molecular features.

NOTE Confidence: 0.881760835647583

00:51:36.950 --> 00:51:45.160 One can dig even deeper we can isolate the D1 medium spiny neurons. The cell types that showing these dramatic prime responses to chronic cocaine.

NOTE Confidence: 0.901450395584106

00:51:45.830 --> 00:52:01.400 And ask the computer are there specific clusters embedded within and there are the computer identified over 20 clusters shown here. One cluster also expresses D2 receptors that's known a small subset of cells expressed both.

NOTE Confidence: 0.874391436576843

00:52:01.960 --> 00:52:07.490 And we identify the cluster of cells that are in Richton Fosby, another immediate early jeans.

NOTE Confidence: 0.930171966552734

00:52:08.060 --> 00:52:26.690 But I don't think that single cell sequencing is yet ready for prime time for the kind of work that we're doing where we want to understand a stimulus induced change in transcription for 2 main reasons first single cell sequencing can only identify 10% of the transcriptome. It's not deep enough to look at all transcripts.

NOTE Confidence: 0.921302974224091

00:52:27.600 --> 00:52:37.870 And I think this is just too much variability. I don't think there are 20 different types of D1 neurons. I think we're capturing neurons at different phases of activation or some other functioning.

NOTE Confidence: 0.93888795375824

00:52:38.740 --> 00:52:40.480 So that remains a work in progress.

NOTE Confidence: 0.940374910831451

00:52:43.780 --> 00:52:47.580 So what is driving this very long lived?

NOTE Confidence: 0.888528764247894

00:52:48.810 --> 00:53:01.070 Opening of chromatin in D1 medium spiny neurons after 30 days withdrawal from cocaine self administration in the old days, meaning up until 5 years ago.

NOTE Confidence: 0.915184557437897

00:53:01.690 --> 00:53:08.560 We would do chip sequencing for histone modifications based on what the field told us.

NOTE Confidence: 0.808064341545105

00:53:09.070 --> 00:53:09.920 Were important?

NOTE Confidence: 0.95644599199295

00:53:11.850 --> 00:53:19.700 But it turns out that there are hundreds of different histone modifications, which makes it impossible to really do a comprehensive analysis.

NOTE Confidence: 0.893134236335754

00:53:20.250 --> 00:53:27.180 So more recently, we've collaborated with Ben Garcia at Penn and one of his postdocs who's now at Albert Einstein Simones Adoli.

NOTE Confidence: 0.910757660865784

00:53:27.720 --> 00:53:38.940 To do a proteomic analysis on nuclei to identify which histone modifications are most dramatically altered under these different experimental conditions.

NOTE Confidence: 0.904072523117065

00:53:39.570 --> 00:53:53.820 Some of those data are shown to the right again. I mentioned several 100, so this is just showing you a very high altitude. Viewers subset of these findings. Let me show you the code, there are 4 known types of histone proteins labeled here by number.

NOTE Confidence: 0.869009852409363

00:53:54.320 --> 00:54:16.370 This refers to Histone H3 lysine 4, Mono Methylation and so on. Blue is down yellow is up and it's possible to identify several types of chromatin marks histone marks that are altered quite differently in the acute cocaine state versus the 30 day withdrawal state.

NOTE Confidence: 0.934080839157104

00:54:17.540 --> 00:54:24.040 And among the marks that are most statistically significantly highlighted.

NOTE Confidence: 0.831834316253662

00:54:24.560 --> 00:54:29.630 Is a mark called H3K79 Dimethylmethylation?

NOTE Confidence: 0.821968615055084

00:54:30.550 --> 00:54:34.120 Another histone variant called H2, a point Z.

NOTE Confidence: 0.843958795070648

00:54:34.770 --> 00:54:39.230 And if one digs into H2, one eight point Z it's particularly H28.

NOTE Confidence: 0.848930656909943

00:54:39.900 --> 00:54:43.740 Point Z acetylation that is dramatically altered differently.

NOTE Confidence: 0.778934478759766

00:54:44.370 --> 00:54:46.370 Acutely versus chronically.

NOTE Confidence: 0.869951367378235

00:54:46.880 --> 00:55:05.990 Now it would have taken us a really long time to get to K 79 demethylation in H2, AZ. They were way low on our list. I think it again underscores the absolute essential feature of using of letting biology teach you what's important, and look at.

NOTE Confidence: 0.891968488693237

00:55:06.500 --> 00:55:27.660 So we're now doing film, using the lab is now doing chip sequencing for these various histone modifications in an effort to identify

what we call chromatin scars. The idea being that chronic drug exposure scars chromatin. It creates changes in the chromatin architecture at specific genomic loci that are then near permanent.

NOTE Confidence: 0.917232155799866

00:55:29.050 --> 00:55:34.200 OneDrive these long lasting changes in gene expression. Let me just show you one example of some of these data.

NOTE Confidence: 0.817592203617096

00:55:34.830 --> 00:55:38.900 This is focusing on H2, AZ and H2, AZ acetylation.

NOTE Confidence: 0.845687627792358

00:55:39.470 --> 00:55:56.080 Doing chip sequencing on nucleus accumbens tissue showing that after acute cocaine. There is increased deposition of H2, AZ and H2, AZ acetylation. The acute being the green versus the pink control.

NOTE Confidence: 0.91400945186615

00:55:56.900 --> 00:56:00.340 But notice the dramatic depletion of these marks.

NOTE Confidence: 0.907191038131714

00:56:01.050 --> 00:56:16.070 After at the 30 day withdrawal time point barely detectable signals so again really highlighting and Validating. The findings from this open ended exploration, which we would not have gotten too without an open ended process.

NOTE Confidence: 0.936546564102173

00:56:22.520 --> 00:56:26.640 Everything that I've told you about today, so far has been correlations.

NOTE Confidence: 0.920385420322418

00:56:27.590 --> 00:56:41.160 One of the approaches that my lab has used over the years is to is the ability to establish causality and I want to demonstrate that with one example. This E2F family of transcription factors.

NOTE Confidence: 0.917526364326477

00:56:41.850 --> 00:56:55.590 Each have family has been widely implicated in the regulation of gene expression mostly in peripheral tissues. There have been very few studies in brain. Most studies in brain have focused on Olga Dendra sites on Mylan producing cells.

NOTE Confidence: 0.885014951229095

00:56:56.290 --> 00:57:13.780 However, based on these repeated datasets, where we continue with lease. Find the E2F family is being among the most highly predicted upstream regulators of primed and desensitized jeans. We decided to take a closer look.

NOTE Confidence: 0.87712299823761

00:57:14.420 --> 00:57:24.530 It turns out that about 1/4 of all prime desensitized genes in nucleus that companies have deduced E2F sequences within their upstream gene promoters.

NOTE Confidence: 0.870107293128967

00:57:25.630 --> 00:57:32.010 And this induction of E2F3 is selective for D1 mediums, binding neurons in response to cocaine.

NOTE Confidence: 0.85746568441391

00:57:32.510 --> 00:57:35.160 Not seen in D2 mediums, binding neurons.

NOTE Confidence: 0.899242341518402

00:57:36.340 --> 00:57:44.870 We're focusing on each have 3 because it's really the only family member out of 7 or so that expressed that appreciable levels in nucleus accumbens.

NOTE Confidence: 0.814095735549927

00:57:45.390 --> 00:57:47.320 Which expressed mainly in nerve cells?

NOTE Confidence: 0.883850753307343

00:57:48.250 --> 00:57:57.830 And there are 2 isoforms of this gene each have 3A which is the one that's regulated each have 3B which is not regulated and really barely expressed even in D2 nerve cells?

NOTE Confidence: 0.93154555591583

00:58:01.190 --> 00:58:10.190 So the approach that my lab has used over the years is one of viral mediated gene transfer in collaboration with Rachel Navy and colleagues at Massachusetts General Hospital.

NOTE Confidence: 0.869500696659088

00:58:10.950 --> 00:58:14.970 We would make viral vectors that either overexpressed each have 3A.

NOTE Confidence: 0.841310620307922

00:58:15.470 --> 00:58:23.580 Whorwood expressa micro RNA targeting the E2 of 38 M RNA and suppress that rnas translation.

NOTE Confidence: 0.891012728214264

00:58:25.030 --> 00:58:39.110 What we can show is that when we overexpress each have 38 in all nucleus accumbens nerve cells we can increase the rewarding response to cocaine. This is using a place conditioning assay for example.

NOTE Confidence: 0.901279747486115

00:58:39.900 --> 00:58:40.920 This is an effect.

NOTE Confidence: 0.827708899974823

00:58:41.560 --> 00:58:49.290 Exhibited by E2F38 with no effect seen when we overexpress the splice form that's not regulated E2F3B.

NOTE Confidence: 0.891727209091187

00:58:51.200 --> 00:59:07.300 Knockdown of E2F38 produces the converse effect now with a higher dose of cocaine that produces a significant place conditioning by itself. We can suppress that place conditioning by reducing it to have 3 levels again no effective to have 3B?

NOTE Confidence: 0.903689086437225

00:59:08.420 --> 00:59:13.380 And a similar effect of E 2 of 3 knockdown on decreasing cocaine self administration.

NOTE Confidence: 0.880994558334351

00:59:14.430 --> 00:59:37.170 This is work done by hand in case in the lab who is a graduate student and more recently for Edison Martinez has gone on to do this in a cell type specific basis now using viral vectors that expressed their trans jeans in a creative Pennant. Fashion express them in mice that expressed. Creina specific cell type showing that the ability of each have 3 overexpression to increase place conditioning responses.

NOTE Confidence: 0.806825637817383

00:59:37.690 --> 00:59:42.540 Is due to its effect in D1 medium spiny neurons not D2 medium spiny neurons?

NOTE Confidence: 0.844848930835724

00:59:43.790 --> 00:59:48.890 We can go beyond this for example, we can do RNA sequencing on the.

NOTE Confidence: 0.860823392868042

00:59:49.510 --> 00:59:53.740 Nucleus accumbens tissue where each have 3A is overexpressed.

NOTE Confidence: 0.880221545696259

00:59:54.390 --> 01:00:03.940 By heat map comparing the effect of chronic cocaine on up or down regulation of Rnas in nucleus accumbens and just asking a normal animal no drug.

NOTE Confidence: 0.891624391078949

01:00:04.790 --> 01:00:23.420 How are the same jeans affected by E2F3 over expression and you can see, there's an appreciable overlap statistics statistically shown with this RRHO rank right hypergeometric overlay approach highly significant coincidence of these 2 manipulations.

NOTE Confidence: 0.891389667987823

01:00:28.450 --> 01:00:48.880 One can then show that each have 3 overexpression also recapitulates a large fraction of the ability of cocaine to produce changes in alternative splicing of RNAs. Just very quickly. There are 4 major forms of RNA splicing each have 38 overexpression nucleus, Cummins recapitulating.

NOTE Confidence: 0.926722526550293

01:00:49.470 --> 01:00:51.840 A significant portion of each.

NOTE Confidence: 0.929201602935791

01:00:52.710 --> 01:01:00.600 In the interest of time, I'm going to skip over some slides here 'cause. I do want to leave some time for questions and we have to leave some time for George.

NOTE Confidence: 0.895331799983978

01:01:01.160 --> 01:01:04.340 To come back, I hope he has no more slides of Maine.

NOTE Confidence: 0.92570161819458

01:01:07.930 --> 01:01:11.560 To conclude that what I've shown you today is a?

NOTE Confidence: 0.937207221984863

01:01:12.090 --> 01:01:21.830 Very reductionistic approach to a problem like drug addiction that we know has very strong psychological social and cultural effects.

NOTE Confidence: 0.919755220413208

01:01:22.370 --> 01:01:33.090 Yet at its core we believe that addiction has a very strong biological component. After all, it reflects the ability of a physical substance certain type of drug to effect.

NOTE Confidence: 0.807394921779633

01:01:33.850 --> 01:01:35.000 A vulnerable brain.

NOTE Confidence: 0.905872225761414

01:01:35.660 --> 01:01:39.990 So we believe that the data sets that we're generating.

NOTE Confidence: 0.908332943916321

01:01:41.530 --> 01:01:50.330 Provide almost like a periodic table a template of all the genes that are being affected in the chronic cocaine treated state.

NOTE Confidence: 0.912616550922394

01:01:51.800 --> 01:02:07.820 Which then could be exploited for therapeutics remember I said at the outset that all of today's treatments focus on the very narrow range of proteins expressed at the synapse that where are smart enough now to study like a dopamine receptor or transporter?

NOTE Confidence: 0.916382551193237

01:02:08.450 --> 01:02:17.150 Not thousands, of other proteins that are expressed throughout the neuron, including hundreds of other proteins at the synapse, which could be viable drug targets.

NOTE Confidence: 0.92293518781662

01:02:19.730 --> 01:02:37.080 So with that let me just make a few conclusions. I showed you how the degree to which chronic cocaine exposure, particularly after long periods of withdrawal dramatically reorganized the transcriptome of specific cell types within the nucleus accumbens.

NOTE Confidence: 0.912871122360229

01:02:37.870 --> 01:02:53.120 I focused today on the nucleus accumbens but the work again underscores the importance of unbiased open ended investigation. We have data and data are needed for many regions within the brain's reward circuitry.

NOTE Confidence: 0.914298176765442

01:02:54.110 --> 01:03:03.650 We need to look well beyond D1 and D2 mediums, finding neurons to interneurons and several types of glial cells, which we also know are very important.

NOTE Confidence: 0.919014155864716

01:03:04.350 --> 01:03:14.120 And we need to look well beyond cocaine to other drugs of abuse and Kayla Brown, in my lab is now generating essentially parallel data sets for opioids.

NOTE Confidence: 0.905165612697601

01:03:15.170 --> 01:03:45.520 Scientifically my lab is most interested today in defining what we term chromatin and scars. The ability of experience in this case drug exposure to produce near permanent changes in the chromatin structure at particular. Genomic sites that mediate these long lasting changes in gene expression that are so important to driving a state of addiction and I gave you 1 example of how we establish that causality I'd skipped over.

NOTE Confidence: 0.91092449426651

01:03:45.520 --> 01:04:05.520 The more recently developed tools where we can manipulate chromatin states in an animal. In a single cell type at a single gene to really establish these causal mechanisms and the hope is that this would provide an unprecedented template for addiction treatments, so with that. Let me stop. I'll show you where I'm from.

NOTE Confidence: 0.899729013442993

01:04:06.140 --> 01:04:10.870 This is Mount Sinai on the Upper East Side right off Central Park.

NOTE Confidence: 0.911269545555115

01:04:11.500 --> 01:04:14.810 And that's where we live. Thank you very much.

NOTE Confidence: 0.189109086990356

01:04:24.400 --> 01:04:25.220 So.

NOTE Confidence: 0.682468056678772

01:04:26.390 --> 01:04:27.370 Sure, Yeah.

NOTE Confidence: 0.5702223777771

01:04:32.770 --> 01:04:33.290 Jane.

NOTE Confidence: 0.534623265266418

01:04:47.760 --> 01:04:52.740 Yes.

NOTE Confidence: 0.521982491016388

01:04:53.540 --> 01:04:54.160 But yeah,

NOTE Confidence: 0.753714025020599

01:05:01.200 --> 01:05:02.780 One yeah, yeah.

NOTE Confidence: 0.892159581184387

01:05:06.100 --> 01:05:10.090 Right yeah, so well So what I would say is that what makes.

NOTE Confidence: 0.858379125595093

01:05:10.890 --> 01:05:33.870 Foss be induced in D1 sells uniquely might not be anything inherent in D1 sells although there are differences, obviously, but it may be the circuitry and in fact, if we take a new quote. We've done this for years, taking their nucleus. Komban slice, adding cocaine are dopamine. Receptor agonist to a slice we don't get fosby induction.

NOTE Confidence: 0.878573834896088

01:05:34.710 --> 01:05:43.950 So we think that fosby induction and regulation of these other intracellular pathways requires ongoing glutamatergic innervation of the nucleus common cells.

NOTE Confidence: 0.904668927192688

01:05:44.480 --> 01:05:57.730 Like to establish these patterns so that you'd get differences between the cell types, even if the molecular constituents are largely the same. And they're not fully the same, so I do think there are intrinsic autonomous differences as well.

NOTE Confidence: 0.894561111927032

01:05:58.430 --> 01:06:00.460 But maybe not so prominently.

NOTE Confidence: 0.543470144271851

01:06:01.860 --> 01:06:03.050 Yeah, and.

NOTE Confidence: 0.575784921646118

01:06:09.490 --> 01:06:09.930 Right.

NOTE Confidence: 0.727608561515808

01:06:27.410 --> 01:06:27.790 Yes.

NOTE Confidence: 0.890461146831512

01:06:28.610 --> 01:06:41.260 I use the word permanent provocatively. We haven't done that experiment. These are all adult animals. Looking 30 days later. So you can assess and put an adjective on how Long live that is.

NOTE Confidence: 0.915016114711761

01:06:42.160 --> 01:06:59.690 But I guess the idea is that a discrete experience in adulthood can produce changes in chromatin that persist for a fairly long time. Even though you and I know that a large majority of the chromatin changes are very label.

NOTE Confidence: 0.912441372871399

01:07:00.530 --> 01:07:26.620 And that's where this open ended approach is so useful because it helps us focus in on those changes that really do persist and as one example during development. We know that do do signals that remain poorly understood. There are changes in a cell that produce its differentiation that then it becomes truly permanent and so our hypothesis is that perhaps behavioral experience produces similar Long live changes.

NOTE Confidence: 0.892080426216125

01:07:27.490 --> 01:07:28.510 Maybe not permanent.

NOTE Confidence: 0.788388252258301

01:07:30.060 --> 01:07:30.730 Yeah, in the back.

NOTE Confidence: 0.597039103507996

01:07:37.780 --> 01:07:49.010 Work with patients with drug use is a lot of.

NOTE Confidence: 0.618706941604614

01:07:52.490 --> 01:07:56.790 What they need?

NOTE Confidence: 0.441620588302612

01:08:02.050 --> 01:08:05.490 Anybody.

NOTE Confidence: 0.624781668186188

01:08:10.130 --> 01:08:14.360 Yeah, no, I agree.

NOTE Confidence: 0.869951665401459
01:08:15.110 --> 01:08:15.800 Absolutely.
NOTE Confidence: 0.171431630849838
01:08:17.810 --> 01:08:18.320 Runt.
NOTE Confidence: 0.532605886459351
01:08:20.950 --> 01:08:23.260 Right.
NOTE Confidence: 0.571620404720306
01:08:24.410 --> 01:08:25.180 Thanks Ron,
NOTE Confidence: 0.16274756193161
01:08:26.150 --> 01:08:27.370 So.
NOTE Confidence: 0.623883962631226
01:08:29.750 --> 01:08:30.580 Yes.
NOTE Confidence: 0.893041431903839
01:08:35.290 --> 01:08:50.310 Yes, absolutely so notice here is the idea that perhaps some of these epigenetic enzymes or other proteins that are mediating these long lasting changes could themselves be drug targets like a Jack inhibitors?
NOTE Confidence: 0.881265997886658
01:08:50.840 --> 01:09:00.950 The specific methyltransferase is I'm not going to go back and slides they specific methyltransferase is 4H3K79 demethylation for example.
NOTE Confidence: 0.922460854053497
01:09:01.470 --> 01:09:06.010 And there are small molecule inhibitors developed for most of these enzymes for the treatment of cancer.
NOTE Confidence: 0.900669157505035
01:09:06.760 --> 01:09:34.160 So it becomes feasible to begin to test that in patients with drug abuse. The challenges that the molecules that have made so far act throughout the body and are quite toxic and so we'll have to wait for molecules that are safe enough innocuous enough in normal people and then try them in a drug abuse population. But something we're very interested in doing manipulating these epigenetic. Enzymes has a dramatic effect on animals behavior and gene expression.
NOTE Confidence: 0.685865342617035
01:09:34.990 --> 01:09:36.580 Should we stop or?
NOTE Confidence: 0.811858713626862

01:09:37.280 --> 01:09:39.930 Thank you all very much.

NOTE Confidence: 0.860211968421936

01:09:51.600 --> 01:09:56.630 Uh it would only be fair now to invite George Henniger up to.

NOTE Confidence: 0.82548588514328

01:09:57.330 --> 01:09:59.670 Lecturing to make a few comments.

NOTE Confidence: 0.803991973400116

01:10:14.050 --> 01:10:29.590 Well, thank you. The committee that set this up. It's a real reward. Most of all I would like to thank my wife Julie.

NOTE Confidence: 0.849046289920807

01:10:35.940 --> 01:10:44.560 63 years when I made associate professor, he real my mother took me aside and said George.

NOTE Confidence: 0.890171825885773

01:10:45.160 --> 01:10:57.680 When you came home at 2:00 AM with the car smelling of Baron's tobacco smoke. We thought you'd never amount to much and I tried to explain the other guys roll and she interrupted and said.

NOTE Confidence: 0.781218886375427

01:10:58.390 --> 01:11:09.650 You know, George everything you've achieved is because of Julie Ann into mothers know their children might need.

NOTE Confidence: 0.845244705677032

01:11:10.390 --> 01:11:12.020 So thank you Julie.

NOTE Confidence: 0.808040261268616

01:11:12.570 --> 01:11:18.860 The I didn't wanna take a lot of time because even here, you've heard a lot.

NOTE Confidence: 0.823939085006714

01:11:19.620 --> 01:11:22.490 I just had to thoughts and.

NOTE Confidence: 0.928630173206329

01:11:23.340 --> 01:11:26.780 Having been here for 53 years there.

NOTE Confidence: 0.892030656337738

01:11:28.300 --> 01:11:35.150 The whole life of the mental Health Center. I wanted to say 2 things about the past.

NOTE Confidence: 0.710201442241669

01:11:35.940 --> 01:11:37.790 In the past is.

NOTE Confidence: 0.88737690448761

01:11:38.620 --> 01:11:40.470 Maybe summarized by.

NOTE Confidence: 0.489535272121429

01:11:41.050 --> 01:11:44.010 Um locks it Vera Tos.

NOTE Confidence: 0.899058699607849

01:11:44.810 --> 01:11:45.990 The University.

NOTE Confidence: 0.904739081859589

01:11:46.860 --> 01:11:59.690 The medical school in the Department and I've been here through 7 presidents who the University 8. Deans of the medical school and 7 chairman of the Department of psychiatry, but that.

NOTE Confidence: 0.898212552070618

01:12:00.420 --> 01:12:02.560 That model of light and truth.

NOTE Confidence: 0.533487975597382

01:12:03.460 --> 01:12:04.620 His prevailed.

NOTE Confidence: 0.856726825237274

01:12:05.170 --> 01:12:22.300 And that's that's what's carried his foreign so that's why this is a great place to study in its been fertile for main the main thing with the establishment of the mental Health Center by Fritz Redlich, an then governor Abraham Ribicoff.

NOTE Confidence: 0.787505567073822

01:12:22.870 --> 01:12:28.310 Um an I had a couple of quotes I won't go along on that, but

NOTE Confidence: 0.815594017505646

01:12:28.890 --> 01:12:33.880 This is a quote from Abraham Ribicoff.

NOTE Confidence: 0.903512716293335

01:12:34.480 --> 01:12:55.430 Let us evaluate are thinking about mental illness and how we have dealt with it. Let us ask ourselves are even the modest advances. We have made in recent years on the right track or do we need an entirely new point of departure? Are we exploring every possibility in innovation psychological social and biological and so.

NOTE Confidence: 0.854771018028259

01:12:56.430 --> 01:13:00.490 That that was the charter of the mental Health Center Ann.

NOTE Confidence: 0.785503268241882

01:13:01.110 --> 01:13:06.770 Few years later, Malcolm Bowers interviewed for its red look for the Department and then that that.

NOTE Confidence: 0.812661170959473

01:13:07.390 --> 01:13:13.920 That video is available in their Department website and Malcolm eyes doctor ever.

NOTE Confidence: 0.785781800746918

01:13:14.490 --> 01:13:16.920 What's your advice to us and Relic said.

NOTE Confidence: 0.794713377952576

01:13:17.760 --> 01:13:18.520 Science.

NOTE Confidence: 0.758633434772491

01:13:19.030 --> 01:13:24.940 Use science to be helpful at summarize the whole thing so.

NOTE Confidence: 0.921768605709076

01:13:25.470 --> 01:13:30.950 Between those 2 this center, which is the cornerstone of the Department it spawned.

NOTE Confidence: 0.7931267619133

01:13:31.620 --> 01:13:37.420 Overtime growth throughout until the modern Department.

NOTE Confidence: 0.654223740100861

01:13:38.090 --> 01:13:50.300 It's been my home an but but the ideal of of what Doc Governor Ribkoff said is still there.

NOTE Confidence: 0.854214370250702

01:13:50.860 --> 01:13:54.040 And so I won't belabor that and let me just say.

NOTE Confidence: 0.684709906578064

01:13:54.810 --> 01:14:00.660 Quickly, about the future, I do that. An.

NOTE Confidence: 0.819009959697723

01:14:02.120 --> 01:14:04.740 And thinking about it, you get old.

NOTE Confidence: 0.772801876068115

01:14:05.440 --> 01:14:06.160 And so.

NOTE Confidence: 0.857326209545136

01:14:06.730 --> 01:14:11.210 People here have had cancer in this auditorium.

NOTE Confidence: 0.884827315807343

01:14:12.110 --> 01:14:18.480 And people in this auditorium are going to get cancer and people in the Department have died of cancer.

NOTE Confidence: 0.876257359981537

01:14:20.100 --> 01:14:24.170 But but look across the street look at what they're doing and.

NOTE Confidence: 0.754701852798462

01:14:25.250 --> 01:14:29.750 That hospital OK there's progress and so.

NOTE Confidence: 0.888494610786438

01:14:30.260 --> 01:14:34.250 On TV last night cancer rates are dropping.

NOTE Confidence: 0.795707046985626

01:14:35.120 --> 01:14:37.990 Why not because of detection?

NOTE Confidence: 0.710019052028656

01:14:38.650 --> 01:14:40.790 Uh or prevention.

NOTE Confidence: 0.888401627540588

01:14:41.420 --> 01:14:45.340 It's for treatment and if you look at the trim, and what they've done.

NOTE Confidence: 0.73395574092865

01:14:46.390 --> 01:14:51.040 It is opened up a new field immuno therapy OK.

NOTE Confidence: 0.614228427410126

01:14:51.990 --> 01:14:53.700 Car car T cells.

NOTE Confidence: 0.774645745754242

01:14:54.310 --> 01:15:04.470 Checkpoint inhibitors there's a whole. These guys are good and so that's our that's our older sibling.

NOTE Confidence: 0.73894727230072

01:15:05.080 --> 01:15:08.270 About how to go about it so.

NOTE Confidence: 0.134558647871017

01:15:08.920 --> 01:15:09.460 Uh.

NOTE Confidence: 0.871739149093628

01:15:10.260 --> 01:15:20.500 Let me just say an example that illustrates that of where we are, and where we need need to go because I'm I really want to talk to the 30 year olds here.

NOTE Confidence: 0.835410535335541

01:15:21.000 --> 01:15:39.140 Who have their 53 years in the Department OK? I won't? But you will recent report of 22. Q 11 syndrome degeorge syndrome. The most prevalent genetic cause of schizophrenia got an animal model for that.

NOTE Confidence: 0.783827424049377

01:15:39.750 --> 01:15:40.550 They found

NOTE Confidence: 0.828061878681183

01:15:41.430 --> 01:15:46.330 Reduce gene expression of a factor that's an anti oxidant.

NOTE Confidence: 0.706501185894012

01:15:47.300 --> 01:15:48.710 Yeah, that was good.

NOTE Confidence: 0.911689400672913

01:15:49.300 --> 01:15:52.150 But the interesting thing is that they gave.

NOTE Confidence: 0.749142408370972

01:15:53.060 --> 01:15:57.140 And an anti oxidant.

NOTE Confidence: 0.823638141155243

01:15:57.670 --> 01:16:03.520 They given antioxidant to the developing animals an actually prevented the condition.

NOTE Confidence: 0.894499659538269

01:16:04.440 --> 01:16:07.070 There's another paper where they been able to prevent.

NOTE Confidence: 0.842953443527222

01:16:07.620 --> 01:16:09.610 Animal of Down syndrome.

NOTE Confidence: 0.850968897342682

01:16:10.460 --> 01:16:13.750 So it so if the Sciences that powerful.

NOTE Confidence: 0.823086678981781

01:16:16.810 --> 01:16:20.490 We just need to apply it here and so.

NOTE Confidence: 0.899685561656952

01:16:21.070 --> 01:16:22.950 I just say to the young people.

NOTE Confidence: 0.872409999370575

01:16:23.670 --> 01:16:27.690 This is extremely rich environment.

NOTE Confidence: 0.832160234451294

01:16:28.440 --> 01:16:40.420 So seize the opportunity and and let me start stand in your way because in your 53 years. You'll be able to make.

NOTE Confidence: 0.804833233356476

01:16:40.980 --> 01:16:49.400 Miraculous advances on Curzan Prevention, so thank you.