WEBVTT

1 00:00:00.180 --> 00:00:02.030 <v ->My pleasure to present our next speaker,</v>

2 00:00:02.030 --> 00:00:05.340 Dr. Ranjit Bindra, who is an Associate Professor

3 00:00:05.340 --> 00:00:09.910 of Therapeutic Radiology here at Yale School of Medicine.

4 00:00:09.910 --> 00:00:12.310 Dr. Bindra is a graduate of Yale School of Medicine,

5 00:00:12.310 --> 00:00:14.340 so we are very proud of that.

6 00:00:14.340 --> 00:00:18.720 And he received his MD and PhD in this program.

7 00:00:18.720 --> 00:00:21.100 And he has also completed his residency

8 00:00:21.100 --> 00:00:24.690 in Radiation Oncology at Sloan-Kettering Cancer Center.

9 00:00:24.690 --> 00:00:27.700 Since then he has come back home and has been

10 00:00:27.700 --> 00:00:30.990 an extremely successful and accomplished physician scientist

11 00:00:30.990 --> 00:00:33.380 with many discoveries that are now finding their way

12 00:00:33.380 --> 00:00:34.880 to clinic.

13 00:00:34.880 --> 00:00:37.150 Today, he is going to talk to us

14 00:00:37.150 --> 00:00:41.670 about how he's exploiting some metabolic vulnerabilities

15 00:00:41.670 --> 00:00:46.260 in glimoas that have a BMP1D mutation.

16 00:00:46.260 --> 00:00:47.480 I give you Dr. Bindra.

17 00:00:47.480 --> 00:00:48.591 Thank you very much.

18 00:00:48.591 --> 00:00:50.841 (applause)

19 00:01:04.030 --> 00:01:04.863 <v ->Okay, great.</v>

20 00:01:04.863 --> 00:01:06.950 Thanks a lot for having me today.

21 00:01:06.950 --> 00:01:09.230 I want to tell you about a really interesting

22 00:01:09.230 --> 00:01:12.710 recent story from our group looking at DIPG mutation

23 00:01:12.710 --> 00:01:15.700 and its effect actually on any de-metabolism.

24 00:01:15.700 --> 00:01:18.310 These are my disclosures which are not relevant today.

25 00:01:18.310 --> 00:01:20.050 We'll start off just with one slide

26 00:01:20.050 --> 00:01:21.810 really on sort of our approach to

27 00:01:21.810 --> 00:01:25.280 novel therapeutics development here at the cancer center.

28 00:01:25.280 --> 00:01:26.700 We'll then move on to the story

29 00:01:26.700 --> 00:01:29.667 of a DIBG-associated mutation in this gene called PPM1D

30 00:01:29.667 --> 00:01:32.570 and how it actually affects a NAD metabolism

31 00:01:32.570 --> 00:01:35.500 and leads to a clinically actionable target.

32 00:01:35.500 --> 00:01:37.460 Then if time permits, we'll cover a little bit

33 00:01:37.460 --> 00:01:39.260 about how we're trying to translate this

34 00:01:39.260 --> 00:01:42.660 directly into the clinic like we've done before.

35 00:01:42.660 --> 00:01:43.570 So, just getting started.

36 00:01:43.570 --> 00:01:46.061 We are very interested in bench to bedside

37 00:01:46.061 --> 00:01:48.850 discoveries and studies in our laboratory.

38 00:01:48.850 --> 00:01:51.380 And a lot of it starts with looking at the landscape

39 00:01:51.380 --> 00:01:52.910 of tumor-associated mutations

40 00:01:52.910 --> 00:01:55.480 like the ones that are shown here.

41 00:01:55.480 --> 00:01:56.800 We like to look at those mutations

42 00:01:56.800 --> 00:01:59.690 and figure out rapid and effective ways to model them,

43 00:01:59.690 --> 00:02:01.970 so often we'll use Cripsr Cast,

44 00:02:01.970 --> 00:02:03.280 but often we'll just use things like

45 00:02:03.280 --> 00:02:05.060 simple open reading frame expression

46 00:02:05.060 --> 00:02:07.430 just so we can get isogenic modeling of each one

47 00:02:07.430 --> 00:02:08.940 of these mutations.

48 00:02:08.940 --> 00:02:10.800 We then move those model cell lines

49 00:02:10.800 --> 00:02:12.300 into synthetic lethal screens.

50 00:02:12.300 --> 00:02:15.500 Often we'll combine them with DNA damaging agents as well.

51 00:02:15.500 --> 00:02:18.090 One of the unique things that we're very, very interested in

52 00:02:18.090 --> 00:02:20.860 is trying to find the sort of Achilles Heels.

53 00:02:20.860 --> 00:02:23.520 So trying to find driver mutations that may induce defects

54 00:02:23.520 --> 00:02:26.322 that we can then exploit for therapeutic gain.

55 00:02:26.322 --> 00:02:29.140 We then move towards more patient-derived,

56 00:02:29.140 --> 00:02:31.556 more relevant cell line models to validate the effects

57 00:02:31.556 --> 00:02:34.250 from our screens and our isogenic cell lines.

58 00:02:34.250 --> 00:02:36.050 And of course we have to move this

59 00:02:36.050 --> 00:02:38.480 into flank and in vivo type modeling

60 00:02:38.480 --> 00:02:40.300 before we can actually move this into clinic.

61 00:02:40.300 --> 00:02:41.690 And finally, as I've mentioned earlier,

62 00:02:41.690 --> 00:02:44.030 we're very interested in trying to drive our discoveries

63 00:02:44.030 --> 00:02:45.480 as quickly as possible,

64 00:02:45.480 --> 00:02:47.890 namely into Phase 1 and Phase 2 trials.

65 00:02:47.890 --> 00:02:50.220 Brain tumors being the bulk of our work,

66 00:02:50.220 --> 00:02:51.880 often we have drug delivery problems,

67 00:02:51.880 --> 00:02:54.430 and so often we'll look to folks

68 00:02:54.430 --> 00:02:57.580 like the Saltzman Laboratory to explore alternate methods

69 00:02:57.580 --> 00:02:59.680 to deliver some of these drugs into the brain.

70 00:02:59.680 --> 00:03:02.184 And we've been working for quite some time

71 00:03:02.184 --> 00:03:03.780 with Mark's group on nano-particle versions

72 00:03:03.780 --> 00:03:05.960 of some of the drugs that we're studying.

73 00:03:05.960 --> 00:03:07.070 So with that sort of backdrop,

74 00:03:07.070 --> 00:03:10.090 let me give you a little overview of this story.

75 00:03:10.090 --> 00:03:12.070 First we need to start with DIPG.

76 00:03:12.070 --> 00:03:12.903 This is a disease

77 00:03:12.903 --> 00:03:14.741 that I am actually relatively obsessed with

78 00:03:14.741 --> 00:03:17.500 having seen my first patient at Sloan-Kettering

79 00:03:17.500 --> 00:03:19.860 and watching that 3-year-old patient die

80 00:03:19.860 --> 00:03:21.280 was really touching for me.

81 00:03:21.280 --> 00:03:22.842 For the clinicians in the room,

82 00:03:22.842 --> 00:03:25.390 you know these films quite well.

83 00:03:25.390 --> 00:03:26.540 For the non-clinicians,

84 00:03:26.540 --> 00:03:28.530 this is an Axial T2 MRI,

85 00:03:28.530 --> 00:03:29.770 and then this is just to orient you

86 00:03:29.770 --> 00:03:31.530 for the non-clinicians.

87 00:03:31.530 --> 00:03:34.170 This is very, very devastating tumor

88 00:03:34.170 --> 00:03:35.010 here in the brainstem,

89 00:03:35.010 --> 00:03:38.290 which largely can be regarded as the Grand Central Station

90 00:03:38.290 --> 00:03:39.720 for the human body.

91 00:03:39.720 --> 00:03:43.420 And these tumors literally will take a child's life

92 00:03:43.420 --> 00:03:45.170 within about 2 years.

93 00:03:45.170 --> 00:03:46.003 Okay?

94 00:03:46.003 --> 00:03:47.500 And a picture is worth a thousand words,

95 00:03:47.500 --> 00:03:49.450 and so I often like to show the pictures of patients

96 00:03:49.450 --> 00:03:51.590 that we've lost in our clinic to this disease

97 00:03:51.590 --> 00:03:53.800 to understand that we need to do something better.

98 00:03:53.800 --> 00:03:55.880 This child lasted about 2 years.

99 00:03:55.880 --> 00:03:59.960 On average, a patient with DIPG in 1990 would live

100 00:03:59.960 --> 00:04:01.230 about 9 months.

101 00:04:01.230 --> 00:04:02.570 How are we doing?

102 00:04:02.570 --> 00:04:05.740 So in the last 20 years, we're still at about 9 months.

103 00:04:05.740 --> 00:04:07.600 It's actually quite depressing.

104 00:04:07.600 --> 00:04:09.730 And one of the things to note here is that biopsies

105 00:04:09.730 --> 00:04:10.890 in this disease are quite rare.

106 00:04:10.890 --> 00:04:13.890 This is a very difficult area to get tissue,

107 00:04:13.890 --> 00:04:15.750 and so much of the treatments were based

108 00:04:15.750 --> 00:04:19.527 on diagnostic MRI images, then with the assumption

109 00:04:19.527 --> 00:04:24.140 that these are just baby versions of adult gliomas.

110 00:04:24.140 --> 00:04:26.080 Once we began biopsying these tumors,

111 00:04:26.080 --> 00:04:28.890 folks like Chris Coley in Neurosurgery Pediatrics here,

112 00:04:28.890 --> 00:04:30.630 who did a lot of these biopsies when he was a fellow

113 00:04:30.630 --> 00:04:32.840 up in Boston, we suddenly realized

114 00:04:32.840 --> 00:04:34.870 that these were not adult tumors.

115 00:04:34.870 --> 00:04:35.980 These were very, very unique.

116 00:04:35.980 --> 00:04:38.150 The spectrum mutations were quite different.

117 00:04:38.150 --> 00:04:40.420 Some of you may recognize one of these mutations.

118 00:04:40.420 --> 00:04:43.800 This is a H3K27M mutation that's found in

119 00:04:43.800 --> 00:04:46.130 about 80 percent of DIPGs.

120 00:04:46.130 --> 00:04:47.970 This gene mutation

121 00:04:47.970 --> 00:04:49.580 profoundly affects chromatin structure

122 00:04:49.580 --> 00:04:52.020 and leads to enormous range of gene expression

123 00:04:52.020 --> 00:04:53.530 and changes in the cell.

124 00:04:53.530 --> 00:04:56.830 But a subset of these, these tumors also have the mutations

125 00:04:56.830 --> 00:04:58.503 in a phosphatase called PPM1D.

126 00:04:59.520 --> 00:05:01.990 So what's the role of PPM1D in DIPG?

127 00:05:01.990 --> 00:05:03.600 We'll get to that in just a moment.

128 00:05:03.600 --> 00:05:06.590 What I'll tell you is, over the last 10 years or so,

129 00:05:06.590 --> 00:05:10.940 there's no known role in epigenetic regulation for PPM1D.

130 00:05:10.940 --> 00:05:12.900 So just zooming in on this mutation.

131 00:05:12.900 --> 00:05:15.300 This is a phosphatase as I mentioned.

132 00:05:15.300 --> 00:05:18.440 And in 2014, so five years ago,

133 00:05:18.440 --> 00:05:21.000 Hyan and colleagues at Duke showed that

134 00:05:21.000 --> 00:05:23.650 these mutations cluster in the C-terminal domain.

135 00:05:23.650 --> 00:05:25.450 They're heterozygous, and they're activating.

136 00:05:25.450 --> 00:05:28.810 So they lead to a hyper stable version of this phosphatase.

137 00:05:28.810 --> 00:05:30.950 And interestingly, even though

138 00:05:30.950 --> 00:05:33.360 this gene was implicated in DIPG 5 years ago,

139 00:05:33.360 --> 00:05:36.320 we've known about this gene for actually about 20 years.

140 00:05:36.320 --> 00:05:39.070 Actually back in '97.

141 00:05:39.070 --> 00:05:40.461 This gene was also known as

142 00:05:40.461 --> 00:05:44.260 Wild-type p53-induced phosphatase 1.

143 00:05:44.260 --> 00:05:45.950 So these are the same gene.

144 00:05:45.950 --> 00:05:48.100 And these genes are actually implicated

145 00:05:48.100 --> 00:05:49.670 in things like breast cancer

146 00:05:49.670 --> 00:05:51.840 as well as ovarian cancer and neuroblast

147 00:05:51.840 --> 00:05:53.380 and medulloblastoma.

148 00:05:53.380 --> 00:05:55.430 The difference is that the gene is actually amplified

149 00:05:55.430 --> 00:05:58.010 in these cases versus a hyper stable activation

150 00:05:58.010 --> 00:06:00.984 via the heterozygous mutation here.

151 00:06:00.984 --> 00:06:03.530 So what do these mutations do?

152 00:06:03.530 --> 00:06:05.580 So PPM1D is actually involved

153 00:06:05.580 --> 00:06:09.881 in dephosphorylating the SQT motif modifications

154 00:06:09.881 --> 00:06:12.260 induced by ATM and ATR.

155 00:06:12.260 --> 00:06:15.070 And these are the types of proteinst that are targeted

156 00:06:15.070 --> 00:06:16.490 by PPM1D shown here.

157 00:06:16.490 --> 00:06:19.257 One of the most commonly or well-established

158 00:06:19.257 --> 00:06:23.670 targets is H2AX, so hyperactive PPM1D actually leads

159 00:06:23.670 --> 00:06:26.060 to an accelerated dephosphorylation of H2AX.

160 00:06:26.060 --> 00:06:29.249 So it's thought to in principle disrupt the DNA repair

161 00:06:29.249 --> 00:06:30.888 and DNA response.

162 00:06:30.888 --> 00:06:33.580 So from our perspective, for our laboratory,

163 00:06:33.580 --> 00:06:35.490 there's sort of a fork in the road.

164 00:06:35.490 --> 00:06:37.950 How do we target these mutations, right?

165 00:06:37.950 --> 00:06:38.783 So on one end,

166 00:06:38.783 --> 00:06:40.617 we could just block aberrant phosphatase activity, right?

167 00:06:40.617 --> 00:06:42.970 And so those that know our lab and IDH1 story,

168 00:06:42.970 --> 00:06:45.020 we don't like doing that, okay?

169 00:06:45.020 --> 00:06:47.100 And there are drugs that have been developed.

170 00:06:47.100 --> 00:06:48.820 Actually for the last 10 or 12 years,

171 00:06:48.820 --> 00:06:51.000 there's about 3 or 4 drugs that have been developed

172 00:06:51.000 --> 00:06:53.430 that simply block the phosphatase activity.

173 00:06:53.430 --> 00:06:55.290 Most of them are not drug-like,

174 00:06:55.290 --> 00:06:56.570 none are in clinical trials,

175 00:06:56.570 --> 00:06:58.950 and overall they haven't been that effective

176 00:06:58.950 --> 00:07:00.920 as an anti-tumor strategy for tumors

177 00:07:00.920 --> 00:07:02.930 that have these types of mutations.

178 00:07:02.930 --> 00:07:04.100 So we're, again, very interested

179 00:07:04.100 --> 00:07:06.000 in exploiting Achilles Heels,

180 00:07:06.000 --> 00:07:08.649 or tumor-associated defects,

181 00:07:08.649 --> 00:07:11.950 hopefully by DNA repair given the role of this

182 00:07:11.950 --> 00:07:13.883 mutation in DNA repair.

183 00:07:14.860 --> 00:07:17.070 So with that, entered our first graduate student

184 00:07:17.070 --> 00:07:18.940 in the laboratory several years ago, Nate Fons.

185 00:07:18.940 --> 00:07:21.790 And Nate set out to model the PPM1D mutation,

186 00:07:21.790 --> 00:07:22.840 and to simply ask a question

187 00:07:22.840 --> 00:07:24.020 whether we could do a drug screen

188 00:07:24.020 --> 00:07:26.230 with an isogenic cell lines.

189 00:07:26.230 --> 00:07:27.910 So it actually took him about a year and half

190 00:07:27.910 --> 00:07:30.510 to make this model, and this is shown here.

191 00:07:30.510 --> 00:07:32.470 This is a truncated activated form.

192 00:07:32.470 --> 00:07:35.080 We targeted that C-terminal domain

193 00:07:35.080 --> 00:07:37.030 where the DIPG mutations are found.

194 00:07:37.030 --> 00:07:38.890 And you can see this hyper activated, or

195 00:07:38.890 --> 00:07:40.910 of high levels of expression by western blot.

196 00:07:40.910 --> 00:07:42.850 And he did all the things a good grad student should,

197 00:07:42.850 --> 00:07:45.550 which is looked at protein stability and confirmed indeed

198 00:07:45.550 --> 00:07:48.510 that this is a hyper stable form of the protein.

199 00:07:48.510 --> 00:07:51.200 And he did funcuatzie these to show

200 00:07:51.200 --> 00:07:53.630 that this mutation was active in the sense that

201 00:07:53.630 --> 00:07:57.020 post-IR could get an accelerated dephosphorylation of H2AX,

202 00:07:57.020 --> 00:07:59.660 and this was dependent upon PPM1D activity

203 00:07:59.660 --> 00:08:01.690 because treatment with a PPM1D inhibitor

204 00:08:01.690 --> 00:08:03.050 abolished that effect.

205 00:08:03.050 --> 00:08:05.800 And this is just a FOSI example shown here.

206 00:08:05.800 --> 00:08:07.500 Then Nate, after about a year and a half,

207 00:08:07.500 --> 00:08:10.300 or 2 years or so, went on to do a screen,

208 00:08:10.300 --> 00:08:12.140 and we used the platform that we developed

209 00:08:12.140 --> 00:08:14.610 to find the IDH induced PARP sensitivity

210 00:08:14.610 --> 00:08:16.800 that some of you heard me talk about before.

211 00:08:16.800 --> 00:08:19.449 This is a 96 well plate medium throughput

212 00:08:19.449 --> 00:08:21.760 viability screen that we developed.

213 00:08:21.760 --> 00:08:23.040 And we were super excited

214 00:08:23.040 --> 00:08:26.265 because our idea was that we were going to essentially get,

215 00:08:26.265 --> 00:08:28.990 IDH impairment sensitivity,

216 00:08:28.990 --> 00:08:31.640 PPM1D hyperactive dis-regulation of DNA repair,

217 00:08:31.640 --> 00:08:34.380 that we would get another hit in that class.

218 00:08:34.380 --> 00:08:36.377 So Nate looked at about 100 DNA repair inhibitors

219 00:08:36.377 --> 00:08:38.100 and DNA damaging agents.

220 00:08:38.100 --> 00:08:40.728 And to our surprise, we found nothing,

221 00:08:40.728 --> 00:08:42.260 which that was always really stressful

222 00:08:42.260 --> 00:08:43.420 when it's your first graduate student,

223 00:08:43.420 --> 00:08:45.200 and that's their screen after 2 years, right?

224 00:08:45.200 --> 00:08:46.690 So it's a tough thesis meeting.

225 00:08:46.690 --> 00:08:51.690 However, it turns out that we had one extra row

226 00:08:52.300 --> 00:08:53.460 in the 96 well plate.

227 00:08:53.460 --> 00:08:54.550 I just love telling this story

228 00:08:54.550 --> 00:08:57.530 because it's sort of the story of how academia often

229 00:08:57.530 --> 00:08:59.010 operates.

230 00:08:59.010 --> 00:09:02.190 We had one extra row, and I was actually doing the plating

231 00:09:02.190 --> 00:09:03.960 back in the day and the folks in my lab just said

232 00:09:03.960 --> 00:09:06.260 remind that I was in the laboratory, and

233 00:09:06.260 --> 00:09:07.960 I actually had plated, we had one extra row

234 00:09:07.960 --> 00:09:11.510 and we put in some NAMPT, a NAMPT inhibitor row

235 00:09:11.510 --> 00:09:13.940 based on a paper by Dan Cahill up in Boston.

236 00:09:13.940 --> 00:09:15.500 He had shown that IDH mutations,

237 00:09:15.500 --> 00:09:17.570 again our laboratory is very interested in those,

238 00:09:17.570 --> 00:09:19.290 those mutations as well.

239 00:09:19.290 --> 00:09:21.750 He had shown that IDH mutations confer sensitivity

240 00:09:21.750 --> 00:09:23.634 to the NAMPT inhibitors

241 00:09:23.634 --> 00:09:25.582 via this NAD depletion phenotype.

242 00:09:25.582 --> 00:09:29.460 And this is the drug we added to this, this set of plates.

243 00:09:29.460 --> 00:09:31.650 Oddly enough, that was the only hit in our screen,

244 00:09:31.650 --> 00:09:33.363 which was very surprising to us.

245 00:09:34.240 --> 00:09:36.880 So what is NAD, and what are NAMPT inhibitors?

246 00:09:36.880 --> 00:09:38.170 This is a pathway.

247 00:09:38.170 --> 00:09:39.790 Again, when we worked on the IDH stuff,

248 00:09:39.790 --> 00:09:41.670 we actually had to relearn the citric acid cycle,

249 00:09:41.670 --> 00:09:44.380 and here we had to learn about NAD

250 00:09:44.380 --> 00:09:45.730 during the course of this work.

251 00:09:45.730 --> 00:09:48.340 And this is the NAD sort of cycle,

252 00:09:48.340 --> 00:09:50.530 and there's multiple different ways to generate NAD

253 00:09:50.530 --> 00:09:52.900 which is sort of the central currency of life

254 00:09:52.900 --> 00:09:55.110 in a metabolizing cell.

255 00:09:55.110 --> 00:09:57.607 And so the first thing we did was actually just

256 00:09:57.607 --> 00:09:59.040 cold called a guy named Charlie Brenner.

257 00:09:59.040 --> 00:10:02.170 He's out at Iowa, and he discovered a very, very

258 00:10:02.170 --> 00:10:06.490 critical pathway in the NAD biosynthetic pathway.

259 00:10:06.490 --> 00:10:07.650 And we called and we said

260 00:10:07.650 --> 00:10:09.160 we've got this very odd

261 00:10:09.160 --> 00:10:12.080 PPM1D induced NAMPT inhibitor sensitivity,

262 00:10:12.080 --> 00:10:13.050 can you help us out?

263 00:10:13.050 --> 00:10:14.430 And just to orient folks,

264 00:10:14.430 --> 00:10:17.780 NAMPT is a critical player in the NAMPT salvage pathway

265 00:10:17.780 --> 00:10:21.930 that essentially regenerates NAD and it's

266 00:10:21.930 --> 00:10:24.620 blocked by these drugs called NAMPT inhibitors.

267 00:10:24.620 --> 00:10:26.050 So just sort of Cliff notes, and again,

268 00:10:26.050 --> 00:10:27.820 aging myself by using Cliff notes

269 00:10:27.820 --> 00:10:29.660 because I know about 90 percent of the audience

270 00:10:29.660 --> 00:10:31.000 does not know what these are.

271 00:10:31.000 --> 00:10:32.620 Nut these were very, very useful

272 00:10:32.620 --> 00:10:34.220 before the days of Google.

273 00:10:34.220 --> 00:10:36.610 And so NAMPT inhibitors are interesting drugs.

274 00:10:36.610 --> 00:10:38.490 There's actually a diverse range of drugs out there.

275 00:10:38.490 --> 00:10:39.830 They're highly potent.

276 00:10:39.830 --> 00:10:42.500 They've actually been tested in Phase 1 and 2 trials.

277 00:10:42.500 --> 00:10:44.420 There's still a few

278 00:10:44.420 --> 00:10:45.660 drugs that are being tested.

279 00:10:45.660 --> 00:10:47.080 Most have actually been shelved

280 00:10:47.080 --> 00:10:48.890 because there really is no biomarker.

281 00:10:48.890 --> 00:10:50.210 There's actually a lot of toxicity

282 00:10:50.210 --> 00:10:52.600 in the face of limited efficacy.

283 00:10:52.600 --> 00:10:54.050 So with that sort of backdrop,

284 00:10:54.050 --> 00:10:56.900 Nate went on to probe this interaction further.

285 00:10:56.900 --> 00:11:00.360 He first ruled out any clonal artifact from CRISPR,

286 00:11:00.360 --> 00:11:02.100 and he showed a multiple CRSPR clones that

287 00:11:02.100 --> 00:11:05.350 we had very nice NAMPT sensitivity in the PPM1D mutants.

288 00:11:05.350 --> 00:11:06.930 He then showed it was a class specific,

289 00:11:06.930 --> 00:11:08.650 not just a drug effect.

290 00:11:08.650 --> 00:11:10.710 He showed that with multiple, structurally unique

291 00:11:10.710 --> 00:11:12.500 NAMPT inhibitors that we could still get

292 00:11:12.500 --> 00:11:16.200 mutant PPM1D induced differential sensitivity.

293 00:11:16.200 --> 00:11:17.110 And then as I mentioned earlier,

294 00:11:17.110 --> 00:11:19.540 we had the activating truncating mutations

295 00:11:19.540 --> 00:11:21.250 as well as the amplifications.

296 00:11:21.250 --> 00:11:23.130 He went on to show that over expression

297 00:11:23.130 --> 00:11:26.930 of both full-length or truncated PPM1D could also

298 00:11:26.930 --> 00:11:29.000 recapitulate the NAMPT sensitivity.

299 00:11:29.000 --> 00:11:32.540 Uh, in contrast, a catalycally inactive version of PPM1D

300 00:11:32.540 --> 00:11:35.335 was unable to confer NAMPT inhibitor sensitivity.

301 00:11:35.335 --> 00:11:38.830 So we then sent ourselves to Charlie Brenner's developed,

302 00:11:38.830 --> 00:11:42.750 high resolution NAD metabolic profiling platform.

303 00:11:42.750 --> 00:11:45.230 And he sent us back some intriguing data

304 00:11:45.230 --> 00:11:48.900 in that really all the NAD precursors were suppressed.

305 00:11:48.900 --> 00:11:50.710 And at base line you can see here Wild site

306 00:11:50.710 --> 00:11:52.030 versus the PPM1D mute.

307 00:11:52.030 --> 00:11:54.450 You can see base line, uh, depressed levels.

308 00:11:54.450 --> 00:11:55.920 When you treat with a NAMPT inhibitor,

309 00:11:55.920 --> 00:11:58.790 then you get critically low levels of NAD

310 00:11:58.790 --> 00:12:01.950 which we believe is contributing to the loss

311 00:12:01.950 --> 00:12:03.890 of viability in those cells.

312 00:12:03.890 --> 00:12:06.130 So then zooming in on this.

313 00:12:06.130 --> 00:12:10.010 We worked with Charlie, uh, to sort of probe

314 00:12:10.010 --> 00:12:12.410 the mechanistic basis for this phenomenon.

315 00:12:12.410 --> 00:12:15.590 Charlie suggested that we start repleting or rescuing,

316 00:12:15.590 --> 00:12:16.960 with various precursors.

317 00:12:16.960 --> 00:12:20.780 Adding NAM, adding NR, and adding NA to test the integrity

318 00:12:20.780 --> 00:12:22.200 of each of these pathways.

319 00:12:22.200 --> 00:12:23.033 Okay?

320 00:12:23.033 --> 00:12:25.560 So, these are synergy or antagonism plots

321 00:12:25.560 --> 00:12:26.700 that I'm showing you right here.

322 00:12:26.700 --> 00:12:28.127 So, this is the drug NAMPT inhibitor,

323 00:12:28.127 --> 00:12:31.390 and then this is the NAD precursor that we're adding.

324 00:12:31.390 --> 00:12:34.370 Red indicates an antagonistic effect,

325 00:12:34.370 --> 00:12:36.510 essentially showing that that pathway is intact.

326 00:12:36.510 --> 00:12:37.343 Okay?

327 00:12:37.343 --> 00:12:39.820 So adding NAM you can see then bypasses the effect

328 00:12:39.820 --> 00:12:40.653 of the NAMPT inhibitor,

329 00:12:40.653 --> 00:12:42.330 so that pathway essentially was intact.

330 00:12:42.330 --> 00:12:46.020 Adding NR, his favorite NAD precursor

331 00:12:46.020 --> 00:12:47.720 also led to antagonism.

332 00:12:47.720 --> 00:12:50.070 But the one intriguing result

333 00:12:50.070 --> 00:12:51.490 was shown here on the left.

334 00:12:51.490 --> 00:12:52.510 When you add NA,

335 00:12:52.510 --> 00:12:53.670 we're unable to antagonize,

336 00:12:53.670 --> 00:12:56.270 suggesting the defect in this pathway to converge

337 00:12:56.270 --> 00:12:59.913 with NAMN which is mediated by this protein called NAPRT.

338 00:13:01.060 --> 00:13:03.468 In parallel, Nate then did a siRNA screen

339 00:13:03.468 --> 00:13:05.600 knocking down each one of these drugs

340 00:13:05.600 --> 00:13:08.950 to see which one would phenocopy the PPM1D mutation

341 00:13:08.950 --> 00:13:10.900 causing NAMPT inhibitor sensitivity.

342 00:13:10.900 --> 00:13:14.070 And he found one gene target of interest.

343 00:13:14.070 --> 00:13:15.590 And indeed that was NAPRT,

344 00:13:15.590 --> 00:13:17.390 and that's shown here in the orange.

345 00:13:18.490 --> 00:13:21.400 We then rushed back to our cell lines and asked the question

346 00:13:21.400 --> 00:13:23.090 well, what is the status of NAPRT expression

347 00:13:23.090 --> 00:13:23.923 in these cell lines?

348 00:13:23.923 --> 00:13:24.790 Maybe there's a problem with it.

349 00:13:24.790 --> 00:13:25.710 And to our surprise,

350 00:13:25.710 --> 00:13:28.860 in all of the lines that had engineered a PPM1D mutation,

351 00:13:28.860 --> 00:13:33.420 they had lost NAPRT expression under these conditions.

352 00:13:33.420 --> 00:13:35.280 We then went ahead and said

353 00:13:35.280 --> 00:13:38.480 well is NAPRT loss accounting for the NAMPT sensitivity?

354 00:13:38.480 --> 00:13:41.910 So he over expressed NAPRT in the PPM1D mutant cells,

355 00:13:41.910 --> 00:13:43.350 and that's shown here in the blue bar,

356 00:13:43.350 --> 00:13:44.900 so they completely rescue the effect.

357 00:13:44.900 --> 00:13:47.693 So this is really being driven by loss of NAPRT.

358 00:13:48.672 --> 00:13:49.505 (throat clearing)

359 00:13:49.505 --> 00:13:51.588 We then moved again in our process flow

360 00:13:51.588 --> 00:13:53.000 to patient-derived models which obviously are more relevant

361 00:13:53.000 --> 00:13:54.970 to the human situation.

362 00:13:54.970 --> 00:13:57.440 And we got some patient-derived

363 00:13:57.440 --> 00:14:00.910 3D DIPG cultures from Michelle Monje out at Stanford.

364 00:14:00.910 --> 00:14:04.450 And you can see here again in the mutant PPM1D

365 00:14:04.450 --> 00:14:06.580 cultures shown here that we had loss of NAPRT.

366 00:14:06.580 --> 00:14:07.730 So we could recapitulate,

367 00:14:07.730 --> 00:14:10.500 we could see this also in patient-derived models,

368 00:14:10.500 --> 00:14:13.890 and that led to profound sensitivity to a NAMPT inhibitor.

369 00:14:13.890 --> 00:14:15.290 And that's shown here, and again,

370 00:14:15.290 --> 00:14:18.403 just by eying these 3D cultures, it's quite striking.

371 00:14:19.270 --> 00:14:21.790 Working with Ranjini our fearless lab manager in the lab,

372 00:14:21.790 --> 00:14:25.560 we developed a PPM1D mutant flank zenograph model.

373 00:14:25.560 --> 00:14:27.050 And then we also showed

374 00:14:27.050 --> 00:14:29.810 that this effect could be recapitulated in vivo

375 00:14:29.810 --> 00:14:32.566 in this flank model shown here.

376 00:14:32.566 --> 00:14:34.950 Now narrowing in on the mechanism.

377 00:14:34.950 --> 00:14:35.783 So we ask,

378 00:14:35.783 --> 00:14:37.770 well the protein is down so what exactly is happening?

379 00:14:37.770 --> 00:14:40.030 This is not thought to be an epigenetic modifier,

380 00:14:40.030 --> 00:14:41.230 this mutation.‘

381 00:14:41.230 --> 00:14:42.810 But could this be possible?

382 00:14:42.810 --> 00:14:45.610 So here's a Tacksman analysis of MRI transcript levels.

383 00:14:45.610 --> 00:14:49.095 You can see here we have reduction of, uh, of NAPRT levels,

384 00:14:49.095 --> 00:14:53.320 in our PPM1D mutant engineered and patient-derived lines.

385 00:14:53.320 --> 00:14:55.810 We then went and did a series of ChIP Assays

386 00:14:55.810 --> 00:14:58.430 at pretty comprehensive panel looking at the promoter,

387 00:14:58.430 --> 00:15:00.170 which I won't show you today that suggested that

388 00:15:00.170 --> 00:15:02.720 there was some sort of repressive effect of the promoter.

389 00:15:02.720 --> 00:15:03.910 And then more importantly,

390 00:15:03.910 --> 00:15:06.280 we showed that there was elevated 5 methyl-cytosine

391 00:15:06.280 --> 00:15:08.020 directly at the NAPRT promoter.

392 00:15:08.020 --> 00:15:09.820 And this is just a methyl-dip assay.

393 00:15:09.820 --> 00:15:12.320 Again, just glossing over this because of time.

394 00:15:12.320 --> 00:15:13.700 But this really suggested to us that

395 00:15:13.700 --> 00:15:16.070 the promoter's actually being silenced

396 00:15:16.070 --> 00:15:17.963 by mutant PPM1D.

397 00:15:19.460 --> 00:15:21.640 So we sought to probe this a little bit deeper,

398 00:15:21.640 --> 00:15:23.690 and I'll show you just a little smattering of the,

399 00:15:23.690 --> 00:15:26.340 of the data that, uh, we've gotten more recently.

400 00:15:26.340 --> 00:15:27.890 Uh, so we brought in a bioinformatics group

401 00:15:27.890 --> 00:15:30.430 and did whole methylene profiling to understand

402 00:15:30.430 --> 00:15:32.500 whether this was focal or global.

403 00:15:32.500 --> 00:15:34.640 Uh, we actually expanded our patient-derived line.

404 00:15:34.640 --> 00:15:35.473 There's sets of lines.

405 00:15:35.473 --> 00:15:39.130 There's actually only a handful of PPM1D mutant DIPG lines

406 00:15:39.130 --> 00:15:40.970 in the world, and we are able to get them.

407 00:15:40.970 --> 00:15:43.130 And then we sort of looked and asked the question

408 00:15:43.130 --> 00:15:46.850 of whether this was a specific, uh, NAPRT promoter specific,

409 00:15:46.850 --> 00:15:49.600 or a global methylation, uh, phenotype.

410 00:15:49.600 --> 00:15:50.880 Uh, so we brought in the folks from TGEN.

411 00:15:50.880 --> 00:15:52.700 We've been working with Mike Berens for quite some time,

412 00:15:52.700 --> 00:15:54.540 and asked them to join.

413 00:15:54.540 --> 00:15:57.020 And then we reached out to folks across the pond,

414 00:15:57.020 --> 00:15:59.410 namely Chris Jones and the Carcaboso Lab,

415 00:15:59.410 --> 00:16:02.420 who some of these PPM1D patient-derived models

416 00:16:02.420 --> 00:16:04.170 for some of our work.

417 00:16:04.170 --> 00:16:07.750 What we first soun- what we first found looking at 850K,

418 00:16:07.750 --> 00:16:10.150 whole methylene in profiling is shown here.

419 00:16:10.150 --> 00:16:12.550 You can see in this red for the beta values,

420 00:16:12.550 --> 00:16:16.030 that largely the PPM1D mutants had a focal,

421 00:16:16.030 --> 00:16:18.790 dense hyper methylation of the NAPRT promoter.

422 00:16:18.790 --> 00:16:21.070 And actually when you look at global methylation profiling,

423 00:16:21.070 --> 00:16:23.000 you can see that on average, again,

424 00:16:23.000 --> 00:16:24.430 yellow are the mutant lines.

425 00:16:24.430 --> 00:16:28.025 You can see this cluster of methylation targets,

426 00:16:28.025 --> 00:16:31.180 essentially a CPG island like methylene phenotype

427 00:16:31.180 --> 00:16:33.160 that we're seeing in the PPM1D mutants.

428 00:16:33.160 --> 00:16:35.640 Again, we're seeing this both in the patient-derived lines

429 00:16:35.640 --> 00:16:39.200 as well as in our engineered lines in this systems.

430 00:16:39.200 --> 00:16:40.740 So just sort of our working model.

431 00:16:40.740 --> 00:16:42.390 This was just published about two weeks ago

432 00:16:42.390 --> 00:16:43.770 in Nature Communications.

433 00:16:43.770 --> 00:16:46.770 What we're finding is that elevated PPM1D activation

434 00:16:46.770 --> 00:16:49.700 leads to silencing of NAPRT likely in the context

435 00:16:49.700 --> 00:16:52.080 of a CPG island like methylene phenotype,

436 00:16:52.080 --> 00:16:55.270 which in activates this press handler salvage pathway

437 00:16:55.270 --> 00:16:58.161 essentially silencing NAPRT leading to the depletion of NAD

438 00:16:58.161 --> 00:17:01.590 and a setup, essentially a metabolic vulnerability

439 00:17:01.590 --> 00:17:03.740 for treatment with NAMPT inhibitors.

440 00:17:03.740 --> 00:17:06.010 There's a lot more work to be done here,

441 00:17:06.010 --> 00:17:07.890 and because of time, I won't go into those questions,

442 00:17:07.890 --> 00:17:10.850 but this work is really just beginning for us.

443 00:17:10.850 --> 00:17:13.320 Bringing it now back to IDH1, so some of you know

444 00:17:13.320 --> 00:17:16.590 some of the adult midline supratentorial gliomas

445 00:17:16.590 --> 00:17:18.290 have IDH mutations.

446 00:17:18.290 --> 00:17:20.560 And there's a really an intriguing leak, link

447 00:17:20.560 --> 00:17:22.110 between PPM1D and IDH1.

448 00:17:22.110 --> 00:17:24.900 I alluded to this earlier from the Dan Cahill work

449 00:17:24.900 --> 00:17:26.860 that actually prompted us to serendipitously

450 00:17:26.860 --> 00:17:29.150 sort of make this discovery.

451 00:17:29.150 --> 00:17:31.440 And what, what Dan and colleagues actually found was

452 00:17:31.440 --> 00:17:33.640 similarly in IDH mutants as well,

453 00:17:33.640 --> 00:17:36.520 they silence NAPRT leading to an NAD depletion.

454 00:17:36.520 --> 00:17:39.330 So we don't understand why adult and pediatric tumors

455 00:17:39.330 --> 00:17:42.670 with these mutations are silencing

456 00:17:42.670 --> 00:17:44.880 this pathway, but there's clearly a theme

457 00:17:44.880 --> 00:17:49.880 across all age groups for these tumors for NAD depletion.

458 00:17:50.160 --> 00:17:52.000 So in the last just 5 minutes or so,

459 00:17:52.000 --> 00:17:53.490 I'll tell you about what we're doing to get this

460 00:17:53.490 --> 00:17:55.000 into the clinic.

461 00:17:55.000 --> 00:17:56.670 So as many of you know we are very interested

462 00:17:56.670 --> 00:17:58.410 in trying to drive some of the work that we do

463 00:17:58.410 --> 00:18:00.300 into patients as soon as possible.

464 00:18:00.300 --> 00:18:02.690 And this is work that I think

465 00:18:02.690 --> 00:18:04.380 many of you seen us present, and this is work

466 00:18:04.380 --> 00:18:07.276 from the Glazer Lab, Stephanie Halene's lab, Morokinaw,

467 00:18:07.276 --> 00:18:09.820 and my laboratory, essentially mapping out

468 00:18:09.820 --> 00:18:11.690 this oncometabolite-induced brachinist

469 00:18:11.690 --> 00:18:13.430 that leads to NAPRT sensitivity.

470 00:18:13.430 --> 00:18:14.710 And so we've done this before,

471 00:18:14.710 --> 00:18:16.430 and we've been able to translate this work

472 00:18:16.430 --> 00:18:18.480 into multiple clinical trials shown here.

473 00:18:18.480 --> 00:18:20.690 And really a testament to the cancer center,

474 00:18:20.690 --> 00:18:23.720 namely folks like, uh, Pat Lorusso, Paul Eder,

475 00:18:23.720 --> 00:18:26.600 Asher Marks, Toma Tebaldi, and again Stephanie Halene

476 00:18:26.600 --> 00:18:30.200 to really drive this into our patients.

477 00:18:30.200 --> 00:18:33.270 So the questions for this were how we're going to get this

478 00:18:33.270 --> 00:18:37.560 into the clinic, recognizing some of these huge caveats

479 00:18:37.560 --> 00:18:39.900 that I'm going spend the last few minutes on.

480 00:18:39.900 --> 00:18:41.710 So first of all, there are a number of barriers

481 00:18:41.710 --> 00:18:45.470 to a systemic NAMPT inhibitor trial, uh, in DIPG

482 00:18:45.470 --> 00:18:47.010 that we'll touch upon in a moment.

483 00:18:47.010 --> 00:18:49.010 We would love to consider combinations

484 00:18:49.010 --> 00:18:50.700 with both radiation and chemotherapy

485 00:18:50.700 --> 00:18:52.980 because we don't think monotherapy for any of these,

486 00:18:52.980 --> 00:18:55.510 these aggressive gliomas is going to be sufficient.

487 00:18:55.510 --> 00:18:58.260 And I'll tell you a little bit about some surprising

488 00:18:58.260 --> 00:19:00.480 results about the blood brain barrier penetration

489 00:19:00.480 --> 00:19:02.600 of some of the drugs that are out there.

490 00:19:02.600 --> 00:19:04.957 So just a few, uh, few points on the first 491 00:19:04.957 --> 00:19:07.370 the first question.

492 00:19:07.370 --> 00:19:10.580 So, as I mentioned, multiple NAMPT inhibitor trials

493 00:19:10.580 --> 00:19:12.790 have been initiated and closed.

494 00:19:12.790 --> 00:19:14.854 Most of them ended with lack of efficacy,

495 00:19:14.854 --> 00:19:17.950 and pretty significant doxylamine toxicity.

496 00:19:17.950 --> 00:19:20.540 A lot of folks would say that the

497 00:19:20.540 --> 00:19:23.210 lack of efficacy was simply that these were solid tumor

498 00:19:23.210 --> 00:19:24.780 Phase 1 trials with no biomarkers.

499 00:19:24.780 --> 00:19:27.630 They were not trying to find for any specific

500 00:19:27.630 --> 00:19:29.660 biomarker that could confer sensitivity.

501 00:19:29.660 --> 00:19:32.527 And the liabilities in particular were

502 00:19:32.527 --> 00:19:34.620 hemologic and retinal toxicity

503 00:19:34.620 --> 00:19:36.950 which have really spooked a lot of folks that are,

504 00:19:36.950 --> 00:19:39.760 are developing NAMPT inhibitors at the moment,

505 00:19:39.760 --> 00:19:41.150 and they've shelved them.

506 00:19:41.150 --> 00:19:43.460 This is just one paper to show you an example of,

507 00:19:43.460 --> 00:19:45.260 of this finding.

508 00:19:45.260 --> 00:19:46.830 So, in parallel to that,

509 00:19:46.830 --> 00:19:50.440 we'd love to explore the concept of combining this

510 00:19:50.440 --> 00:19:52.810 with other clinically relevant regimens for glioma,

511 00:19:52.810 --> 00:19:54.280 namely DIPG.

512 00:19:54.280 --> 00:19:56.510 And it turns out as many of you know in the audience here,

513 00:19:56.510 --> 00:19:59.170 temozolomide is a mainstay of brain tumor treatment.

514 00:19:59.170 --> 00:20:01.500 And temozolomide itself actually has been shown

515 00:20:01.500 --> 00:20:04.960 to cause an NAD depletion by metabolic stress.

516 00:20:04.960 --> 00:20:06.940 In parallel, what about things like radiation,

517 00:20:06.940 --> 00:20:10.000 another mainstay for DIPG and other gliomas?

518 00:20:10.000 --> 00:20:12.150 And I do apologize for I rat out colleagues I know

519 00:20:12.150 --> 00:20:14.090 to quote a paper from 1978.

520 00:20:14.090 --> 00:20:16.836 I promise I'm going to get a more recent one.

521 00:20:16.836 --> 00:20:18.210 But it turns out that radiation actually depletes

522 00:20:18.210 --> 00:20:19.460 NAD levels as well.

523 00:20:19.460 --> 00:20:21.270 And so where am I going with this?

524 00:20:21.270 --> 00:20:23.010 We, we have now NAMPT inhibitors,

525 00:20:23.010 --> 00:20:25.387 possibly radiation temodar - those are, that's like the,

526 00:20:25.387 --> 00:20:27.242 the stupe trial plus NAMPT inhibitor -

527 00:20:27.242 --> 00:20:30.410 so an opportunity for what I would call trimodality

528 00:20:30.410 --> 00:20:31.770 synergy with NAMPT inhibitors.

529 00:20:31.770 --> 00:20:34.200 So we're really excited about possibly incorporating

530 00:20:34.200 --> 00:20:37.070 these modalities into a future clinical trial.

531 00:20:37.070 --> 00:20:37.920 So the last little point,

532 00:20:37.920 --> 00:20:39.500 again I just want to give you a flavor for this

533 00:20:39.500 --> 00:20:40.333 because of time.

534 00:20:40.333 --> 00:20:41.560 There's a lot more to it.

535 00:20:41.560 --> 00:20:43.780 What about CNS penetration?

536 00:20:43.780 --> 00:20:46.003 So, one thing we learn is that your drug is no,

537 00:20:46.003 --> 00:20:48.783 no better than how well it can get into the blood,

538 00:20:48.783 --> 00:20:51.520 past the blood brain barrier for glioma trials.

539 00:20:51.520 --> 00:20:53.330 Turns out that most NAMPT inhibitors

540 00:20:53.330 --> 00:20:55.070 are CNS impermeable.

541 00:20:55.070 --> 00:20:57.210 The ones that are permeable actually have

542 00:20:57.210 --> 00:20:59.700 that retina toxicity that I mentioned earlier.

543 00:20:59.700 --> 00:21:01.600 So this is a bit of a conundrum.

544 00:21:01.600 --> 00:21:03.580 And so one thing that we're interested in looking at

545 00:21:03.580 --> 00:21:04.970 is Convection Enhanced Delivery.

546 00:21:04.970 --> 00:21:06.920 Some of you may this, may know of this approach

547 00:21:06.920 --> 00:21:09.980 where you directly inject a drug into the brainstem

548 00:21:09.980 --> 00:21:12.670 or into the brain to bypass the blood brain barrier.

549 00:21:12.670 --> 00:21:15.220 Folks like Joe Piepmeier and colleagues, uh, have p -

550 00:21:15.220 --> 00:21:16.970 have done pioneering work in this field.

551 00:21:16.970 --> 00:21:18.610 And believe it or not, this is actually now,

552 00:21:18.610 --> 00:21:19.560 now quite common.

553 00:21:19.560 --> 00:21:22.880 There's probably about 7 or 8 trials in kids and adults

554 00:21:22.880 --> 00:21:25.520 testing CED of novel agents.

555 00:21:25.520 --> 00:21:27.360 Uh, we would argue that this is a great idea,

556 00:21:27.360 --> 00:21:29.880 but we know within a few hours those drugs you inject,

557 00:21:29.880 --> 00:21:31.210 they wash right away.

558 00:21:31.210 --> 00:21:33.739 Um, and so if the way to encapsulate those drugs

559 00:21:33.739 --> 00:21:36.620 in some sort of particle, i.e. nano-particle,

560 00:21:36.620 --> 00:21:39.700 we could then find a way to prolong, uh, the deliv-

561 00:21:39.700 --> 00:21:42.280 the drug delivery and exposure in the tumor.

562 00:21:42.280 --> 00:21:43.510 So who could we got to for that?

563 00:21:43.510 --> 00:21:45.090 Well, of course we could go right across the street

564 00:21:45.090 --> 00:21:45.923 to Mark Saltzman.

565 00:21:45.923 --> 00:21:48.790 And Mark and Jianbing Zhou and folks have,

566 00:21:48.790 --> 00:21:50.110 have really done pioneering work

567 00:21:50.110 --> 00:21:53.732 in developing brain penetrating PEG and related

568 00:21:53.732 --> 00:21:56.580 nano-particles and have shown in

569 00:21:56.580 --> 00:21:59.430 some really seminal papers including this one in PNAS,

570 00:21:59.430 --> 00:22:02.410 that you could use them to treat gliomablastoma.

571 00:22:02.410 --> 00:22:03.958 So we've been working with Mark for quite some time.

572 00:22:03.958 --> 00:22:06.530 So some of you know over the last couple years

573 00:22:06.530 --> 00:22:08.910 we've had a very, a long fruitful collaboration.

574 00:22:08.910 --> 00:22:10.660 We've actually shown by proof of concept

575 00:22:10.660 --> 00:22:12.780 that we could take DNA repair inhibitors,

576 00:22:12.780 --> 00:22:15.190 like ATR inhibitors, uh, and encapsulate them

577 00:22:15.190 --> 00:22:17.430 in nano-particles and use them to treat, gliomas.

578 00:22:17.430 --> 00:22:20.620 And this is just one of our papers that came out recently.

579 00:22:20.620 --> 00:22:22.360 So that's actually exactly what we're doing now

580 00:22:22.360 --> 00:22:23.193 for NAMPT inhibitors.

581 00:22:23.193 --> 00:22:26.970 And this is actually a YCC co-pilot grant

582 00:22:26.970 --> 00:22:29.280 looking at whether we can capsulate NAMPT inhibitors

583 00:22:29.280 --> 00:22:30.490 in nano-particles.

584 00:22:30.490 --> 00:22:32.810 And this is work from Yazhe Wang and Jason Breckta,

585 00:22:32.810 --> 00:22:34.990 raduncт resident in my laboratory showing that

586 00:22:34.990 --> 00:22:37.680 yes, we can and that these particles effectively can

587 00:22:37.680 --> 00:22:40.763 release drug and actually deplete NAD

588 00:22:40.763 --> 00:22:42.520 in this setting.

589 00:22:42.520 --> 00:22:44.860 So just to wrap up here in the last 2 minutes.

590 00:22:44.860 --> 00:22:47.570 So, we really are firm believers that

591 00:22:47.570 --> 00:22:49.180 metabolic vulnerabilities can be exploited

592 00:22:49.180 --> 00:22:50.790 in both adult and pediatric gliomas.

593 00:22:50.790 --> 00:22:52.550 We've shown this for IDH in the adults,

594 00:22:52.550 --> 00:22:54.810 and now we're showing for PPM1D in the kids.

595 00:22:54.810 --> 00:22:57.317 We believe that just like IDH,

596 00:22:57.317 --> 00:23:00.173 and we're trying to translate this into the clinic.

597 00:23:00.173 --> 00:23:03.940 We're really falling up as fast as we can

598 00:23:03.940 --> 00:23:05.900 to understand why PPM1D mutations

599 00:23:05.900 --> 00:23:07.900 are inducing NAPRT silencing.

600 00:23:07.900 --> 00:23:10.810 And, we do believe that there's an opportunity

601 00:23:10.810 --> 00:23:13.900 here to take existing treatments like radiation and temodar

602 00:23:13.900 --> 00:23:16.050 and bring in NAMPT inhibitors into the fray.

603 00:23:16.050 --> 00:23:18.270 And we're very actively exploring

604 00:23:18.270 --> 00:23:20.250 whether CED and nano-particles may address

605 00:23:20.250 --> 00:23:22.610 some of the issues that I've talked about earlier.

606 00:23:22.610 --> 00:23:24.130 So with that I'll just wrap up.

607 00:23:24.130 --> 00:23:26.370 I'll thank all the folks that did the work

608 00:23:26.370 --> 00:23:28.890 in the laboratory, and all of them are shown here

609 00:23:28.890 --> 00:23:30.280 at our recent retreat.

610 00:23:30.280 --> 00:23:31.160 Nate has moved on.

611 00:23:31.160 --> 00:23:33.360 He's now our first, first grad student,

612 00:23:33.360 --> 00:23:35.477 and now a post-doc at the NCI.

613 00:23:35.477 --> 00:23:37.160 And of course I'd like to thank the folks that

614 00:23:37.160 --> 00:23:38.250 fund this work as well.

615 00:23:38.250 --> 00:23:39.288 And we have time for a few questions.

616 00:23:39.288 --> 00:23:40.121 (applause)