WEBVTT

1
00:00:00.390 --> 00:00:10.860
robert Lucas: Biological timing here in Manchester, and I wanted to just formally welcome you all to today's special seminar. Some of you at least one that we had hoped to the power

2
00:00:12.330 --> 00:00:19.500
robert Lucas: Showcase Summer Research day. So we'd booked out the lexicon and the Smith building and mud breakout area in the hill building and

3
00:00:20.100 --> 00:00:29.040
robert Lucas: We're looking forward to a day of science and conviviality and and then of course coven 19 happened and and then of course the hill building called fire.

4
00:00:29.580 --> 00:00:35.730
robert Lucas: And way things are going. We're just waiting for the samples to escape from the BSF so they can visit upon us a plague of frogs.

5
00:00:36.570 --> 00:00:44.760
robert Lucas: And but we are not disheartened. And it's been it's been a really great year lots of lots of exciting things happening and

6
00:00:45.660 --> 00:00:54.510
robert Lucas: Among other things to mention, of course, that that they've been five members of our community who are clinical scientists who've served time

7
00:00:55.200 --> 00:01:03.900
robert Lucas: On the clinical response to coven so thanks to them. We've also had a lot of really nice papers and grant funded and I can't go through all of them, but I wanted to mention

8
00:01:04.890 --> 00:01:15.330
robert Lucas: Just a few things for a personal level. So we've had three new five year independently funded research fellowship at Stanford and to new this year so

9
00:01:15.990 --> 00:01:22.800
robert Lucas: Congratulations to john shell to a net to Ricardo to David and Tim, for that great great achievement.

10
00:01:23.370 --> 00:01:32.610
robert Lucas: And and we very much continue that upbeat tone for for the seminar today, which we're delighted to to invite john forgive us.

11
00:01:33.150 --> 00:01:41.400
robert Lucas: And so some of you may have seen nature's nice guide last week on how to identify fake news in code stories.

12
00:01:41.850 --> 00:01:54.390
robert Lucas: And they gave some specific advice about being wary of information that was attributed to vague or untraceable sources such as, and I quote, a doctor friend of a friend or Dutch scientists

13
00:01:54.960 --> 00:01:55.380
Yeah.

14
00:01:58.980 --> 00:02:04.500
robert Lucas: John does have Dutch ancestry, but I'm pleased to say, is anything but vague or untraceable

15
00:02:05.460 --> 00:02:20.220
robert Lucas: And so we're delighted that covert has allowed us lab, the opportunity for him to visit us virtually and thanks to you all for taking time to come along and hear his seminar. And with that, I'll pass over to Andrew is going to share the same

16
00:02:23.010 --> 00:02:31.980
andrew loudon: Oh, thank you everyone for coming. And it's a wonderful audience and it's still growing. So I'm going to go on admitting people. So you're here clicks in the background.

17
00:02:33.150 --> 00:02:39.210
andrew loudon: But can I ask you all to mute your microphones. If you haven't already done so, and possibly switch off your videos.

18
00:02:39.630 --> 00:02:52.680
andrew loudon: And as we go through the seminar, please use the chat function at the bottom with any questions that arise that will I'll try and collate business we go ahead and that'll make it easier to draw a discussion at the end together.

19
00:02:53.580 --> 00:02:56.700
John Hogenesch: And drive to pop off for a second to share my screen. I have to

20
00:02:57.780 --> 00:02:59.340
John Hogenesch: Pop off for one second. I'll be right back.

21
00:02:59.460 --> 00:03:01.200
andrew loudon: It. Don't worry, I'll keep talking.

22
00:03:02.850 --> 00:03:14.850
andrew loudon: So while John's not care. I can tell. Some racy stories, but it's a real pleasure to welcome john is a personal friend of mine and I'm immensely distinguished scientist in the field of

23
00:03:15.510 --> 00:03:27.900
andrew loudon: Biological timing. He's currently a professor of pediatrics and Cincinnati and genetics chair systems biology and the Interim Director of Human Genetics at the Children's Hospital in Cincinnati.

24
00:03:28.440 --> 00:03:33.840
andrew loudon: And before moving there he was professor and vice chair of pharmacology at the University of Pennsylvania.

25
00:03:34.650 --> 00:03:45.210
andrew loudon: He did his PhD in Neuroscience at Northwestern University and as Robin said he was born in the Netherlands, but grew up in Gainesville, Florida and

26
00:03:45.990 --> 00:03:52.650
andrew loudon: He's back again. I can see now and I gather, Johnny, went to the same high school as Tom Petty who you all know.

27
00:03:53.190 --> 00:03:59.970
andrew loudon: Was the lead singer of Tom Petty and the heartbreakers and two members of the Eagles rock band in the same school and

28
00:04:00.600 --> 00:04:11.280
andrew loudon: Stephen Stills of Crosby, Stills and Nash, which really dates me so he it's remarkable school you went to john and I think you've offered to sing a song from one of the

29
00:04:11.970 --> 00:04:19.920
andrew loudon: Reps. And to do that song called honky tonk nighttime man, which is all about delayed sleep face syndrome. So, we expect that right at the end.

30
00:04:20.640 --> 00:04:33.000
andrew loudon: Thank you very much. John's had an outstanding career today, his lab studies genome biology, he's discovered early on in his career. Several of the new basic Felix.

31
00:04:33.510 --> 00:04:45.360
andrew loudon: Felix transcription factors including n past two female to roar alpha and of course female. One is the man that discovered female one and that's the gene that many of us use in our genetic studies.

32
00:04:46.290 --> 00:04:52.200
andrew loudon: He's had a wide interest in clock regulation and gene expression in plants flies nice man.

33
00:04:52.830 --> 00:05:05.760
andrew loudon: And as a genome biologist, he's managed to integrate the disciplines and particularly folks it in the area of circadian medicine, which of course is the current topic of this talk.

34
00:05:06.360 --> 00:05:13.500
andrew loudon: Is one of the highest cited scientists in the field. He's not doing 40,000 citations already and

35
00:05:13.890 --> 00:05:23.130
andrew loudon: He's running around about two and a half thousand citations, a year so that that just speaks volumes for this year, quality and interested what john has done.

36
00:05:23.430 --> 00:05:33.450
andrew loudon: And it's a real pleasure to hand over to you. JOHN and to ask you to speak. And I don't know if I need to click any buttons at this end or whether you can just shoot off.

37
00:05:33.720 --> 00:05:34.620
John Hogenesch: I think I can do it.

38
00:05:34.920 --> 00:05:35.460
andrew loudon: Okay, though.

39
00:05:38.460 --> 00:05:39.300
John Hogenesch: Are we good

40
00:05:40.260 --> 00:05:47.160
John Hogenesch: Yes. Looks good. Alright, so I'm Andrew and Rob asked me to talk about circadian medicine today. So I'm going to

41
00:05:48.240 --> 00:06:01.950
John Hogenesch: Right now I am the Division Director of Human Genetics at Cincinnati Children's Hospital, which is the US, the second largest pediatric hospital and as you mentioned, I'm going to talk today about genome biology and how it relates to the clock.

42
00:06:05.670 --> 00:06:13.170
John Hogenesch: So here's sort of a summary. I'm going to first give you a brief introduction into circadian rhythms. For those of you who are not experts in the field.

43
00:06:13.740 --> 00:06:24.420
John Hogenesch: Then I'm going to tell you really about several stories first that hospital medicine itself is rhythmic second that when you take your drugs can matter.

44
00:06:25.380 --> 00:06:31.800
John Hogenesch: Third, how we at Cincinnati Children's Hospital are pursuing circadian medicine with our buildings, how we're building our buildings.

45
00:06:32.550 --> 00:06:42.990
John Hogenesch: With our electronic medical records and how we're moving it on to our patients. I'm going to finish off with how we're learning about the clock from our patients.

46
00:06:46.980 --> 00:06:54.510
John Hogenesch: So our field got it started in the late 60s, early 1970s, based on the results of this fly biologists here see more Benzer

47
00:06:55.050 --> 00:07:06.720
John Hogenesch: Dr. Spencer was working with a graduate student run Kafka, and they had a heretical hypothesis. At the time, which was that the genetics influenced behavior. Remember it was the 16th.

48
00:07:07.560 --> 00:07:15.090
John Hogenesch: At the time, people felt that your environment really shaped how you turned out. If you grew up in a good house, you'd be a good person. If you grew up in a badass to be a bad person.

49
00:07:15.540 --> 00:07:24.510
John Hogenesch: And so they challenge this notion, with the fruit live so they set up a behavioral asking where they looked for flies that got up a little earlier every day.

50
00:07:25.320 --> 00:07:33.480
John Hogenesch: Like, type, type a flies and they they found them and then they realize that there was a genetic contribution they call those flights per short

51
00:07:33.960 --> 00:07:42.420
John Hogenesch: They also found flies that got up a little bit later. Every day called per, per long or per L and they found flies that were completely a rhythmic

52
00:07:42.990 --> 00:07:52.680

John Hogenesch: And when they did the genetics, they realized that all of those low side map back to the same chromosome. And because it was the early 1970s molecular biology really wasn't wasn't

53
00:07:53.640 --> 00:08:08.940
John Hogenesch: Smooth and it took 14 years for that Lucas to be really cloned by the by the Ross Bosch Hall and young labs and of course that was what was awarded the the 2017 prize and Physiology and Medicine.

54
00:08:09.990 --> 00:08:21.780
John Hogenesch: The Nobel Prize in Physiology of medicine went to those three researchers, but more or less. It all started based on the biology in the interest of this this a very famous BYE BYE. I'LL JUST SEE MORE adventure.

55
00:08:23.730 --> 00:08:26.640
John Hogenesch: So I can't really see you but, raise your hands if you have kids.

56
00:08:29.670 --> 00:08:42.600
John Hogenesch: So I this. This is really how most of us are acquainted with circadian rhythms. This is actually work from client and all following the local motor activity of the human infant from age three weeks. All the, all the way to age 26 weeks.

57
00:08:43.680 --> 00:08:52.020
John Hogenesch: And what you can see is that locomotor activity is really largely disorganized, the infant is awake in the in the

58
00:08:53.640 --> 00:09:06.540
John Hogenesch: With the white light bars and not moving with the dark bars so more or less randomly randomly trotting along here for, for the first several weeks and then they slip into a very long period rhythm.

59
00:09:07.590 --> 00:09:18.180
John Hogenesch: And right around this particular infant week 17 they snap into a circadian rhythm, where the infant's getting up more or less around 8am and going to bed or somewhere between seven and 8pm

60
00:09:19.440 --> 00:09:36.120
John Hogenesch: And so my colleague and I, at Penn my boots and and I made this into a greeting card and now when someone has a baby, we send them the card and we say you are here and week 17 is where life becomes livable. Just to remind them that yes it's horrible. But it's but it's also temporary

61
00:09:37.980 --> 00:09:48.900

John Hogenesch: That's, that's all true, actually. It's not just humans and flies that have rhythm. So it turns out that most organisms on the planet have rhythms cyanobacteria fungi Charles Darwin here had a rhythm.

62
00:09:50.010 --> 00:09:51.300
John Hogenesch: insects, birds.

63
00:09:52.680 --> 00:09:59.520
John Hogenesch: This frog Toad, I guess, plants and such. I have to be careful because Andrew got his degree in zoology, but you guys don't know that.

64
00:10:00.960 --> 00:10:12.120
John Hogenesch: So it turns out that most organisms on the planet have circadian rhythms, not all, there's a there's cave fish that lack 24 hour rhythms. Some of them have adapted longer rhythms like 48 hours or 12 hours.

65
00:10:13.380 --> 00:10:24.930
John Hogenesch: And they're apparently the reindeer does not have a circadian rhythm, because it lives at the very tip of the earth and seasonal cues are likely more important for its for it's a survival than daily cues.

66
00:10:26.010 --> 00:10:33.300
John Hogenesch: But for the most part, most organisms have rhythms. This includes students and postdocs, this is work from my colleague till Rosenberg

67
00:10:34.020 --> 00:10:44.850
John Hogenesch: from Munich, showing that that that sleep duration on your free days. Typically the weekends, but now during Cobra that could be almost any day and your work days.

68
00:10:45.600 --> 00:10:54.120
John Hogenesch: There's a huge gap so sleep, just to remind you, as a product have to sort of processes. The first processes. The, the homeostatic how much sleep you need

69
00:10:54.390 --> 00:11:06.360
John Hogenesch: And the second process is the timing of the sleep because you can't just randomly sleep throughout the 24 hour cycle. It's far more efficient if it's consolidated and that consolidation of sleep is regulated in part by the circadian clock.

70
00:11:09.360 --> 00:11:14.370
John Hogenesch: It's not just the sleep wake cycle and locomotor activity. It turns out that most of your physiology.

71
00:11:14.820 --> 00:11:21.330
John Hogenesch: Garrett Fitzgerald have shown several years ago that something like 63% of all physiological measures followed a circadian rhythm.

72
00:11:22.050 --> 00:11:38.940
John Hogenesch: Is includes core body temperature heart rate, blood pressure, your visa dilation platelet counts, a number of different hormones, including melatonin growth hormone and corticosteroid and lung function skeletal muscle function, etc. All sort of follow it. This is 24 hour rhythmic pattern.

73
00:11:40.620 --> 00:11:48.780
John Hogenesch: So here's a slide of ambulatory blood pressure monitoring a BPM. This is a really the gold standard for the

74
00:11:49.470 --> 00:12:06.420
John Hogenesch: For the diagnosis of hypertension. This is actually my blood pressure. Several years ago when I had at the time, four year old twins. And so there's this is this is my blood pressure taken every 15 minutes during the day and every 30 minutes at night for two consecutive days.

75
00:12:07.860 --> 00:12:18.210
John Hogenesch: So you can see that there's a couple of high blips here. I was at the time about 140 over 90 which was at the time just pre hypertensive now that's that's that's hypertensive

76
00:12:18.990 --> 00:12:30.000
John Hogenesch: According to last sprint trial. And so I'm on a antihypertensive now this is the twins bedtime. I was on the the entry level floor of our house and they were on the second floor. I wasn't even

77
00:12:30.330 --> 00:12:40.830
John Hogenesch: I wasn't even putting them down and you can see how to four year olds whining could get my blood pressure up. And of course there's minute morning commute, which was on the train and very civilized, but still got me going.

78
00:12:41.790 --> 00:12:55.110
John Hogenesch: But, more or less, you can see that there's a big dip during the shaded part this is really the the nighttime, the presumptive nighttime. And you can see that my plush my pressure actually dips quite a bit while I'm sleeping.

79
00:12:57.210 --> 00:13:04.440
John Hogenesch: About 2020 millimeters or so. And so it turns out that if you're a dipping hypertensive you have actually

80
00:13:05.130 --> 00:13:12.180
John Hogenesch: A much better prognosis than a non dipping hypertensive if you're a non dipping female, for example, over age 55

81
00:13:13.050 --> 00:13:25.530
John Hogenesch: You have four times likely to get a heart attack or stroke over the next 20 years than if you're dipping hypertensive and if you're a man, it's you're basically twice as likely to

82
00:13:26.190 --> 00:13:43.710
John Hogenesch: To have a heart attack or stroke over age 55 if you're a non dipping hypertensive so the bad news was I was slightly hide the good news. It was, I'm a Dipper and being a Dipper is is good for your a good prognosticator of your health in the next 10 or 20 years

83
00:13:46.920 --> 00:13:51.210
John Hogenesch: This is actually the molecular clock works that Andrew sort of briefly spoke about earlier.

84
00:13:52.590 --> 00:13:59.520
John Hogenesch: This the clock really is at its heart a transcription will translational feedback loop where two core activator is female and clock.

85
00:14:00.690 --> 00:14:10.680
John Hogenesch: bind DNA and regulate the expression of hundreds or thousands of output genes. These output genes include the period in Cryptochrome

86
00:14:11.250 --> 00:14:26.490
John Hogenesch: Proteins, you can see that the PR encrypted Chrome's form a complex with each other and with a number of kinases casing kind of one delta, for example, and the entire complex is actively imported into the nucleus.

87
00:14:27.630 --> 00:14:39.420
John Hogenesch: Where the PR and cry repress or complex eventually builds up and physically interacts with clock and female, resulting in clenching their transcription, including the transcription of the PR and cry.

88
00:14:40.410 --> 00:14:51.510
John Hogenesch: Structural jeans and then later in the cycle PR and cry are actively degraded by F box binding proteins and when they're active actively degraded that lets clock and female hop back on the DNA.

89
00:14:51.810 --> 00:14:58.560

John Hogenesch: Again and initiate a second round of transcription. So this is what we mean when we say the core, the core loop if you eliminate be now.

90
00:14:59.190 --> 00:15:04.860
John Hogenesch: You eliminate rhythms and physiology and the end behavior. If you eliminate clock and its partner.

91
00:15:05.160 --> 00:15:12.120
John Hogenesch: And pass to you eliminate rhythms and physiology behavior. If you eliminate per one per to rhythms are gone. If you eliminate cry and cry to

92
00:15:12.420 --> 00:15:22.050
John Hogenesch: Rhythms rhythms are gone. So all of these factors are required for normal rhythmic city of physiology and behavior, despite what you may have recently heard

93
00:15:27.150 --> 00:15:38.280
John Hogenesch: Um, just to remind you, biological clocks are are imprecise. So they're not they're not exactly 24 hours. And so to compensate for that we have, we have entertainment systems.

94
00:15:38.640 --> 00:15:45.600
John Hogenesch: And the principal and treatment of locomotor activity and sleep, for example, is light. So just to remind you, like is perceived through the eye.

95
00:15:46.080 --> 00:16:00.360
John Hogenesch: Through the retina, where there's two classes of photoreceptors image forming photoreceptors and a non image forming photoreceptor called melon option and these two systems collaborate to relay light information to a small nuclei in your hypothalamus called the hypothalamic polemic

96
00:16:01.530 --> 00:16:10.080
John Hogenesch: The Super charismatic nucleus of the of the hypothalamus and inside each one of these SDN neurons and also glial cells lives a core clock.

97
00:16:11.970 --> 00:16:16.200
John Hogenesch: That I just sort of spoke to you about what email and clock and PR one and part two.

98
00:16:16.950 --> 00:16:29.310
John Hogenesch: Which received this light information and and and sort of get become more accurate by by being in TRAINED EVERY DAY. So at this point, I'd like for you to take out your phones. If you don't have them out already.

99
00:16:33.450 --> 00:16:35.340
John Hogenesch: So if you go into your settings.

100
00:16:37.620 --> 00:16:38.640
Here, I'll do it as well.

101
00:16:39.660 --> 00:16:41.070
John Hogenesch: Turns out there is a

102
00:16:42.780 --> 00:16:45.690
John Hogenesch: A mode, both in Android and iOS.

103
00:16:46.710 --> 00:16:47.850
John Hogenesch: Under display.

104
00:16:49.200 --> 00:16:50.730
John Hogenesch: Called night shift mode.

105
00:16:53.070 --> 00:16:55.860
John Hogenesch: And so I have mine set from 10pm to

106
00:16:56.490 --> 00:16:57.420
7am

107
00:16:58.440 --> 00:17:13.380
John Hogenesch: Where it turns out your body's most sensitive to certain frequencies of light certain spectrum of light. And if you turn on night shift mode, it takes away some of the intensity and changes the color of the light in your phone and may get you a few extra minutes of sleep.

108
00:17:14.400 --> 00:17:20.100
John Hogenesch: So that's probably the most useful thing you're going to hear today. So if you want to drop off or read the paper or whatever, that's fine by me.

109
00:17:23.220 --> 00:17:30.120
John Hogenesch: Right, I'm going to switch to the sort of research portion of the talk, I'm going to tell you about four stories and this is the first story.

110
00:17:30.780 --> 00:17:47.820
John Hogenesch: And that is hospital medicine is rhythmic so when I got to Cincinnati Children's Hospital in 2016 I was interested in trying to exploit the electronic medical record to try to understand about drug timing and so we began to study how drugs are prescribed in the hospital.

111
00:17:48.900 --> 00:18:04.080
John Hogenesch: And one of our first really shocking results. Was this observation that that drugs are both ordered, which is the top panel here in orange and delivered, which is the bottom panel in gray.

112
00:18:05.520 --> 00:18:09.060
John Hogenesch: And a rhythmic pattern peeking in according to our to

113
00:18:09.090 --> 00:18:10.290
Aliz Owolabi, Edinburgh: Our to sort of shifts

114
00:18:10.740 --> 00:18:20.250
John Hogenesch: We have a we have a 7pm to 7am shift a 7am to 7pm shifts and a 7am shift to a

115
00:18:21.420 --> 00:18:32.310
John Hogenesch: Shift so overlapping shift. And it turns out that like every hospital and Western medicine. We have a practice called rounding where the physician and team go by the bed.

116
00:18:33.240 --> 00:18:39.750
John Hogenesch: And they look at the vital signs they interview the patient perform procedures and occasionally are more than occasionally

117
00:18:40.050 --> 00:18:50.460
John Hogenesch: Order medicines and it turns out that the spike in orders is right in the middle of this rounding period in red and the drugs are getting with a delay of a couple hours.

118
00:18:51.360 --> 00:19:00.690
John Hogenesch: Right around 11:11am. So it turns out that all these hydrology and orders I drowsiness antihypertensive it's used in an acute setting and skipping by IV.

119
00:19:01.980 --> 00:19:10.590
John Hogenesch: Are occurring with a occurring with a 24 hour rhythm in accord with the hospital shift changes and rounding times

120
00:19:11.610 --> 00:19:13.110
John Hogenesch: It's not just hydrazine.

121
00:19:15.180 --> 00:19:24.600
John Hogenesch: We've looked now at well over a dozen drugs and found that virtually all of them are both watered and given with the same rhythmic pattern.

122
00:19:24.990 --> 00:19:33.360
John Hogenesch: Picking between between 8am and 10am and a second shift change. The second sort of peak in the late afternoon between 4pm and 6pm

123
00:19:33.930 --> 00:19:44.970
John Hogenesch: And the drugs are the orders are placed to go down to the pharmacy, they're filled by the pharmacy. They go back up to the ICU or the floor unit and they're administered with a sort of with about a two hour delay or so.

124
00:19:47.070 --> 00:19:55.110
John Hogenesch: This is well and good for certain medications, but here are two classes where you don't want to have a rhythm and there's obviously an acute rhythm.

125
00:19:55.440 --> 00:20:07.500
John Hogenesch: The first is analgesics. So this is the the ordering unforced first doses of morphine on the top here and you can see that they they actually have a this this rhythmic pattern.

126
00:20:07.890 --> 00:20:14.040
John Hogenesch: And the bottom is see the management or Tylenol, same sort of pattern. They're both ordered and given with a circadian rhythm.

127
00:20:14.460 --> 00:20:21.240
John Hogenesch: But you don't want to treat pain selectively in the morning. In fact, people complain most about pain in the afternoon or evening and

128
00:20:21.930 --> 00:20:29.610
John Hogenesch: So you want to be vigilant for pain 24 seven. You don't want to be just paying specific attention to paint. Just, just because it's the Morning shift.

129
00:20:30.240 --> 00:20:35.610
John Hogenesch: So this is problematic. The second problematic piece is on the right hand side.

130
00:20:36.180 --> 00:20:43.830
John Hogenesch: These are this is vancomycin in the upper right hand painter panel that's a sort of last line antibiotic used to treat sepsis. And you can see that

131
00:20:44.400 --> 00:20:56.970
John Hogenesch: vancomycin orders and first doses are also given with this rhythmic pattern peaking between 8am and 10am and being givens between say 999 am and 11am

132
00:20:57.690 --> 00:21:08.940
John Hogenesch: But you don't want to treat sepsis in a circadian fashion, you know, treat sepsis. When the patient has signs of a bacterial infection. And so these are both areas of of

133
00:21:10.320 --> 00:21:20.730
John Hogenesch: Of interest for us. How can we operationalize procedures in the hospital that ensure that we give vancomycin at the first sign of infection and we treat pain.

134
00:21:21.540 --> 00:21:32.670
John Hogenesch: We treat pain more efficiently than just in the morning. So these are areas of growth for for our hospital and I bet you if you guys look in your hospital records yield more or less see the same sort of patterns.

135
00:21:35.100 --> 00:21:47.250
John Hogenesch: I started off this research by wanting to look at efficacy and we eventually got back to that. And I'm going to point out a couple things here. This is the lowering of diastolic and systolic blood pressure, according to the time in which the

136
00:21:47.820 --> 00:21:52.620
John Hogenesch: Drug is given, it has about a 15 minute half half life. So it's a very sort of quick acting drug

137
00:21:53.730 --> 00:22:12.960
John Hogenesch: And what you can see is that we've analyzed about almost 8000 people and for 8000 doses. And what you can see is that the the efficacy of the drug how well it lowers blood pressure varies by by by about 20% and it peaks in the at midnight.

138
00:22:14.070 --> 00:22:24.390
John Hogenesch: And there's also another peak 12 hours later at noon. So the drugs are more effective. THERE ARE BETTER BETTER ABLE TO this drug is better able to lower blood pressure at two times of the day.

139
00:22:25.620 --> 00:22:34.290
John Hogenesch: So this is also have interest in it, just to remind you, the, the effect sizes here. This is a 20% reduction and efficacy is similar to what seen with

140
00:22:34.860 --> 00:22:46.800
John Hogenesch: With pharmacogenomics. So not only does your Gina type affect how medicines work transport metabolism drug action, but also the time at which you give them can influence how well they work.

141
00:22:51.030 --> 00:22:59.160

John Hogenesch: Um, so this is really the tip of the iceberg. There's troves of available patient data on that are sort of out there if you look

142
00:22:59.520 --> 00:23:11.910
John Hogenesch: Over the course of the last say 70 years of of what are, what is called Kronos therapy or the study of time and how how procedures and drugs work there's been about a little bit over 100 different

143
00:23:13.080 --> 00:23:15.660
John Hogenesch: Hundred different studies in people and

144
00:23:17.100 --> 00:23:19.530
John Hogenesch: There's, there's a lot of

145
00:23:20.580 --> 00:23:31.470
John Hogenesch: Typically, these, these studies are not really well powered so most of the studies have only a few dozen people. Some of them have 100 and a few of them have almost up to 1000

146
00:23:32.220 --> 00:23:40.530
John Hogenesch: But the studies I just showed you. We had 8000 doses. So the electronic medical record what going after historical data.

147
00:23:40.950 --> 00:23:50.940
John Hogenesch: Is really at scale. And that's just our at our hospital system. If you think about all the hospitals in the world that have electronic records. You guys have been electronic released last decade in the UK. Correct.

148
00:23:52.560 --> 00:24:04.200
John Hogenesch: So there's just all this troves of data out there that have been sort of under exploited and so what I'd like to do is is really see the community begin to exploit this going to exploit these sort of data sets.

149
00:24:06.450 --> 00:24:18.810
John Hogenesch: So I'm going to go on to the next steps here a we want to analyze more drugs BB went to go multi site. So we began to collaborate with a very large hospital system on the West Coast called Providence St. Joseph

150
00:24:19.260 --> 00:24:29.430
John Hogenesch: Which is the fourth largest hospital system in the United States. So we are now working with them to see if the the findings that we have extend to adults different age groups, etc, etc.

151
00:24:30.060 --> 00:24:37.140

John Hogenesch: We've already done some pilot work with Jake up at Vanderbilt University where we've seen the same patterns and how drugs are ordered

152
00:24:37.410 --> 00:24:45.420
John Hogenesch: And given in their health system which is both adult and pediatric so we're very sure that this pattern is the same in all of Western medicine.

153
00:24:45.870 --> 00:24:52.260
John Hogenesch: And it has real implications for how the hospital operates and I'd like to invite any colleagues in Manchester.

154
00:24:52.830 --> 00:25:10.740
John Hogenesch: We have our institutional review board IRB protocol and we have our code to mine the data and produce the graphs already available and we're happy to give those to you and and really test really get take this, take this line of research international rather than just national

155
00:25:13.260 --> 00:25:18.510
John Hogenesch: The second story I want to tell you is when you take your drugs really matters. And this is work with my postdoc Mark Reuben.

156
00:25:19.290 --> 00:25:38.820
John Hogenesch: My partner in crime Dave Smith, who's asleep boarded a otolaryngologist and my former boss and current always friend Garrett Fitzgerald, who is a cardiologist by by training and and and former chair of the University of Pennsylvania, where I was for 10 years

157
00:25:42.570 --> 00:25:59.100
John Hogenesch: So this is research looking at a retrospective analysis of all all chronotherapy studies in humans between say 1960 and and this year. And so, turns out there's only a total of 160 human trials that tested more than one time.

158
00:26:00.390 --> 00:26:11.790
John Hogenesch: And every time it matters we marked in blue here in the study. And every time it didn't matter we marked in an orange. What you can see is that about 75% of the time.

159
00:26:12.480 --> 00:26:25.680
John Hogenesch: When you actually take your drug can influence how well it works in the middle panel, you're looking at the indications. So, hypertension, cancer, asthma dyslipidemia arthritis myocardial injury, heart attack allergy.

160
00:26:26.760 --> 00:26:32.370

John Hogenesch: So these drugs are really the most commonly prescribed drugs in in all of medicine.

161
00:26:32.940 --> 00:26:39.840
John Hogenesch: And if you look for a governing principle about what's able to predict whether or not the drug is going to have a time of day effect. It turns out

162
00:26:40.500 --> 00:26:47.670
John Hogenesch: That drug PK the half life of the drug, how long it's resident in your system is a is really the prognosticator

163
00:26:48.180 --> 00:26:55.470
John Hogenesch: So if the half life is, say for example, under, under say eight hours, it's very likely that when you take the drug is going to matter.

164
00:26:55.710 --> 00:27:05.730
John Hogenesch: If it's over, say 15 hours, it's very likely that the drug. Isn't that when you take the drug is not going to matter and that seems to be the governing principle and and how and how these

165
00:27:06.870 --> 00:27:10.320
John Hogenesch: How the how the timing of drugs works. Despite that,

166
00:27:11.880 --> 00:27:21.180
John Hogenesch: As far as I know, I used to be in Pharma and I've kept in touch with a number of groups, the phase one and phase two. A trials are not done by time of day.

167
00:27:21.690 --> 00:27:28.530
John Hogenesch: So even though we've known about this for going on seven years and it seems to matter about 75% of the time.

168
00:27:28.950 --> 00:27:42.840
John Hogenesch: Big Pharma continues to do their trials of their of their short half life drugs, the same way they always did picking a single time and not exploring whether or not one the drug is dosed influenced how well it was metabolized or

169
00:27:43.380 --> 00:27:47.970
John Hogenesch: Or whether or not it influenced how well it worked, which is a bit of a shame and

170
00:27:49.110 --> 00:28:03.450
John Hogenesch: But also a possible point of improvement. If for example if if Rob becomes the next head of JFK, he could, he could mandate that

all drugs with a short half life less than eight hours be tested at two times of day.

171
00:28:06.450 --> 00:28:15.450
John Hogenesch: Another interest of mine and I think Andrew briefly touched on it has been trying to understand not just where things are. But when they are

172
00:28:16.170 --> 00:28:29.910
John Hogenesch: And so starting at Novartis almost 20 years ago I began to develop these databases, looking at how genes were expressed in the human in the mouse and the rat according to what body site, they were taken from. So this early work the gene Atlas.

173
00:28:31.710 --> 00:28:33.870
John Hogenesch: Was about trying to figure out what tissues.

174
00:28:35.190 --> 00:28:37.860
John Hogenesch: These, these a genome was expressed

175
00:28:38.910 --> 00:28:43.020
John Hogenesch: But I was also interested in interested in what time they turned on.

176
00:28:43.980 --> 00:28:53.820
John Hogenesch: And so up starting like five or six years ago we we eventually circle back and looked at the intersection of where a gene is expressed

177
00:28:54.150 --> 00:29:02.100
John Hogenesch: And also when is expressed according to the circadian rhythm and you can see a couple of references down at the bottom. This was a penis paper in 2014

178
00:29:02.820 --> 00:29:09.300
John Hogenesch: And a Science Translational Medicine paper a couple years ago where we looked in humans at where and when drugs.

179
00:29:10.080 --> 00:29:19.830
John Hogenesch: Women all genes were expressed and it turned out that about about 1000 drugs are metabolized transported or act on a clock regulated gene product.

180
00:29:20.280 --> 00:29:27.750
John Hogenesch: So that's really the opportunity for our community is to is to follow up on these results and determine

181

00:29:28.230 --> 00:29:42.420
John Hogenesch: On which drugs should be given and at what time. And just to remind you may take 500 million to a billion dollars to develop a drug, but these types of studies study, trying to figure out what its best given are much cheaper and could have an immense

182
00:29:43.440 --> 00:29:47.280
John Hogenesch: Impact for for for for medicine and for health.

183
00:29:48.540 --> 00:29:57.420
John Hogenesch: So here's, here's one of our one of our sort of observations which was that 56 of the of the top 100 best selling drugs in the US and

184
00:29:59.040 --> 00:29:59.520
John Hogenesch: Were

185
00:30:00.600 --> 00:30:10.110
John Hogenesch: Were either metabolize transported or acted on a clock regulated product and this includes all kinds of indications. So really, it shows it shows that that

186
00:30:10.770 --> 00:30:21.690
John Hogenesch: The oscillator your biological rhythms could impact how how many different classes probably close to all of them may actually operate in the human body.

187
00:30:24.990 --> 00:30:32.010
John Hogenesch: Now, we were interested also in the study of humans and I mentioned the human results already what I did not tell you is how we did it.

188
00:30:32.910 --> 00:30:41.370
John Hogenesch: And so the way that we did. It was obviously we didn't kill people every two hours for two days because that would be illegal and unethical.

189
00:30:41.970 --> 00:30:44.490
John Hogenesch: So we had to figure out a way to look at human rhythms.

190
00:30:45.360 --> 00:30:49.290
John Hogenesch: In the absence of having really kinetic studies longitudinal studies.

191
00:30:49.530 --> 00:31:02.490
John Hogenesch: We can do longitudinal studies from the scan. Maybe we can do it from the blood, but for all the internal organs. We can't do

longitudinal studies. So we developed an algorithm that would enable us to do that called Cyclops and the way that it works is

192
00:31:03.630 --> 00:31:11.460
John Hogenesch: By taking advantage of this principle that if you have to, to, to have any kind of data. But in this case, this is gene expression data.

193
00:31:12.030 --> 00:31:24.090
John Hogenesch: Of two genes, a level three and up XM one that are half pie out of, out of phase. If you plot them one versus the other, they form this circle in the lower left hand corner.

194
00:31:24.600 --> 00:31:33.150
John Hogenesch: So here's your next one on the Y axis and Isla L three on the x axis and regardless of the order in which you plot this data.

195
00:31:34.230 --> 00:31:40.680
John Hogenesch: They form this circle so left hand panel is order data. You can see the two patterns there half pie out of phase.

196
00:31:41.370 --> 00:31:49.650
John Hogenesch: And you can see that if you plot the X versus why they form a circle, the right hand panel panel is an order to randomize data, you can see if there are no patterns here.

197
00:31:50.280 --> 00:31:59.610
John Hogenesch: But even though there are no patterns, the relationship between the two is preserved. So if you just randomly plot the data from the left. On the right hand panel. It's still forms the circle.

198
00:32:00.630 --> 00:32:06.360
John Hogenesch: And so once you have the circle. You know the relationship of every point with respect to every other point in the circle.

199
00:32:07.590 --> 00:32:15.060
John Hogenesch: And so this is how we've solved the problem of sampling from large data sets. It takes advantage of a

200
00:32:15.660 --> 00:32:23.550
John Hogenesch: Really of shift workers. So most people come in for procedures say they're coming in to have a liver biopsy, for example, and they come in during the day.

201
00:32:24.090 --> 00:32:33.600

John Hogenesch: But if we have about 150 to 200 people. There's going to be enough shift workers in that in that study for us to be able to order the data, at least in in

202
00:32:34.110 --> 00:32:50.430
John Hogenesch: In about about 14 different cases we've been able to order data from liver from kidney from skeletal muscle etc and based based solely on this principle of there's there's to pursue either jeans or principal components that are half pie out of phase.

203
00:32:51.900 --> 00:32:54.930
John Hogenesch: So here are rhythms and humor human liver drug targets.

204
00:32:55.290 --> 00:33:10.590
John Hogenesch: You can see in the upper left hand corner, there's a drug target called a GT R one. This is the target of the angiotensin receptor blockers. Here's some clock chains clock crying want and DDP here's dope. I mean, the car box lists, which is the target of the DDC is used to treat

205
00:33:12.000 --> 00:33:15.870
John Hogenesch: Parkinson's disease. You can see they're highly rhythmic here's a

206
00:33:17.100 --> 00:33:24.600
John Hogenesch: P P for for A and B and P five, um, they're all very rhythmic here's people are which is extremely rhythmic

207
00:33:25.530 --> 00:33:43.440
John Hogenesch: And lower right hand panel is a gene. I'm going to tell you about called Z Anthony dehydrogenase, which is also rhythmic prompted by this rhythmic pattern and human liver, we started working on studies of how this particular drugs that target that target.

208
00:33:47.310 --> 00:33:56.100
John Hogenesch: xanthan dehydrogenase maybe altered by time of day in an animal model. So we tested this and in the mouse.

209
00:33:57.180 --> 00:34:06.240
John Hogenesch: On this is with collaborators Lisa Metallica and Holland, Belgium and what we did was we dosed a mouse at two different time points and just remind you hear

210
00:34:07.200 --> 00:34:18.570
John Hogenesch: sth or is Anthony oxidase is an enzyme that convert typos anthem does chanting and has a second reaction at catalyzed his which is the conversion of xanthan to uric acid. This is on the upper hand pattern.

211
00:34:19.290 --> 00:34:33.030
John Hogenesch: Pattern. And so we use this drug allergy allopurinol which is used to treat hyper Yersinia such as in gout or tumor license syndrome or inflammatory bowel disease in an animal model and

212
00:34:34.260 --> 00:34:43.800
John Hogenesch: We toasted at at presumptive peak message and trough message probably also the product presumptive pea protein and peak.

213
00:34:44.940 --> 00:35:02.970
John Hogenesch: To trough protein levels. And so we dose of the drug at two different times and you can see if we stop the build up of of hypos Anthea to xanthan if we stopped that step, we should have a really an accumulation of hypos and thing and we do by giving it at the trough message level and

214
00:35:04.260 --> 00:35:13.920
John Hogenesch: You should also end up with the more xanthan if you're blocking the conversion of xanthan the uric acid. And that's also the case here, you can see that right over here.

215
00:35:15.150 --> 00:35:27.450
John Hogenesch: And the real critical result is. Can you lower uric acid levels because you're a cast is the compound that forms crystals, as in the case of gout or kidney stones and here we show that you can make you can more or less.

216
00:35:28.500 --> 00:35:29.160
John Hogenesch: Cars.

217
00:35:30.210 --> 00:35:37.740
John Hogenesch: Double the lowering of uric acid, simply by altering the timing of timing of the drug. So all the animals are the same. They're all fed the same in the same

218
00:35:38.010 --> 00:35:48.240
John Hogenesch: By a very M, et cetera, et cetera. The only difference here is the time of which you give the drug. And here you can see that drug works about twice as well by my work by getting the timing right so

219
00:35:48.840 --> 00:35:55.230
John Hogenesch: Our next study here is really this is all based on sort of the metabolites being profiled from from

220
00:35:56.100 --> 00:36:07.290
John Hogenesch: The periphery. We're actually now looking inside internal organs to see if we can we can actually observe the reduction of uric acid, specifically in the kidney. So that's our next sort of study.

221
00:36:09.540 --> 00:36:14.130
John Hogenesch: So I won't spend a lot of time on this, but there's been a lot of interest in

222
00:36:14.670 --> 00:36:24.240
John Hogenesch: In time stamping humans for obvious reasons. You could think about you can think about time stamping being valuable for phase disorders circadian sort of

223
00:36:24.480 --> 00:36:32.250
John Hogenesch: Sleep Disorders, but you could also think about it in terms of in terms of how can we make medicines work well again to remind you about a quarter of all

224
00:36:32.820 --> 00:36:43.950
John Hogenesch: Workers are on the shift now in the Western world. So about 20 to 25% of all workers are now shift workers and so even though it may say 12pm or or 6pm

225
00:36:44.340 --> 00:36:49.800
John Hogenesch: On the wall clock their body may be at a very different time. And so we and others.

226
00:36:50.490 --> 00:36:57.300
John Hogenesch: Are interested in this, in this in time stamping Human. Human beings, so we can so we can really understand their clock time

227
00:36:57.840 --> 00:37:12.720
John Hogenesch: Which is, in many cases, not similar to the time on the wall. I won't say anything further about this line of research, other than it's important. It's going on all over the place, including the UK and nobody really hasn't looked yet, but we're, we're, we're actually pretty close.

228
00:37:14.190 --> 00:37:20.400
John Hogenesch: So I'm going to finish off with explaining what we're doing at Children's Hospital to sort of take advantage of the circadian system.

229
00:37:21.150 --> 00:37:26.700
John Hogenesch: And so a children's we're applying these principles of circadian medicine to our buildings.

230
00:37:27.270 --> 00:37:34.620
John Hogenesch: With, for example, Circadian were lighting systems to our operational procedures when we give medicines for what conditions.

231
00:37:35.490 --> 00:37:47.040
John Hogenesch: When do we do when, when do we do feeding in some cases. And finally, ensuring our patients with unrecognized eating disorders are seen by specialists. So in August, which is, I guess, almost a

232
00:37:47.640 --> 00:37:56.310
John Hogenesch: Little bit over four weeks away will open the first circadian and complex sleep disorder clinic in pediatric medicine and the third clinic.

233
00:37:56.850 --> 00:38:09.870
John Hogenesch: And in the US. To date, the first clinic was opened at Northwestern University and Harvard has recently opened up a circadian clinic and we've opened the third clinic here in the first in pediatrics in Cincinnati.

234
00:38:12.150 --> 00:38:18.390
John Hogenesch: So we're going to start with building our buildings. So we're putting up a new 225 bed critical care building

235
00:38:19.080 --> 00:38:27.720
John Hogenesch: And I suggested to the to the faculty member who's responsible for this particular facility Jim Greenberg that

236
00:38:28.230 --> 00:38:38.250
John Hogenesch: That we might want to consider the lighting and I showed him several articles on on really how lighting systems can influence people's experiences. It's largely been done in behavioral medicine so

237
00:38:38.820 --> 00:38:46.080
John Hogenesch: Seattle, Swedish, for example, has developed one of these Children's Hospital of Philadelphia has their behavioral medicine unit.

238
00:38:46.770 --> 00:38:52.050
John Hogenesch: Really outfitted with these lighting systems that can give full spectrum light and also strong intensity

239
00:38:52.740 --> 00:39:00.000
John Hogenesch: So you can see the light goes. Here's bluish light. Here's sort of orange light. And here's sort of the natural light from the, from the outside.

240
00:39:00.420 --> 00:39:09.270
John Hogenesch: And so we built our lighting system to be able to go from from up to 10,000 Lux and clone any spectra that's visible outside

241
00:39:09.990 --> 00:39:17.370

John Hogenesch: So, for example, recently I was touring the hospital with somebody and I measured for for lux.

242
00:39:17.940 --> 00:39:32.250
John Hogenesch: In the Nick you extremely dense almost you can be almost can't see it yet need to adapt to that level of light before you can really form useful images and then I walked outside, even on a cloudy day was 4000 lux. So there's a huge a huge

243
00:39:33.900 --> 00:39:36.270
John Hogenesch: Huge change in the light levels in the hospital.

244
00:39:37.470 --> 00:39:46.020
John Hogenesch: So we're in the process of installing this lighting system in about 80 of 80 of the Nick you beds at of the hundred and 10 Nikki beds.

245
00:39:46.350 --> 00:39:53.160
John Hogenesch: And also we have 20 portable light systems to use them to pick you, and really what we're going to do is test the hypothesis that

246
00:39:53.850 --> 00:40:02.010
John Hogenesch: That natural lighting is is a is better than sort of the terrible hospital lighting that we've all seen when we've been in the hospital where

247
00:40:02.400 --> 00:40:07.140
John Hogenesch: God forbid been in the lab and noticed that the it's it's very harsh light.

248
00:40:07.740 --> 00:40:14.460
John Hogenesch: It's not very not very bright and it's not conducive really to working. And so we're going to test this hypothesis and build this

249
00:40:14.820 --> 00:40:23.430
John Hogenesch: The building the system and open up a bit a bit more than 12 months will be live and we're already starting to make decisions about

250
00:40:23.940 --> 00:40:27.060
John Hogenesch: The nursing teams educating the nursing teams and staff.

251
00:40:27.660 --> 00:40:41.370
John Hogenesch: Their natural reaction is to put a tent over an infant and really stop them from seeing natural light, but is that the right decision. There have been about, you know, a half a dozen studies or so that have shown that infants that have cycled lighting.

252
00:40:42.960 --> 00:40:47.280
John Hogenesch: Leave the Nikki, about two weeks faster than those that received dem dem bright light.

253
00:40:47.760 --> 00:41:03.210
John Hogenesch: The entire time. So we're hopeful that being able to really clone the natural lighting system will enable enable our infants to go home, happier and healthier than they would if we kept the same sort of archaic lighting systems. We have since hospitals first opened

254
00:41:05.220 --> 00:41:15.330
John Hogenesch: The second area that you may not sort of be aware of is is feeding. And so this is work with the bone marrow transplant unit a randomized crossover trial of restricted feeding.

255
00:41:15.810 --> 00:41:26.430
John Hogenesch: So it turns out that if you're getting a bone marrow transplant. You need to be sort of isolated away from the most of the staff and certainly the rest of the patients in the hospital because you may get an infection.

256
00:41:27.090 --> 00:41:37.530
John Hogenesch: And a lot of these patients are unable to feed for four weeks or even months at a time. And so what you do is you feed them through intravenously.

257
00:41:37.920 --> 00:41:44.550
John Hogenesch: called, it's called parental feeding total potential feeding all their calories, everything comes in through an IV line.

258
00:41:44.880 --> 00:41:55.260
John Hogenesch: And it turns out that these patients are either are either sort of fed 24 hours a day, which is bad, you know this from human studies or selectively at night.

259
00:41:56.070 --> 00:42:05.550
John Hogenesch: And so their peripheral clocks. For example, in the liver and the gut and the kidney etc are out of phase with their with their sort of behavioral clock.

260
00:42:06.120 --> 00:42:11.610
John Hogenesch: And as a consequence, probably. Turns out that almost all these patients have hypertension.

261
00:42:12.420 --> 00:42:20.250
John Hogenesch: So we're going to do is we're going to randomize the two groups, Dave, that a night bed and follow blood pressure on labs glucose monitoring.

262
00:42:20.550 --> 00:42:34.410
John Hogenesch: So counts met a metabolic sort of parameters body weight etc and test the hypothesis that feeding them in accord with their circadian oscillator during the day is better than feeding them either 24 seven or selectively at night.

263
00:42:37.500 --> 00:42:45.510
John Hogenesch: This last bit. I'm going to tell you about really boils down to the core interest of our labs or my lab, which is really the core oscillator

264
00:42:46.050 --> 00:42:58.710
John Hogenesch: And so, for example, we have cellular essays, where we can track how the clock runs and cells and selectively targeted gene either decreases expression as we've done here with beam out or put in another Leo of a female

265
00:43:00.630 --> 00:43:06.540
John Hogenesch: There are these amazing systems developed by people like David Welsh and Joe Takahashi where

266
00:43:07.230 --> 00:43:16.230
John Hogenesch: We have a mouse. It's engineered with the luciferase reporter and you're able to actually take tissues out of that mouse, put them in addition follow and follow really how

267
00:43:16.890 --> 00:43:32.220
John Hogenesch: How the circadian system behaves in a dish. And we also have these behavioral essays either running wheels and locomotor activity, or in the case below we could actually study the breathing and in first sleep using this piece of electric film. So these are really the tools of the trade.

268
00:43:34.200 --> 00:43:43.950
John Hogenesch: I'm going to argue that sleep timing is poorly understood. We only know a handful of genes that have been shown to regulate either sleep timing or sleep duration PR to PR three cry to

269
00:43:44.400 --> 00:43:51.120
John Hogenesch: Cry one CK one delta and deck to almost all this work has been done by the foo and Pathak labs at UCSF.

270
00:43:52.410 --> 00:43:55.020
John Hogenesch: Mike young actually recently showed that cry one

271
00:43:56.340 --> 00:44:02.910

John Hogenesch: Leland cry one about 1% frequency is responsible for for DSP is delayed sleep face syndrome.

272
00:44:03.540 --> 00:44:12.630
John Hogenesch: And our lab and the lab showed that there are humans that carry mutations in Dec two that are able to survive and thrive, even on five hours sleep.

273
00:44:13.110 --> 00:44:17.070
John Hogenesch: And not feel like like complete crap after two or three days.

274
00:44:17.490 --> 00:44:27.270
John Hogenesch: I was hoping there'd be something wrong with them. But it turns out they're perfectly perfectly happy. So there are there are short sleepers amongst us that can get by with very little sleep and nothing apparently bad seems to happen to them.

275
00:44:28.950 --> 00:44:32.430
John Hogenesch: So here's the bit about delayed sleep play syndrome in music.

276
00:44:32.940 --> 00:44:40.320
John Hogenesch: And this is one of my favorite bands, because I'm as I, as you guys mentioned, I was. I grew up in North Florida and just to the north of Gainesville as a city called

277
00:44:40.500 --> 00:44:47.730
John Hogenesch: Jacksonville, which you may have heard of. That's where the Republican National Convention is going to be held in about two months indoors, by the way.

278
00:44:49.770 --> 00:45:01.500
John Hogenesch: We'll have to see how that turns out. And one of their songs. It's an old Merle Haggard number is honky tonk nighttime, man. So here you can see here's the introductory line. I'm a hockey nighttime man this guy that likes to stay up at night.

279
00:45:02.070 --> 00:45:08.700
John Hogenesch: I can't stand the light I get my rest in the daytime and I go do my running around at night. So here's a person, which is clearly the SPS

280
00:45:09.510 --> 00:45:13.920
John Hogenesch: I had the blues this morning had the blues all day today. So he got up early and he was depressed.

281
00:45:14.430 --> 00:45:21.270

John Hogenesch: He wishes a tornado would blow those blues way, actually. You don't want the tornado to blow those blues away. It'll blow everything away, not just not just your blues.

282
00:45:21.900 --> 00:45:32.670
John Hogenesch: And then his heart starts beating when the sun starts thinking low. So we know that that blood pressure and heart rate begin to rise even before you're awake. And so here it is in music.

283
00:45:33.300 --> 00:45:41.040
John Hogenesch: By Leonard Skinner done, I highly highly recommend that you go listen to the tune on YouTube, don't, don't play the Merle Haggard version. It's not as good. This is a much better song.

284
00:45:42.540 --> 00:45:54.510
John Hogenesch: I would argue that children represent a ideal. Ideal platform for understanding the genetic basis of sleep, and that is because if you're an adult and you stay up until 2am

285
00:45:55.050 --> 00:46:06.690
John Hogenesch: Nobody really says anything you can do it all you want, but if you're a kid and you stay up until 2am your four years old, your mom is going to go to the doctor and she's going to say my four year old can't get to sleep for 2am

286
00:46:07.140 --> 00:46:13.170
John Hogenesch: And so these research opportunities are going to present themselves in the pediatric world much quicker.

287
00:46:14.160 --> 00:46:21.060
John Hogenesch: And so, so far we've we've enrolled over 50 families now and we've seen clear cases of D SPS

288
00:46:21.930 --> 00:46:33.540
John Hogenesch: Including a teenager. I'm going to tell you about a minute and also a circadian disorders and in in syndrome it kids. So this is there's a gene called emperor.

289
00:46:34.080 --> 00:46:42.150
John Hogenesch: Here's a map to K one here's NPR three part of the gator one complex and we've seen these circadian phenotypes and and really these three difference

290
00:46:42.780 --> 00:46:49.020
John Hogenesch: Least three different syndrome and disorders, all of which were not being seen by specialists. So that's really the the impetus for us.

291

00:46:49.320 --> 00:46:58.020
John Hogenesch: formulating this circadian and complex. Sleep Disorders Clinic was making sure that the syndrome of children who already have lots and lots of challenges don't face another challenge.

292
00:46:59.340 --> 00:47:06.300
John Hogenesch: According to their, their circadian rhythms and sleep needs. So we want to make sure that these children are seen by specialists.

293
00:47:07.350 --> 00:47:19.590
John Hogenesch: So here's a healthy 14 year old female who's local to Cincinnati, she she formerly went to sleep at 6am in the morning and slept into about 4pm which made school very challenging.

294
00:47:20.100 --> 00:47:36.810
John Hogenesch: And over a six month period, using the tools of the trade light therapy cognitive behavioral therapy, a face shifting dose of melatonin and Clonidine as a hypnotic my my collaborator in crime was able to get her toggled to 11pm to 7am

295
00:47:37.890 --> 00:47:48.330
John Hogenesch: We enrolled her in our protocol G back and found out that her dad was a shift worker and her grandmother was a shift worker so that always gets your attention when you see when you see a pedigree.

296
00:47:49.860 --> 00:47:59.760
John Hogenesch: A trio of individuals, all with the same sort of disorder. And so we sequenced the family. We did excellent sequencing. And we did, did the

297
00:48:01.500 --> 00:48:14.760
John Hogenesch: Did the genetics and saw that this particular gene CIA RT or Kronos was in this interval and it has a charged to uncharged change, which is a you know a big change.

298
00:48:16.020 --> 00:48:25.560
John Hogenesch: A few years ago now, our lab and Toyota cumings lab in Japan showed that this gene Kronos or or aka ca R T is a

299
00:48:26.610 --> 00:48:40.500
John Hogenesch: non traditional repressive of clock and email. So with displaces CBP and P 300 bonafide histone Trent a single transfer races and stops the activity of clock and beam out differently from how the cryptic rooms do it.

300
00:48:42.150 --> 00:48:48.060
John Hogenesch: And so we're in the process now of generating a crisper mouse and we've tested this illegal and culture. I just left a slide off.

301
00:48:48.390 --> 00:48:55.290
John Hogenesch: And showed that it does have a phenotype. And so, culture, and we're currently in the process of breeding up mice. Now after CRISPR

302
00:48:55.740 --> 00:49:06.000
John Hogenesch: Sort of put this puck in the net and we have a whole bunch of other families coming behind, and our goal is to understand sleep from the human side by studying children and their parents.

303
00:49:08.250 --> 00:49:15.390
John Hogenesch: So I'm going to skip this bit, because we've gone on for a while. So I'm just going to tell you one last story. This is about a disease called Smith kings more syndrome.

304
00:49:16.110 --> 00:49:23.760
John Hogenesch: Where there's a rare form of autism caused by activating mutations in EM tour these children have a lot of problems. But, notably

305
00:49:24.180 --> 00:49:33.210
John Hogenesch: The, the other LD learning disability and and developmental delay LD and DD, they also have larger heads and larger bodies. I'm towards involved in growth.

306
00:49:33.660 --> 00:49:46.050
John Hogenesch: And seizures and my, my partner in genetics here at Children's Carlos Prada decided he was going to test wrap up my son and MTR inhibitor to treat this overactive form of em towards seems obvious, right. But it hadn't been done before.

307
00:49:47.280 --> 00:49:57.000
John Hogenesch: And when he did that stuff, aggression, which is another sort of hallmark of these kids these kids actually don't hit themselves repeatedly and this child.

308
00:49:57.900 --> 00:50:06.630
John Hogenesch: His aggressions subsided, but a severe sleep problem emerged. So this is from the dad, we observed the sleeping pattern of seven to 10 days of good sleep.

309
00:50:07.170 --> 00:50:15.330
John Hogenesch: Another say week or so of okay sleep than a week week or so of terrible asleep, two, two and a half hours a night, and then a week of

310
00:50:15.720 --> 00:50:25.620

John Hogenesch: Okay, sleep again. So each cycle lasting around 24 days. This actually made me think about, is it possible that that that they've induced a circadian disorder in this child.

311
00:50:27.270 --> 00:50:29.820
John Hogenesch: And this is where things get weird and evolve Michael Ross Bosch

312
00:50:30.420 --> 00:50:40.320
John Hogenesch: So the dad, who's in Cincinnati decided to send a note to a whole bunch of sleep physicians, the only one who returned his email was in Montreal, the Montreal sleep doctor

313
00:50:40.890 --> 00:50:49.950
John Hogenesch: wasn't really a circadian specialist. So he sent the email to Michael Ross Bosch and Boston and Michael sent it to me and I walked across

314
00:50:50.700 --> 00:51:01.200
John Hogenesch: The Office and handed the case to Dave Who's this before to the empty and Dave handed handed the data paper that we wrote a couple years ago with Andrew Lou on em tour, then

315
00:51:01.590 --> 00:51:17.400
John Hogenesch: The dad handed the paper to Carlos product, who works about 50 meters away from me. So, this we went about three 3000 miles to close a 50 meter gap. It just, we weren't talking right then and but the good news is we now are and we have this kid sorted out, and several like in sorted out.

316
00:51:18.450 --> 00:51:27.090
John Hogenesch: So Andrew and I had shown in 2018 or so that rapamycin could cause a period lengthening and cells.

317
00:51:28.440 --> 00:51:39.870
John Hogenesch: Or knockdown of em tour with short hair pin RNAs, both of them produce a period lengthening themselves did. Oh, for the SDN if you gave rapamycin or were tested the SDN of a of a

318
00:51:40.470 --> 00:51:49.260
John Hogenesch: Heterozygous em tour mouse, the period length got long and the amplitude was reduced. And so our hypothesis was that

319
00:51:49.860 --> 00:51:58.260
John Hogenesch: In fact, even if you study. Look, look, a motor activity in these heterozygous mice, either in constant light or constant darkness, you find that the period length is LinkedIn.

320

00:51:59.010 --> 00:52:03.000
John Hogenesch: So our hypothesis is that if you give too much wrapping my son.

321
00:52:03.990 --> 00:52:13.620
John Hogenesch: You have little empty activity and you end up with the SPS if you have too much empty activity, you have this rare form of autism calls with things more syndrome.

322
00:52:14.130 --> 00:52:22.470
John Hogenesch: And so our idea is really can we use sleep as an output on probably with a Fitbit or with an activity of political activity unit.

323
00:52:22.800 --> 00:52:32.520
John Hogenesch: And really figured out what dose of them have rapamycin we need to really keep these kids balanced and so currently we've now made

324
00:52:33.360 --> 00:52:50.220
John Hogenesch: About 50 or so cell lines that that that with with patient specific mutations. We've actually made every patient's mutation with this disorder on earth and have them now operating in cells and we're in the process of generating an animal models for for these as well.

325
00:52:51.420 --> 00:52:57.120
John Hogenesch: And so here's an example of modeling a particular patient specific mutation. This is a deletion, a

326
00:52:57.900 --> 00:53:11.400
John Hogenesch: Three amino acid deletion here and you can see that when you delete these three amino acids. The, the period length gets long and the amplitude is reduced. So we're able to model this behavior, either in cells and soon mice, and we've

327
00:53:12.480 --> 00:53:17.550
John Hogenesch: We've started a we've started about seven patients now all over the US.

328
00:53:17.940 --> 00:53:29.790
John Hogenesch: On rapamycin and shown some improvements already, including the self aggression behavior, which is all but disappeared in our Cincinnati child, he doesn't he no longer hurts himself anymore. And he is sleeping.

329
00:53:30.300 --> 00:53:39.300
John Hogenesch: sleeping like a champ. So I'm hopeful that we'll be able to help this particular disorder. And just to remind you there's other empty properties.

330
00:53:39.960 --> 00:53:43.920
John Hogenesch: For example, there's the gator one complex was I mentioned earlier.

331
00:53:44.220 --> 00:53:56.190
John Hogenesch: Which is three different genes and and they have epilepsy and sleeping problems as well. So it's not just this rare disorder, there's much less rare disorders where this the same the same trick rap rap of my son and low dose rapamycin may work.

332
00:53:57.450 --> 00:54:10.980
John Hogenesch: So here's what finishing slide, nothing can be done by one lab or site anymore. I think anything truly worthwhile is is going to need cooperation across, across borders and across hospital systems.

333
00:54:11.880 --> 00:54:22.320
John Hogenesch: So I think it's long past time for us to work together on biomarkers on rhythms in hospital medicine and learning how the timing procedures and drugs in the hospital can influence how well they work.

334
00:54:22.920 --> 00:54:28.320
John Hogenesch: Different therapeutic intervention studies radiation surgery, for example, those are all but unstudied

335
00:54:28.740 --> 00:54:34.260
John Hogenesch: And then things like light food and temperature studies. Can we get the food timing right. Can we get the lighting correct in the hospital.

336
00:54:34.650 --> 00:54:39.270
John Hogenesch: And we're going to also need to go to government bodies and the US. A lot of these

337
00:54:40.080 --> 00:54:46.710
John Hogenesch: Procedures and a lot of these timing studies are regulated by the FDA. So we have to get them to really be cognizant of the clock.

338
00:54:47.040 --> 00:54:52.620
John Hogenesch: Still, if you look at a drug drug label it, it would say, taking the morning or taking the evening.

339
00:54:52.830 --> 00:55:03.480
John Hogenesch: Well that's well and good for you know 80% of the people, but that's not going to solve things for, the shift workers, right. So we need to relate things not to the morning in the evening, but rather take before bed take after waking

340
00:55:03.900 --> 00:55:07.860
John Hogenesch: Those are, those are simple steps that our community can have to have a

341
00:55:09.000 --> 00:55:18.360
John Hogenesch: Potentially massive, massive impact on on the world. And so I'd like to work with Andrew with banditos with Rob with with

342
00:55:19.050 --> 00:55:34.500
John Hogenesch: With you guys on on on getting the same type of regulatory and making these studies really happen instead of just going to conferences and talking about it actually do it would be great to work together with you. And with that, I'll take any questions you may have.

343
00:55:39.390 --> 00:55:42.720
andrew loudon: That's wonderful. JOHN. Do you want to undo this screen.

344
00:55:43.710 --> 00:55:45.090
andrew loudon: Sharing from your end

345
00:55:46.530 --> 00:55:49.200
andrew loudon: I hope, I hope people can hear me.

346
00:55:50.220 --> 00:55:58.620
andrew loudon: So what I'd like you all to do is a button for reactions on the bottom right, you can all click the click of a button. Now I've just clicked it

347
00:55:59.490 --> 00:56:07.440
andrew loudon: A sea of collapses emerging john electronic claps from all over the UK and elsewhere. That was a truly wonderful talk.

348
00:56:08.370 --> 00:56:18.900
andrew loudon: I've got a whole list of questions that have appeared on the the chat function, but just to kick off your last comments really strike home and as you may find

349
00:56:19.440 --> 00:56:33.120
andrew loudon: During the chat and also later by email, there's a lot of interest here in just these things so collaboration across boundaries and internationally. I think is definitely the way to go.

350
00:56:34.170 --> 00:56:42.750
andrew loudon: I've got just summarizing a couple of questions that are online here. One is this issue of finding the right circadian phase of an individual

351
00:56:43.800 --> 00:56:48.870
andrew loudon: We use mice, of course, which is terribly inbred and very specific to their period.

352
00:56:50.340 --> 00:57:03.840
andrew loudon: What, what is the actual natural range. Do you think of human circadian free running periods and how good is the technology to assess someone's face before you involve yourself in krone medicine.

353
00:57:05.520 --> 00:57:07.260
John Hogenesch: That's a tough question to answer.

354
00:57:08.910 --> 00:57:19.710
John Hogenesch: We don't typically don't have humans free running because it's not the right thing to do. We have taken human cells out into a dish and screened every gene and the genome.

355
00:57:20.130 --> 00:57:29.610
John Hogenesch: And the human clock is capable of operating between say 18 hours and about 35 hours or so. So that's sort of the operational limit.

356
00:57:30.120 --> 00:57:34.440
John Hogenesch: Above which we can't push things any further because there's it goes completely rhythmic

357
00:57:34.890 --> 00:57:46.590
John Hogenesch: And that's just at the cellular level. I don't know how that would work at the behavioral level. If you were able to put people in a cave for long periods of time and ascertain their, their period. Now, how accurate do we need to be

358
00:57:48.240 --> 00:58:06.600
John Hogenesch: Well, the ideal test would be a single time point test where we could infer the strength of the oscillator and your phase. And right now there are several methods that work on human blood. But when I like the most is really the Hakim Kramer study with the CD 14 positive

359
00:58:07.650 --> 00:58:11.730
John Hogenesch: Cells sorting the cells and then then looking by nano string.

360
00:58:13.290 --> 00:58:21.120
John Hogenesch: And that that works pretty well. If the person is phase between say 8am and midnight, but does not work well in the middle of the night.

361
00:58:22.140 --> 00:58:27.600
John Hogenesch: We've done a similar study taking human skin. Actually, the, the epidermis layer of the skin.

362
00:58:27.990 --> 00:58:36.240
John Hogenesch: And shown that it works pretty well as well but people are are afraid of needles and procedures. So that's not ideal, either. So my my gut is

363
00:58:36.870 --> 00:58:43.710
John Hogenesch: That we're going to need to have, you need to have a study and it's going to be need need to work across populations and across age groups.

364
00:58:44.070 --> 00:58:50.910
John Hogenesch: And so that's something that I think only the community can do together. I don't think we'll be able to solve it in a single laboratory or site.

365
00:58:51.390 --> 00:58:59.130
John Hogenesch: So I think that's room for room for improvement, our sort of fundamental limits now are facing people between two and three hours. That's really where the

366
00:58:59.460 --> 00:59:02.070
John Hogenesch: cutting edges with a single skin sample.

367
00:59:02.490 --> 00:59:15.030
John Hogenesch: Not good enough for circadian phase disorders, but probably good enough for administering drugs. So that's really our short term focus is to be able to face people well enough to make sure they're getting their antihypertensive etc at the right time.

368
00:59:15.750 --> 00:59:31.440
andrew loudon: Okay. And then another question that's come from a colleague Manchester's Gareth kitchen is issue of drug half life of course one of the challenges in medicine is to hit the target and avoid the bystander effect usually often hepatic related

369
00:59:32.670 --> 00:59:41.430
andrew loudon: So are we going to have to re engineer quite a lot of common drugs. So they've got shorter half light so that we can optimize treatment with minimum bystander effect.

370
00:59:42.870 --> 00:59:43.620
John Hogenesch: So that again.

371

00:59:43.920 --> 00:59:52.950
andrew loudon: Are we going to have to re engineer some of the major drugs that are in use, so that they have shorter half line so that we can optimize circadian treatments.

372
00:59:53.430 --> 01:00:08.610
John Hogenesch: That would certainly be attractive for for drugs that had a toxicity or unwanted side effects. You might be able to dial them out by getting by getting really the the the the pK correct. So that's an opportunity for drug discovery, I would say.

373
01:00:09.660 --> 01:00:14.460
John Hogenesch: repurposing an old drug with a with a short half life and using it appropriately.

374
01:00:15.630 --> 01:00:30.060
andrew loudon: Okay, and I've got another question here from Sue Kimber and colleagues about the question of constant light at night in hospitals and how how you tackle this while you're still allow the doctors to do essential interventions.

375
01:00:30.960 --> 01:00:38.040
John Hogenesch: Yeah, it's a tough one right. So that's what that was really the impetus for the lighting system that we mentioned that can can really do full spectrum.

376
01:00:38.520 --> 01:00:45.570
John Hogenesch: Between zero lux and 10,000 lux. Another issue is the light that's put off by machines. So even though the

377
01:00:46.230 --> 01:00:52.350
John Hogenesch: Philips electronics makes a lot of the medical equipment that we use. And they also make activity units.

378
01:00:53.280 --> 01:01:04.740
John Hogenesch: But it turns out that the wing that makes activity units Philips restaurants and the wings that makes the, the medical devices don't talk to one another. So you have these super bright blue and green.

379
01:01:05.130 --> 01:01:13.020
John Hogenesch: LEDs on the medical devices that are really, really bright and provide light constantly at night.

380
01:01:13.890 --> 01:01:20.670
andrew loudon: Okay, and then final question. I've got here is about babies for those of us that have had them in the past or have them at present.

381

01:01:21.840 --> 01:01:27.930
andrew loudon: Are they sensitive to light cycles in early life. The first 17 weeks. And what's the effect of light.

382
01:01:28.440 --> 01:01:34.800
John Hogenesch: It sure looks like they are. It hasn't been a super well studied arena. Like I said, there has been about

383
01:01:35.310 --> 01:01:39.390
John Hogenesch: Four studies that have looked at cycled lighting versus constant dim light.

384
01:01:39.810 --> 01:01:51.540
John Hogenesch: And they all found about a two week difference in the residency time in the nick you under cycled lighting conditions and I can send those references along if you need them. They also found things like reduction and crying.

385
01:01:52.200 --> 01:02:03.000
John Hogenesch: Better feeding when they had cycled lighting. A lot of the parameters that we actually do look at in the nick you are improved by the cycled lighting conditions. So they must be seeing it.

386
01:02:04.710 --> 01:02:20.400
John Hogenesch: At least at 28 to 30 weeks, it must be. But I, but I'm guessing it's really the entire time. If you take a flashlight and you put it up against your hand, you can see light and penetrate pretty pretty deeply at least a an inch or so of hand there.

387
01:02:21.600 --> 01:02:30.210
John Hogenesch: And it's likely that, that, that, in fact, I emailed a colleague recently asking if anyone had ever looked in sheep, and he was unable to tell me if they that

388
01:02:30.870 --> 01:02:36.330
andrew loudon: Well, I do apologize is the man who you contacted have worked, obviously.

389
01:02:37.530 --> 01:02:45.930
andrew loudon: My final comment is my feeling is that it's the responsibility for those of us in large medical faculty is like we are in Manchester.

390
01:02:46.320 --> 01:02:53.190
andrew loudon: Actually to think about starting to teach this stuff so that the younger generation of clinicians that go forwards.

391
01:02:53.910 --> 01:03:03.270

andrew loudon: Are aware of the importance of this area of science. And that's a huge challenge with a very cramped agenda and press time

392
01:03:03.600 --> 01:03:11.730
andrew loudon: And it's not a trivial issue, but it's something I think that we're all going to have to address or grapple with over the next 10 to 15 years

393
01:03:12.180 --> 01:03:22.080
andrew loudon: And maybe some international effort here. I think will be will be very useful since standard operating procedures for instance for conditions will be very handy.

394
01:03:22.770 --> 01:03:28.500
andrew loudon: I've been relying on the chat function. There are a few more questions there. If you have a pressing question to ask.

395
01:03:28.740 --> 01:03:43.650
andrew loudon: I suggest you put it forward to know because we need to move on to the next part of this shortly in which john is going to meet up with a smaller group of colleagues for a session. So if we don't have any major

396
01:03:45.120 --> 01:03:55.380
andrew loudon: Burning questions. Can I ask you again to thank john and give him another electronic Round of applause, with the hand signal and

397
01:03:55.860 --> 01:04:05.850
andrew loudon: I'd like to personally thank you john for the enormous amount of effort you put into this talk and giving us a really great overview of this important and growing area.

398
01:04:06.450 --> 01:04:06.870
John Hogenesch: Very well.

399
01:04:07.830 --> 01:04:24.450
andrew loudon: So those are the those of you that are involved in the next 12 sessions stay online and I'm going to disappear and thank all of you from all over the UK and elsewhere for taking part in this this wonderful talk. Goodbye.

400
01:04:28.260 --> 01:04:37.980
David Bechtold: I just wanted to say anybody who's joining myself and john afterwards I did set up a separate zoom give john a chance to get a drink.