512: PCE_3 Presents From Prebiotic Chemistry to Contemporary Biochemistry III

1
00:00:05,510 --> 00:00:02,310
hello everyone

2
00:00:07,909 --> 00:00:05,520
and welcome to our pce3 session uh the

3
00:00:11,910 --> 00:00:07,919
last one on transitions from prebiotic

4
00:00:15,110 --> 00:00:11,920
chemistry to contemporary biochemistry

5
00:00:17,670 --> 00:00:15,120
and in this session we're going to have

6
00:00:20,230 --> 00:00:17,680
five speakers speakers each of them will

7
00:00:21,189 --> 00:00:20,240
have 15 minutes about 12

8
00:00:22,630 --> 00:00:21,199
minutes

9
00:00:25,189 --> 00:00:22,640
per presentation and then a few

10
00:00:27,670 --> 00:00:25,199
questions but since our last

11
00:00:30,310 --> 00:00:27,680
presentation has been with john where

12
00:00:32,150 --> 00:00:30,320
we would like to invite all speakers to

13
00:00:33,190 --> 00:00:32,160

come up to the stage at the end of the

14
00:00:35,510 --> 00:00:33,200
session

15
00:00:38,229 --> 00:00:35,520
and to have we'll have about 15 minutes

16
00:00:39,990 --> 00:00:38,239
for questions so i didn't say my name is

17
00:00:41,430 --> 00:00:40,000
moran frankel pinter and i'm an

18
00:00:43,910 --> 00:00:41,440
assistant professor at the hebrew

19
00:00:46,069 --> 00:00:43,920
university of jerusalem and with me i

20
00:00:49,190 --> 00:00:46,079
have my co-convener

21
00:00:51,110 --> 00:00:49,200
dr anton patra from georgia

22
00:00:53,350 --> 00:00:51,120
from georgia tech he's a research

23
00:00:55,430 --> 00:00:53,360
scientist and a kawaii in the nasa

24
00:00:58,389 --> 00:00:55,440
center for origins of life

25
00:01:00,310 --> 00:00:58,399
so we're very happy to start and

26
00:01:01,349 --> 00:01:00,320
i'll just say that as i mentioned we

27
00:01:03,510 --> 00:01:01,359
have five

28
00:01:06,230 --> 00:01:03,520
presentations one of which the second

29
00:01:08,550 --> 00:01:06,240
one is going to be recorded but other

30
00:01:11,670 --> 00:01:08,560
than that all of them are in person

31
00:01:13,590 --> 00:01:11,680
and the first speaker is actually

32
00:01:15,429 --> 00:01:13,600
not going to be cesarem nor silvan but

33
00:01:17,109 --> 00:01:15,439
it's going to be bradley berger so we

34
00:01:19,350 --> 00:01:17,119
have a surprise

35
00:01:22,310 --> 00:01:19,360
bradley berker

36
00:01:28,230 --> 00:01:24,710
nasa postdoctoral management fellow at

37
00:01:29,830 --> 00:01:28,240
nasa headquarters so bradley

38
00:01:30,710 --> 00:01:29,840

common

39
00:01:33,510 --> 00:01:30,720
hello

40
00:01:33,520 --> 00:01:46,710
thank you moran

41
00:01:50,230 --> 00:01:48,469
yes cesar is

42
00:01:52,310 --> 00:01:50,240
really sad that he couldn't make it to

43
00:01:55,109 --> 00:01:52,320
absycon this time it's always one of his

44
00:01:57,749 --> 00:01:55,119
favorite conferences to go to but

45
00:02:00,230 --> 00:01:57,759
international travel is still a giant

46
00:02:02,789 --> 00:02:00,240
headache today so he got delayed at the

47
00:02:04,950 --> 00:02:02,799
last moment so i'm a pitch hitting for

48
00:02:07,510 --> 00:02:04,960
him and this uh work that we worked

49
00:02:09,990 --> 00:02:07,520
together on

50
00:02:12,550 --> 00:02:10,000
so i'll be talking about the shared

51
00:02:17,830 --> 00:02:12,560
prebiotic origins of terrans and purine

52
00:02:21,350 --> 00:02:17,840
nucleosides in a warm little pond model

53
00:02:23,750 --> 00:02:21,360
now i find it helpful to start out with

54
00:02:25,589 --> 00:02:23,760
what environment we're talking about so

55
00:02:27,750 --> 00:02:25,599
we can all get on the same page when

56
00:02:29,350 --> 00:02:27,760
we're talking prebiotic chemistry as

57
00:02:32,470 --> 00:02:29,360
there are a lot of different

58
00:02:34,309 --> 00:02:32,480
environments that we like to speculate

59
00:02:36,710 --> 00:02:34,319
where life could have come from and

60
00:02:39,990 --> 00:02:36,720
where the chemistry could have happened

61
00:02:42,949 --> 00:02:40,000
and so this work in my preferred model

62
00:02:44,710 --> 00:02:42,959
is the warm little pond so this involves

63
00:02:47,509 --> 00:02:44,720

having some

64
00:02:50,630 --> 00:02:47,519
land masses out there with some water on

65
00:02:52,790 --> 00:02:50,640
it and these ponds would be enriched in

66
00:02:54,869 --> 00:02:52,800
all sorts of organics and hopefully

67
00:02:57,589 --> 00:02:54,879
you've heard a lot of talks

68
00:02:59,589 --> 00:02:57,599
um throughout this conference talking

69
00:03:01,430 --> 00:02:59,599
about this model and the different

70
00:03:02,949 --> 00:03:01,440
organics that are in there

71
00:03:05,110 --> 00:03:02,959
so i'm not going to list them all

72
00:03:07,509 --> 00:03:05,120
because that it's a quite extensive list

73
00:03:10,550 --> 00:03:07,519
but they're overall

74
00:03:11,830 --> 00:03:10,560
highly or fairly reduced organic

75
00:03:15,030 --> 00:03:11,840
compounds

76
00:03:18,149 --> 00:03:15,040
and of note that i'd like to point out

77
00:03:21,990 --> 00:03:18,159
as key to the work that cesar and i do

78
00:03:24,710 --> 00:03:22,000
is that it's rich in urea and ammonium

79
00:03:27,430 --> 00:03:24,720
formate which would have been

80
00:03:28,869 --> 00:03:27,440
likely quite ubiquitous on a prebiotic

81
00:03:31,750 --> 00:03:28,879
earth

82
00:03:32,949 --> 00:03:31,760
and my focus in prebiotic chemistry what

83
00:03:35,750 --> 00:03:32,959
always

84
00:03:37,910 --> 00:03:35,760
captures my imagination is

85
00:03:42,070 --> 00:03:37,920
how to form

86
00:03:42,949 --> 00:03:42,080
uh informational caring polymers

87
00:03:45,670 --> 00:03:42,959
in

88
00:03:48,149 --> 00:03:45,680

mostly how to stitch them together

89
00:03:50,390 --> 00:03:48,159
but another important aspect that my

90
00:03:53,350 --> 00:03:50,400
research has focused on is how to form

91
00:03:55,509 --> 00:03:53,360
the informational units what we like to

92
00:03:57,110 --> 00:03:55,519
think of as the purines and the

93
00:03:59,830 --> 00:03:57,120
pyrimidines from

94
00:04:00,789 --> 00:03:59,840
modern dna and rna

95
00:04:02,390 --> 00:04:00,799
it's

96
00:04:04,869 --> 00:04:02,400
likely that

97
00:04:07,990 --> 00:04:04,879
early organisms would have used

98
00:04:10,470 --> 00:04:08,000
a similar suite of molecules maybe not

99
00:04:13,190 --> 00:04:10,480
those exact ones

100
00:04:15,429 --> 00:04:13,200
but something similar that uses hydrogen

101
00:04:16,949 --> 00:04:15,439
bonding to store and carry the

102
00:04:18,949 --> 00:04:16,959
information

103
00:04:22,230 --> 00:04:18,959
and so there's been a lot of talks and a

104
00:04:24,550 --> 00:04:22,240
lot of research on how to create the

105
00:04:26,629 --> 00:04:24,560
purines and the pyrimidines but one of

106
00:04:30,150 --> 00:04:26,639
the things that we notice

107
00:04:31,510 --> 00:04:30,160
coming from the synthetic pathways

108
00:04:32,629 --> 00:04:31,520
is

109
00:04:35,350 --> 00:04:32,639
they don't

110
00:04:37,990 --> 00:04:35,360
they not only lead to

111
00:04:40,950 --> 00:04:38,000
these specific informational units that

112
00:04:43,510 --> 00:04:40,960
we're looking for but they give a nice

113
00:04:45,350 --> 00:04:43,520

diversity of chemistry that isn't often

114
00:04:47,189 --> 00:04:45,360
talked about or really explored in

115
00:04:47,990 --> 00:04:47,199
prebiotic chemistry

116
00:04:50,469 --> 00:04:48,000
and

117
00:04:51,830 --> 00:04:50,479
so doing a lot of the reactions we

118
00:04:54,550 --> 00:04:51,840
noticed that

119
00:04:57,030 --> 00:04:54,560
these pterodines and terrans

120
00:04:59,030 --> 00:04:57,040
also pop out quite

121
00:05:02,469 --> 00:04:59,040
strongly from a lot of the prebiotic

122
00:05:04,710 --> 00:05:02,479
reactions that we are doing

123
00:05:06,150 --> 00:05:04,720
and so you can see these are quite

124
00:05:09,749 --> 00:05:06,160
similar to

125
00:05:11,110 --> 00:05:09,759
the purines that we have out there and

126
00:05:14,070 --> 00:05:11,120
in fact

127
00:05:16,950 --> 00:05:14,080
there is a very close synthetic pathway

128
00:05:19,670 --> 00:05:16,960
to lead to the formation of either

129
00:05:22,710 --> 00:05:19,680
uh purines or the pterydines that we're

130
00:05:26,230 --> 00:05:22,720
exploring here and so this is a classic

131
00:05:28,710 --> 00:05:26,240
tribe synthetic route that starts with

132
00:05:31,270 --> 00:05:28,720
the 4-5 diaminoprimidine

133
00:05:33,670 --> 00:05:31,280
which is core to a lot of the synthetic

134
00:05:35,029 --> 00:05:33,680
chemistry out there for prebiotic

135
00:05:36,550 --> 00:05:35,039
molecules

136
00:05:39,670 --> 00:05:36,560
and

137
00:05:41,990 --> 00:05:39,680
you simply

138
00:05:42,870 --> 00:05:42,000

react it via this upper pathway and you

139
00:05:51,749 --> 00:05:42,880
form

140
00:05:54,710 --> 00:05:51,759
under the same exact conditions instead

141
00:05:56,550 --> 00:05:54,720
of having formic acid if you had gly

142
00:05:59,430 --> 00:05:56,560
axle down there instead you form

143
00:06:02,309 --> 00:05:59,440
teradines and so this branches off

144
00:06:06,309 --> 00:06:02,319
distinctly to form these two

145
00:06:11,590 --> 00:06:09,110
and if we go back and we look at

146
00:06:15,510 --> 00:06:11,600
the becker synthesis

147
00:06:17,350 --> 00:06:15,520
published in science in 2019

148
00:06:20,950 --> 00:06:17,360
his group

149
00:06:23,350 --> 00:06:20,960
explored how to create purines and

150
00:06:25,350 --> 00:06:23,360
pyrimidines at the same time and this is

151
00:06:27,029 --> 00:06:25,360
a pretty great paper and i suggest

152
00:06:27,830 --> 00:06:27,039
checking it out if you haven't seen it

153
00:06:30,710 --> 00:06:27,840
yet

154
00:06:33,189 --> 00:06:30,720
as it shows

155
00:06:35,189 --> 00:06:33,199
the simultaneous synthesis of both of

156
00:06:38,150 --> 00:06:35,199
the informational carrying molecules

157
00:06:39,749 --> 00:06:38,160
that are important to us in in prebiotic

158
00:06:42,150 --> 00:06:39,759
chemistry

159
00:06:43,189 --> 00:06:42,160
but one thing to note specifically down

160
00:06:45,270 --> 00:06:43,199
here

161
00:06:50,230 --> 00:06:45,280
is on the

162
00:06:52,390 --> 00:06:50,240
purine synthetic pathway this

163
00:06:54,629 --> 00:06:52,400

reaction scheme here

164
00:06:56,629 --> 00:06:54,639
passes through a diaminoprimine

165
00:07:00,150 --> 00:06:56,639
intermediate which could yield

166
00:07:02,629 --> 00:07:00,160
pterydines and so after

167
00:07:05,029 --> 00:07:02,639
speaking with uh becker cesar

168
00:07:07,350 --> 00:07:05,039
said that um this follows pretty

169
00:07:09,430 --> 00:07:07,360
conventional organic chemistry routes

170
00:07:11,990 --> 00:07:09,440
where it's pretty clean

171
00:07:13,830 --> 00:07:12,000
you isolate the compounds and you can

172
00:07:15,830 --> 00:07:13,840
see them come forward

173
00:07:18,390 --> 00:07:15,840
and one of the things that we are always

174
00:07:19,749 --> 00:07:18,400
interested in is what happens if you

175
00:07:23,270 --> 00:07:19,759
dirty it up

176
00:07:24,070 --> 00:07:23,280
and so we took the initial experiment

177
00:07:26,550 --> 00:07:24,080
um

178
00:07:28,790 --> 00:07:26,560
and we started with the becker synthetic

179
00:07:30,550 --> 00:07:28,800
pathway but we dirtied it up by

180
00:07:33,430 --> 00:07:30,560
including urea

181
00:07:35,510 --> 00:07:33,440
ammonium formate and ribose at different

182
00:07:37,350 --> 00:07:35,520
steps of the pathway so we are not

183
00:07:40,150 --> 00:07:37,360
isolating anything in the middle we are

184
00:07:41,029 --> 00:07:40,160
just doing one pot reactions

185
00:07:43,909 --> 00:07:41,039
and

186
00:07:45,589 --> 00:07:43,919
not cleaning it up any step of the way

187
00:07:49,350 --> 00:07:45,599
and when we did this

188
00:07:51,350 --> 00:07:49,360

we just wanted to start out to verify if

189
00:07:52,550 --> 00:07:51,360
this synthetic pathway worked when it

190
00:07:54,469 --> 00:07:52,560
was dirty

191
00:07:56,469 --> 00:07:54,479
and what we saw was

192
00:07:59,990 --> 00:07:56,479
pretty gratifying

193
00:08:02,390 --> 00:08:00,000
so the reactions in these dirty pathways

194
00:08:05,029 --> 00:08:02,400
did yield

195
00:08:06,150 --> 00:08:05,039
uh some of the nucleosides that we were

196
00:08:11,110 --> 00:08:06,160
looking for

197
00:08:14,950 --> 00:08:12,790
when we started with the with the

198
00:08:18,710 --> 00:08:14,960
hydroxyl group up here

199
00:08:20,550 --> 00:08:18,720
um the major product was a formulated

200
00:08:22,469 --> 00:08:20,560
uh triamino

201
00:08:24,869 --> 00:08:22,479
pyrimidine there

202
00:08:26,790 --> 00:08:24,879
however when we used it with the with

203
00:08:29,029 --> 00:08:26,800
the amming group up there we did get

204
00:08:30,869 --> 00:08:29,039
quantitative yield so it was nice seeing

205
00:08:33,110 --> 00:08:30,879
that the reactions

206
00:08:36,149 --> 00:08:33,120
that becker proposed

207
00:08:38,790 --> 00:08:36,159
did work under these dirty settings

208
00:08:40,630 --> 00:08:38,800
with the varying yields however it got

209
00:08:45,269 --> 00:08:40,640
really quite interesting

210
00:08:48,630 --> 00:08:45,279
for us once we started including um

211
00:08:51,670 --> 00:08:48,640
ribose and ribofuranos into the reaction

212
00:08:53,110 --> 00:08:51,680
so now we start with the uh with the

213
00:08:56,790 --> 00:08:53,120

triamino

214
00:08:59,509 --> 00:08:56,800
the triamine and we start with urea in

215
00:09:02,070 --> 00:08:59,519
the ammonium formate from the beginning

216
00:09:03,350 --> 00:09:02,080
then we go through the synthetic pathway

217
00:09:06,310 --> 00:09:03,360
where we did

218
00:09:09,430 --> 00:09:06,320
uh just one acid cycle

219
00:09:12,949 --> 00:09:09,440
and then we added the ribofuranos under

220
00:09:16,630 --> 00:09:12,959
a high ph and did some wet dry wet

221
00:09:19,509 --> 00:09:16,640
cycling conditions at 65 degrees

222
00:09:21,670 --> 00:09:19,519
and suddenly we saw a lot

223
00:09:23,910 --> 00:09:21,680
of different

224
00:09:27,509 --> 00:09:23,920
molecules pop out here

225
00:09:29,910 --> 00:09:27,519
most notably the predominant ones were

226
00:09:31,750 --> 00:09:29,920
the terrans

227
00:09:34,470 --> 00:09:31,760
or the um

228
00:09:37,509 --> 00:09:34,480
the formulated products and we got very

229
00:09:40,710 --> 00:09:37,519
little guanosine in a scene in other of

230
00:09:45,509 --> 00:09:43,430
purines from the synthesis

231
00:09:46,710 --> 00:09:45,519
so we started to see

232
00:09:48,389 --> 00:09:46,720
this other

233
00:09:50,870 --> 00:09:48,399
really important

234
00:09:53,430 --> 00:09:50,880
molecule to modern biochemistry start to

235
00:09:55,829 --> 00:09:53,440
pop out just from these dirtied up

236
00:09:59,910 --> 00:09:55,839
synthetic pathways that we've known and

237
00:10:05,509 --> 00:10:02,550
and in fact when we change the ribose

238
00:10:06,870 --> 00:10:05,519

concentration we start to see a really

239
00:10:08,949 --> 00:10:06,880
remarkable

240
00:10:10,389 --> 00:10:08,959
preference towards

241
00:10:13,350 --> 00:10:10,399
towards the

242
00:10:15,430 --> 00:10:13,360
neoterins overall so when we have a

243
00:10:17,430 --> 00:10:15,440
extremely high ribose concentration of

244
00:10:19,590 --> 00:10:17,440
ten to one equivalents

245
00:10:23,990 --> 00:10:19,600
um

246
00:10:26,710 --> 00:10:24,000
we do get the guanine and the neoterins

247
00:10:29,509 --> 00:10:26,720
that are still popping out of solution

248
00:10:32,790 --> 00:10:29,519
with the neoterins being the predominant

249
00:10:34,949 --> 00:10:32,800
species but once we lower the ribose to

250
00:10:37,269 --> 00:10:34,959
a two to one equivalent we don't see

251
00:10:39,590 --> 00:10:37,279
guanosine and guanines anymore instead

252
00:10:42,069 --> 00:10:39,600
we only see the terrans pop out of the

253
00:10:44,550 --> 00:10:42,079
solution

254
00:10:46,389 --> 00:10:44,560
so now we have this uh these parallel

255
00:10:48,790 --> 00:10:46,399
pathways depending on the amount of

256
00:10:51,670 --> 00:10:48,800
ribose that we have so if you follow the

257
00:10:53,350 --> 00:10:51,680
top pathway where you start with this

258
00:10:55,430 --> 00:10:53,360
compound right here

259
00:10:56,710 --> 00:10:55,440
and you add ribose and you take it

260
00:10:58,550 --> 00:10:56,720
through

261
00:11:00,870 --> 00:10:58,560
two different types of conditions with

262
00:11:03,509 --> 00:11:00,880
10 equivalents of ribose you can get

263
00:11:05,750 --> 00:11:03,519

either the guanosine or the terrans

264
00:11:07,750 --> 00:11:05,760
however

265
00:11:09,670 --> 00:11:07,760
if you only have the small amount of

266
00:11:12,150 --> 00:11:09,680
ribose in there under either the

267
00:11:14,550 --> 00:11:12,160
standard conditions or the ureamodium

268
00:11:19,269 --> 00:11:14,560
formate conditions then you get all of

269
00:11:19,279 --> 00:11:23,509
and in fact it gets

270
00:11:28,069 --> 00:11:25,670
remarkable so we we wanted to take it

271
00:11:31,190 --> 00:11:28,079
one step further and ask well what if

272
00:11:33,030 --> 00:11:31,200
you don't add the ribose

273
00:11:35,350 --> 00:11:33,040
after you've synthesized it what if you

274
00:11:36,710 --> 00:11:35,360
just start with one pot with it all

275
00:11:39,910 --> 00:11:36,720
mixed in there

276
00:11:41,750 --> 00:11:39,920
and so we have the urea and the ribose

277
00:11:43,590 --> 00:11:41,760
together with our starting material and

278
00:11:45,910 --> 00:11:43,600
there is ammonium 4 made in here i just

279
00:11:48,630 --> 00:11:45,920
didn't include it in this scheme and you

280
00:11:52,310 --> 00:11:48,640
take it through the acid cycle and then

281
00:11:54,629 --> 00:11:52,320
do the dry wet cycling at the high ph

282
00:11:58,310 --> 00:11:54,639
or you just skip the acid cycle and you

283
00:12:01,030 --> 00:11:58,320
go straight to the high ph cycling

284
00:12:03,750 --> 00:12:01,040
then what we see is quantitative

285
00:12:05,910 --> 00:12:03,760
formation of the the terrans and the

286
00:12:11,590 --> 00:12:05,920
neoterns in the solution and we don't

287
00:12:14,629 --> 00:12:12,870
and so

288
00:12:17,430 --> 00:12:14,639

for the last step

289
00:12:20,069 --> 00:12:17,440
since we are running this in a urea rich

290
00:12:23,910 --> 00:12:20,079
solution we wondered well since we've

291
00:12:26,230 --> 00:12:23,920
got urea can we phosphorylate this on

292
00:12:28,389 --> 00:12:26,240
some pretty conventional prebiotic

293
00:12:31,509 --> 00:12:28,399
chemistry because if you have urea

294
00:12:33,350 --> 00:12:31,519
present in phosphate it can form this

295
00:12:36,710 --> 00:12:33,360
metaphosphate intermediate and then

296
00:12:39,910 --> 00:12:36,720
create organophosphate compounds

297
00:12:42,230 --> 00:12:39,920
so we took this reaction mixture

298
00:12:45,350 --> 00:12:42,240
actually we took the neoterin

299
00:12:47,350 --> 00:12:45,360
at the end after we had synthesized it

300
00:12:49,269 --> 00:12:47,360
and then we added

301
00:12:51,030 --> 00:12:49,279
the phosphate to the mixture and took it

302
00:12:53,990 --> 00:12:51,040
through

303
00:12:56,629 --> 00:12:54,000
dry wet cycling at 65 degrees

304
00:12:59,030 --> 00:12:56,639
and we saw a whole bevy of

305
00:13:01,030 --> 00:12:59,040
phosphorylated species and dimers and

306
00:13:03,350 --> 00:13:01,040
trimers pop out and all sorts of

307
00:13:05,269 --> 00:13:03,360
different phosphates adorned to it

308
00:13:06,949 --> 00:13:05,279
so it's a great pathway to making

309
00:13:12,790 --> 00:13:06,959
organophosphate

310
00:13:15,829 --> 00:13:12,800
and nucleotides as well

311
00:13:17,750 --> 00:13:15,839
so we have this scheme that you can see

312
00:13:20,150 --> 00:13:17,760
in our paper where it can take you

313
00:13:22,069 --> 00:13:20,160

through step by step adding ribose at

314
00:13:23,670 --> 00:13:22,079
various steps but you can start with the

315
00:13:25,829 --> 00:13:23,680
prebiotic meloo

316
00:13:29,190 --> 00:13:25,839
take it through some very

317
00:13:32,470 --> 00:13:29,200
nice simple um

318
00:13:35,269 --> 00:13:32,480
environmental cycling and end up with

319
00:13:40,470 --> 00:13:35,279
at the very end nucleotides and these

320
00:13:45,509 --> 00:13:42,470
and i'd like to acknowledge our funding

321
00:13:47,750 --> 00:13:45,519
sources through the nsf in nasa

322
00:13:50,310 --> 00:13:47,760
through a grant from the center for

323
00:13:52,550 --> 00:13:50,320
chemical evolution at georgia tech

324
00:13:55,110 --> 00:13:52,560
and my research has also been supported

325
00:13:57,189 --> 00:13:55,120
by the nasa post doctoral program

326
00:13:59,990 --> 00:13:57,199
which was administered by the university

327
00:14:02,310 --> 00:14:00,000
space research association at the time

328
00:14:03,590 --> 00:14:02,320
and i'll remind you that you can look

329
00:14:06,150 --> 00:14:03,600
for this

330
00:14:09,030 --> 00:14:06,160
uh paper in the next issue of the

331
00:14:12,069 --> 00:14:09,040
chemistry a european journal where we've

332
00:14:13,750 --> 00:14:12,079
had the honor of making a cover for the

333
00:14:21,990 --> 00:14:13,760
issue as well

334
00:14:26,389 --> 00:14:24,150
thank you bradley we have time for one

335
00:14:30,629 --> 00:14:26,399
quick question

336
00:14:35,030 --> 00:14:32,470
all right all right so i can ask

337
00:14:38,230 --> 00:14:35,040
something really quickly so um in these

338
00:14:39,670 --> 00:14:38,240

um experiments you've shown um you know

339
00:14:41,990 --> 00:14:39,680
the kind of the

340
00:14:44,389 --> 00:14:42,000
end point of the experiment did you also

341
00:14:46,150 --> 00:14:44,399
looked at what happens throughout

342
00:14:47,990 --> 00:14:46,160
the reactions so

343
00:14:49,750 --> 00:14:48,000
monitoring them

344
00:14:50,949 --> 00:14:49,760
monitoring the kinetics or product

345
00:14:53,910 --> 00:14:50,959
distribution

346
00:14:57,189 --> 00:14:53,920
oh yeah so yeah we monitor each stage of

347
00:14:59,670 --> 00:14:57,199
the way and we can see the different

348
00:15:01,910 --> 00:14:59,680
formulated products of the carbamylated

349
00:15:02,870 --> 00:15:01,920
products that go along and so we can see

350
00:15:04,949 --> 00:15:02,880
the

351
00:15:07,350 --> 00:15:04,959
very interesting chemistry that happens

352
00:15:10,230 --> 00:15:07,360
step by step through the process since

353
00:15:13,189 --> 00:15:10,240
we did isolate them and analyze them via

354
00:15:16,230 --> 00:15:13,199
nmr and mass spec for each of them and

355
00:15:19,030 --> 00:15:16,240
so we do see that we didn't do

356
00:15:19,829 --> 00:15:19,040
the kinetics nor the thermodynamics for

357
00:15:21,350 --> 00:15:19,839
it

358
00:15:24,389 --> 00:15:21,360
so we don't have that but we do have

359
00:15:26,550 --> 00:15:24,399
yields in the intermediates as well

360
00:15:28,230 --> 00:15:26,560
okay thanks bradley so let's thank

361
00:15:34,870 --> 00:15:28,240
bradley again

362
00:15:39,110 --> 00:15:37,110
so next up we're gonna have next up

363
00:15:41,030 --> 00:15:39,120

we're gonna have a

364
00:15:51,990 --> 00:15:41,040
pre-recorded talk

365
00:15:57,509 --> 00:15:54,870
hello i'm liam longo and today i'm going

366
00:15:59,670 --> 00:15:57,519
to talk about bioester biochemistry in

367
00:16:01,269 --> 00:15:59,680
metabolic evolution

368
00:16:03,189 --> 00:16:01,279
just this april i've started an

369
00:16:05,670 --> 00:16:03,199
independent position at elsi at the

370
00:16:07,509 --> 00:16:05,680
tokyo institute of technology but what

371
00:16:09,509 --> 00:16:07,519
i'm going to talk about today

372
00:16:12,230 --> 00:16:09,519
is conversations i've had with sean

373
00:16:14,629 --> 00:16:12,240
mcglynn my former postdoctoral advisor

374
00:16:16,550 --> 00:16:14,639
and my two collaborators josh goldford

375
00:16:18,069 --> 00:16:16,560
and harrison smith

376
00:16:20,389 --> 00:16:18,079
we're all very interested in the

377
00:16:21,990 --> 00:16:20,399
evolution of metabolism and today's talk

378
00:16:24,069 --> 00:16:22,000
is going to contain some of the ideas

379
00:16:28,069 --> 00:16:24,079
we've run across as we've tried to come

380
00:16:33,110 --> 00:16:30,949
so what is a thioester

381
00:16:35,910 --> 00:16:33,120
the structure of a thioester looks very

382
00:16:38,949 --> 00:16:35,920
similar to that of an ester or an amide

383
00:16:41,110 --> 00:16:38,959
except that the oxygen of the ester or

384
00:16:43,110 --> 00:16:41,120
the nitrogen of the amide has been

385
00:16:45,590 --> 00:16:43,120
replaced with a sulfur

386
00:16:47,110 --> 00:16:45,600
in the hierarchy of transfer potentials

387
00:16:50,069 --> 00:16:47,120
thioesters are considered to be

388
00:16:52,150 --> 00:16:50,079

similarly stable or more stable than acl

389
00:16:55,189 --> 00:16:52,160
phosphates but

390
00:16:56,310 --> 00:16:55,199
less stable than either an ester or an

391
00:16:58,629 --> 00:16:56,320
amide

392
00:17:02,310 --> 00:16:58,639
and so in biology we often see that

393
00:17:05,669 --> 00:17:02,320
thioesters ultimately funnel into esters

394
00:17:08,309 --> 00:17:05,679
or amides on the right hand side i have

395
00:17:10,549 --> 00:17:08,319
the dedu formulation of the thioester

396
00:17:12,870 --> 00:17:10,559
world

397
00:17:15,029 --> 00:17:12,880
according to dadu

398
00:17:17,590 --> 00:17:15,039
primordial amino acids

399
00:17:21,189 --> 00:17:17,600
could be activated by reaction with the

400
00:17:22,870 --> 00:17:21,199
thiol to generate a thioester derivative

401
00:17:25,909 --> 00:17:22,880
of an amino acid

402
00:17:28,309 --> 00:17:25,919
and these thioester derived amino acids

403
00:17:32,470 --> 00:17:28,319
could then react with each other to form

404
00:17:33,909 --> 00:17:32,480
multimers or short statistical peptides

405
00:17:35,990 --> 00:17:33,919
in this way

406
00:17:38,070 --> 00:17:36,000
thioesters could have been one of the

407
00:17:39,590 --> 00:17:38,080
first systems that allowed

408
00:17:42,230 --> 00:17:39,600
polymerization

409
00:17:45,190 --> 00:17:42,240
of amino acids

410
00:17:47,750 --> 00:17:45,200
ultimately the thioester-derived amino

411
00:17:50,150 --> 00:17:47,760
acid would be converted into

412
00:17:53,350 --> 00:17:50,160
an adenylate and this adenylate would

413
00:17:55,190 --> 00:17:53,360

then go to react to form a peptide

414
00:17:56,470 --> 00:17:55,200
the conversion reaction

415
00:17:59,430 --> 00:17:56,480
would involve

416
00:18:01,990 --> 00:17:59,440
reaction of an amp

417
00:18:04,310 --> 00:18:02,000
with the thioester derivative to form an

418
00:18:05,669 --> 00:18:04,320
acyl phosphate

419
00:18:07,430 --> 00:18:05,679
this reaction

420
00:18:09,909 --> 00:18:07,440
is pretty interesting

421
00:18:11,830 --> 00:18:09,919
in part because it echoes some of the

422
00:18:14,470 --> 00:18:11,840
results from rocker

423
00:18:17,750 --> 00:18:14,480
and what racker observed was that the

424
00:18:20,390 --> 00:18:17,760
catalytic mechanism of gap dh

425
00:18:22,630 --> 00:18:20,400
involves the formation of a thioester an

426
00:18:24,950 --> 00:18:22,640
acl enzyme intermediate that is

427
00:18:26,789 --> 00:18:24,960
eventually resolved by attack

428
00:18:30,390 --> 00:18:26,799
from orthophosphate

429
00:18:32,390 --> 00:18:30,400
to result in an acyl phosphate

430
00:18:34,870 --> 00:18:32,400
racker interpreted that catalytic

431
00:18:37,190 --> 00:18:34,880
mechanism as being an indication that

432
00:18:38,390 --> 00:18:37,200
maybe thioesters

433
00:18:40,150 --> 00:18:38,400
predated

434
00:18:43,190 --> 00:18:40,160
acl phosphates

435
00:18:45,190 --> 00:18:43,200
very similar to this framing in deduve's

436
00:18:47,510 --> 00:18:45,200
thioester world

437
00:18:50,230 --> 00:18:47,520
ultimately these adenylated amino acids

438
00:18:52,150 --> 00:18:50,240

would be formed directly by aminoacyl

439
00:18:55,110 --> 00:18:52,160
trna synthetases

440
00:18:58,549 --> 00:18:55,120
and then those adenylated amino acids

441
00:19:01,350 --> 00:18:58,559
would funnel into the translation system

442
00:19:03,510 --> 00:19:01,360
that we know and love today

443
00:19:04,549 --> 00:19:03,520
invoking a thioester world can solve a

444
00:19:06,710 --> 00:19:04,559
problem

445
00:19:09,110 --> 00:19:06,720
namely the poor solubility and

446
00:19:13,190 --> 00:19:09,120
potentially poor availability of

447
00:19:14,710 --> 00:19:13,200
phosphate to early metabolic networks

448
00:19:17,190 --> 00:19:14,720
the question of whether you can have

449
00:19:21,430 --> 00:19:17,200
metabolism in the absence of phosphate

450
00:19:23,510 --> 00:19:21,440
was addressed in josh's 2017 cell paper

451
00:19:26,710 --> 00:19:23,520
he showed that in the absence of any

452
00:19:29,669 --> 00:19:26,720
coupling to fosso anhydride hydrolysis

453
00:19:31,510 --> 00:19:29,679
or any utilization of phosphate at all

454
00:19:34,470 --> 00:19:31,520
you can still achieve a network of some

455
00:19:38,150 --> 00:19:34,480
300 metabolites with just the energetics

456
00:19:39,830 --> 00:19:38,160
associated with coupling to a thioester

457
00:19:42,150 --> 00:19:39,840
this is one of the first hints that a

458
00:19:44,789 --> 00:19:42,160
phosphate-free metabolic core might

459
00:19:46,789 --> 00:19:44,799
persist in contemporary metabolic

460
00:19:49,430 --> 00:19:46,799
structures

461
00:19:52,230 --> 00:19:49,440
as an iu structural biologist i wondered

462
00:19:55,270 --> 00:19:52,240
how distributed are thioesters and acyl

463
00:19:57,190 --> 00:19:55,280

phosphates another potential primordial

464
00:20:00,789 --> 00:19:57,200
energy currency

465
00:20:03,830 --> 00:20:00,799
across the metabolic map of life

466
00:20:06,789 --> 00:20:03,840
so using keg we identified all of the

467
00:20:08,070 --> 00:20:06,799
relevant compounds and their reactions

468
00:20:10,789 --> 00:20:08,080
as you can see

469
00:20:14,470 --> 00:20:10,799
thioesters are more common than acyl

470
00:20:16,630 --> 00:20:14,480
phosphates and so are their reactions

471
00:20:19,190 --> 00:20:16,640
furthermore if we look at the keg

472
00:20:21,590 --> 00:20:19,200
metabolic map we see that thioesters

473
00:20:23,750 --> 00:20:21,600
tend to be more connected to one another

474
00:20:24,950 --> 00:20:23,760
their reactions are more associated with

475
00:20:27,350 --> 00:20:24,960
each other

476
00:20:30,149 --> 00:20:27,360
acl phosphates on the other hand

477
00:20:32,310 --> 00:20:30,159
are more fragmented across the metabolic

478
00:20:35,350 --> 00:20:32,320
map

479
00:20:37,830 --> 00:20:35,360
and while it's not shown here

480
00:20:39,029 --> 00:20:37,840
acyl phosphates come in basically two

481
00:20:42,390 --> 00:20:39,039
flavors

482
00:20:45,029 --> 00:20:42,400
either adenylates where you have an amp

483
00:20:46,789 --> 00:20:45,039
moiety or where the moiety is just an

484
00:20:48,390 --> 00:20:46,799
orthophosphate

485
00:20:50,710 --> 00:20:48,400
thioesters on the other hand are

486
00:20:53,430 --> 00:20:50,720
significantly more diverse

487
00:20:55,110 --> 00:20:53,440
not only are they enzyme intermediates a

488
00:20:57,350 --> 00:20:55,120

feature of thioesters that we can't

489
00:20:59,750 --> 00:20:57,360
capture in this analysis

490
00:21:02,310 --> 00:20:59,760
but they're also associated with six

491
00:21:04,230 --> 00:21:02,320
different sulfur donors that are not

492
00:21:05,430 --> 00:21:04,240
part of the pantothene family of

493
00:21:06,950 --> 00:21:05,440
compounds

494
00:21:10,310 --> 00:21:06,960
and of course the pantothene family of

495
00:21:12,070 --> 00:21:10,320
compounds would be coenzyme a acp and

496
00:21:13,830 --> 00:21:12,080
the like

497
00:21:15,110 --> 00:21:13,840
returning to my roots in structural

498
00:21:17,350 --> 00:21:15,120
biology

499
00:21:20,070 --> 00:21:17,360
i wanted to look at the diverse folds

500
00:21:22,789 --> 00:21:20,080
that support thioester reactions

501
00:21:25,750 --> 00:21:22,799
and so what we did is we took the

502
00:21:29,990 --> 00:21:25,760
thioester associated reactions in keg

503
00:21:31,750 --> 00:21:30,000
and using hmm profiles from a database

504
00:21:34,950 --> 00:21:31,760
of different protein evolutionary

505
00:21:37,430 --> 00:21:34,960
lineages we were able to determine what

506
00:21:40,470 --> 00:21:37,440
fraction of the protein universe is

507
00:21:42,630 --> 00:21:40,480
associated with thioester chemistry

508
00:21:45,029 --> 00:21:42,640
as you can see here the number of

509
00:21:47,190 --> 00:21:45,039
protein evolutionary lineages that are

510
00:21:49,190 --> 00:21:47,200
associated with thioesters

511
00:21:51,750 --> 00:21:49,200
greatly exceeds the number of lineages

512
00:21:54,230 --> 00:21:51,760
that are associated with acyl phosphates

513
00:21:56,870 --> 00:21:54,240

looking at just the thioester associated

514
00:21:59,029 --> 00:21:56,880
evolutionary lineages i determined what

515
00:22:02,870 --> 00:21:59,039
fraction of the protein families are

516
00:22:05,990 --> 00:22:02,880
associated with thioester activity

517
00:22:09,990 --> 00:22:06,000
in doing so i was able to estimate which

518
00:22:11,750 --> 00:22:10,000
families emerged to utilize thioesters

519
00:22:14,470 --> 00:22:11,760
versus those families that acquired

520
00:22:16,950 --> 00:22:14,480
thioester associated activities later in

521
00:22:18,789 --> 00:22:16,960
their evolutionary history what excited

522
00:22:20,789 --> 00:22:18,799
me is one of the protein folds that

523
00:22:22,870 --> 00:22:20,799
popped out of this analysis

524
00:22:24,549 --> 00:22:22,880
was called nat iv

525
00:22:27,350 --> 00:22:24,559
and so nat iv

526
00:22:30,390 --> 00:22:27,360
is a quintessential thioester associated

527
00:22:32,549 --> 00:22:30,400
protein fold because the majority of its

528
00:22:34,789 --> 00:22:32,559
protein families are associated with

529
00:22:37,029 --> 00:22:34,799
thioester utilization

530
00:22:39,350 --> 00:22:37,039
this protein family is fully distributed

531
00:22:40,549 --> 00:22:39,360
across the tree of life in archaea in

532
00:22:43,350 --> 00:22:40,559
bacteria

533
00:22:44,870 --> 00:22:43,360
and it is associated with the binding of

534
00:22:46,390 --> 00:22:44,880
the cofactor

535
00:22:48,710 --> 00:22:46,400
co-a

536
00:22:50,950 --> 00:22:48,720
this coe binding site is remarkably

537
00:22:53,750 --> 00:22:50,960
similar to the binding sites of other

538
00:22:57,110 --> 00:22:53,760

nucleotide containing cofactors such as

539
00:23:02,390 --> 00:22:57,120
the rosmann binding of nad and the p

540
00:23:03,669 --> 00:23:02,400
loop ntpases binding mode to atp

541
00:23:05,110 --> 00:23:03,679
furthermore

542
00:23:07,350 --> 00:23:05,120
if you look at the binding mode in

543
00:23:10,549 --> 00:23:07,360
greater detail you'll see that while the

544
00:23:13,590 --> 00:23:10,559
pantothene moiety and the pyrophosphate

545
00:23:15,510 --> 00:23:13,600
moiety are bound very well by this fold

546
00:23:18,549 --> 00:23:15,520
you find that the phosphate and the

547
00:23:20,470 --> 00:23:18,559
nucleus side binding tends to be poorly

548
00:23:23,590 --> 00:23:20,480
supported

549
00:23:25,909 --> 00:23:23,600
and so what this suggests is that maybe

550
00:23:28,470 --> 00:23:25,919
this protein fold emerged

551
00:23:31,430 --> 00:23:28,480
prior to the complete development of the

552
00:23:33,190 --> 00:23:31,440
co-a cofactor

553
00:23:35,110 --> 00:23:33,200
and so this is kind of an interesting

554
00:23:38,230 --> 00:23:35,120
avenue to think about how the

555
00:23:40,070 --> 00:23:38,240
co-evolution of cofactors and proteins

556
00:23:41,909 --> 00:23:40,080
may have occurred

557
00:23:44,549 --> 00:23:41,919
and now let's turn for a second to the

558
00:23:47,029 --> 00:23:44,559
limitations of thioesters

559
00:23:49,350 --> 00:23:47,039
and the first limitation that we noticed

560
00:23:51,590 --> 00:23:49,360
is that compared to

561
00:23:54,870 --> 00:23:51,600
phospho anhydrides or even acl

562
00:23:56,950 --> 00:23:54,880
phosphates thioesters cannot activate

563
00:24:00,470 --> 00:23:56,960

carboxylic acids

564
00:24:02,630 --> 00:24:00,480
and so here we have a carboxylic acid

565
00:24:04,230 --> 00:24:02,640
attacking a phosphorus

566
00:24:06,230 --> 00:24:04,240
and this is going to form an acl

567
00:24:09,110 --> 00:24:06,240
phosphate this is the reaction that

568
00:24:11,269 --> 00:24:09,120
happens essentially in all ligases

569
00:24:13,750 --> 00:24:11,279
the acl phosphate is then attacked by

570
00:24:15,990 --> 00:24:13,760
another compound completing the ligase

571
00:24:18,549 --> 00:24:16,000
reaction

572
00:24:20,789 --> 00:24:18,559
in the case of thioesters however if a

573
00:24:22,149 --> 00:24:20,799
carboxylic acid were to attack the

574
00:24:24,310 --> 00:24:22,159
carbonyl

575
00:24:25,669 --> 00:24:24,320
the resulting compound would be an acid

576
00:24:30,630 --> 00:24:25,679
anhydride

577
00:24:31,669 --> 00:24:30,640
unstable in water

578
00:24:35,510 --> 00:24:31,679
and so

579
00:24:38,710 --> 00:24:35,520
thioesters don't provide a useful avenue

580
00:24:42,070 --> 00:24:38,720
to activate a second compound

581
00:24:44,549 --> 00:24:42,080
related to this is that acyl phosphate

582
00:24:46,630 --> 00:24:44,559
has two potential points of attack you

583
00:24:48,390 --> 00:24:46,640
can attack either the phosphorus or you

584
00:24:50,710 --> 00:24:48,400
could attack the carbonyl

585
00:24:52,789 --> 00:24:50,720
thioesters effectively have only one

586
00:24:55,269 --> 00:24:52,799
place that can be attacked by a

587
00:24:58,710 --> 00:24:55,279
nucleophile that means that phosphor

588
00:25:01,750 --> 00:24:58,720

anhydrides and acl phosphates have a lot

589
00:25:03,830 --> 00:25:01,760
more chemical flexibility than a

590
00:25:05,510 --> 00:25:03,840
thioester might have

591
00:25:09,110 --> 00:25:05,520
particularly with respect to the

592
00:25:11,909 --> 00:25:09,120
activation of carboxylic acids

593
00:25:14,390 --> 00:25:11,919
so does this mean that phosphates are

594
00:25:16,789 --> 00:25:14,400
naturally the energy currency in a world

595
00:25:19,269 --> 00:25:16,799
where activation of carboxylic acids is

596
00:25:21,510 --> 00:25:19,279
important

597
00:25:23,909 --> 00:25:21,520
not necessarily

598
00:25:26,789 --> 00:25:23,919
here i have another paper from josh this

599
00:25:29,029 --> 00:25:26,799
time from 2019 and what he showed is

600
00:25:31,669 --> 00:25:29,039
that you can take a metabolic pathway

601
00:25:33,110 --> 00:25:31,679
such as the reverse tca cycle and you

602
00:25:35,269 --> 00:25:33,120
can replace the steps that were

603
00:25:36,149 --> 00:25:35,279
associated with phosphate

604
00:25:38,789 --> 00:25:36,159
and

605
00:25:41,350 --> 00:25:38,799
use thioesters instead

606
00:25:43,830 --> 00:25:41,360
and so to do this in this case he

607
00:25:45,110 --> 00:25:43,840
proposed just two additional types of

608
00:25:47,510 --> 00:25:45,120
reactions

609
00:25:50,470 --> 00:25:47,520
in the first one he proposed a primitive

610
00:25:53,590 --> 00:25:50,480
malleol coalies and this is a reaction

611
00:25:56,390 --> 00:25:53,600
where an acetyl thioester and glyoxylate

612
00:25:58,950 --> 00:25:56,400
react to form a malleal thioester

613
00:26:01,190 --> 00:25:58,960

and in the second reaction it's simply a

614
00:26:03,669 --> 00:26:01,200
trans-thioestrofication

615
00:26:05,190 --> 00:26:03,679
between a malleal thioester and

616
00:26:07,029 --> 00:26:05,200
succinate

617
00:26:09,750 --> 00:26:07,039
and so with just these two simple

618
00:26:13,110 --> 00:26:09,760
modifications a pathway that would seem

619
00:26:15,909 --> 00:26:13,120
to be dependent on the utilization of

620
00:26:17,590 --> 00:26:15,919
phosphate can become phosphate free and

621
00:26:21,830 --> 00:26:17,600
you can potentially circumvent this

622
00:26:24,149 --> 00:26:21,840
problem of activation of carboxylates

623
00:26:25,990 --> 00:26:24,159
the second limitation of thioesters that

624
00:26:28,070 --> 00:26:26,000
sean and i have thought about or

625
00:26:30,070 --> 00:26:28,080
wondered about at great length is

626
00:26:32,870 --> 00:26:30,080
whether or not the hydrolysis of

627
00:26:35,110 --> 00:26:32,880
thioesters is coupled to significant

628
00:26:37,990 --> 00:26:35,120
conformational change

629
00:26:39,830 --> 00:26:38,000
so we know that atp and gtp hydrolysis

630
00:26:40,950 --> 00:26:39,840
can be coupled to large conformational

631
00:26:43,590 --> 00:26:40,960
changes

632
00:26:45,269 --> 00:26:43,600
but actually very little is known about

633
00:26:46,950 --> 00:26:45,279
the extent to which this occurs with

634
00:26:48,470 --> 00:26:46,960
thioesters

635
00:26:51,190 --> 00:26:48,480
it's hard to show an absence of

636
00:26:54,310 --> 00:26:51,200
knowledge so i have here kind of acute

637
00:26:56,950 --> 00:26:54,320
pubmed search analysis if you search for

638
00:27:00,230 --> 00:26:56,960

conformational change in hydrolysis

639
00:27:01,510 --> 00:27:00,240
with no third term you get about 1200

640
00:27:05,430 --> 00:27:01,520
hits

641
00:27:08,549 --> 00:27:05,440
if you add atp as a required third hit

642
00:27:10,710 --> 00:27:08,559
you drop that down to about a half of

643
00:27:14,390 --> 00:27:10,720
the total number of hits

644
00:27:17,430 --> 00:27:14,400
but if you use co a or thioester you get

645
00:27:19,590 --> 00:27:17,440
virtually no significant hits and so

646
00:27:22,789 --> 00:27:19,600
we've wondered whether or not the lack

647
00:27:24,950 --> 00:27:22,799
of thioester hydrolysis coupled to large

648
00:27:27,510 --> 00:27:24,960
conformational changes is a

649
00:27:29,990 --> 00:27:27,520
representation of our ignorance or if

650
00:27:33,350 --> 00:27:30,000
it's perhaps some fundamental limitation

651
00:27:35,669 --> 00:27:33,360
of thioesters just due to their size or

652
00:27:37,029 --> 00:27:35,679
their hydrolysis properties which of

653
00:27:38,710 --> 00:27:37,039
course would be very different than a

654
00:27:40,789 --> 00:27:38,720
fosso anhydride

655
00:27:42,950 --> 00:27:40,799
if anyone in the audience knows of a

656
00:27:45,350 --> 00:27:42,960
large protein conformational change

657
00:27:47,510 --> 00:27:45,360
coupled with thioester hydrolysis please

658
00:27:49,830 --> 00:27:47,520
email sean and i immediately we would be

659
00:27:51,110 --> 00:27:49,840
very curious to hear about it and with

660
00:27:52,950 --> 00:27:51,120
that i would like to thank you for

661
00:27:55,669 --> 00:27:52,960
listening and i would like to thank my

662
00:27:59,380 --> 00:27:55,679
collaborators for our fun discussions

663
00:28:06,310 --> 00:27:59,390

over the past few months

664
00:28:12,549 --> 00:28:09,269
okay so as unfortunately liam uh was not

665
00:28:15,110 --> 00:28:12,559
able to join us online uh we are going

666
00:28:18,310 --> 00:28:15,120
to move to our next speaker

667
00:28:20,389 --> 00:28:18,320
um let's see

668
00:28:25,269 --> 00:28:20,399
so next up we have

669
00:28:30,230 --> 00:28:27,830
from only molars group

670
00:28:37,590 --> 00:28:30,240
he will talk about gdp synthesis by a

671
00:28:42,789 --> 00:28:40,070
thank you

672
00:28:44,630 --> 00:28:42,799
yeah so today i'm excited to

673
00:28:46,950 --> 00:28:44,640
share with you a project

674
00:28:50,149 --> 00:28:46,960
that our lab was working on to identify

675
00:28:53,830 --> 00:28:50,159
a ribozyme capable of synthesizing the

676
00:28:55,110 --> 00:28:53,840
nucleoside triphosphate gtp

677
00:28:58,549 --> 00:28:55,120
so

678
00:29:01,269 --> 00:28:58,559
we know that in extant biology

679
00:29:03,750 --> 00:29:01,279
ntps are involved in many different

680
00:29:06,070 --> 00:29:03,760
biochemical processes besides being the

681
00:29:07,190 --> 00:29:06,080
monomers of rna they're also involved in

682
00:29:09,110 --> 00:29:07,200
energy

683
00:29:12,070 --> 00:29:09,120
signaling and certain nucleotide

684
00:29:14,310 --> 00:29:12,080
derivatives can act as coenzymes

685
00:29:16,630 --> 00:29:14,320
and the way that modern biology makes

686
00:29:18,710 --> 00:29:16,640
ntps is through the use of protein

687
00:29:21,350 --> 00:29:18,720
kinases

688
00:29:24,070 --> 00:29:21,360

what we wanted to investigate was

689
00:29:26,389 --> 00:29:24,080
whether or not

690
00:29:28,470 --> 00:29:26,399
this catalysis prior to coded protein

691
00:29:29,990 --> 00:29:28,480
catalysts could have been mediated by

692
00:29:32,070 --> 00:29:30,000
ribozymes

693
00:29:34,310 --> 00:29:32,080
and if rna is indeed capable of this

694
00:29:36,789 --> 00:29:34,320
type of catalysis then that might

695
00:29:40,870 --> 00:29:36,799
indicate an important role for rna in

696
00:29:41,669 --> 00:29:40,880
the replication of an rna world organism

697
00:29:44,070 --> 00:29:41,679
the

698
00:29:46,310 --> 00:29:44,080
replication of which

699
00:29:47,750 --> 00:29:46,320
might rely on three important chemical

700
00:29:49,350 --> 00:29:47,760
steps

701
00:29:50,870 --> 00:29:49,360
so first we have the synthesis of

702
00:29:52,950 --> 00:29:50,880
nucleosides

703
00:29:55,110 --> 00:29:52,960
their chemical activation

704
00:29:56,789 --> 00:29:55,120
and then the polymerization into rna

705
00:30:00,070 --> 00:29:56,799
strands

706
00:30:02,710 --> 00:30:00,080
and our lab was primarily interested in

707
00:30:04,870 --> 00:30:02,720
identifying rna that can catalyze this

708
00:30:06,549 --> 00:30:04,880
step in the middle

709
00:30:10,870 --> 00:30:06,559
and the way we do that is we use a

710
00:30:12,870 --> 00:30:10,880
technique called in vitro selections

711
00:30:14,230 --> 00:30:12,880
the general principle of an individual

712
00:30:17,029 --> 00:30:14,240
selection

713
00:30:19,990 --> 00:30:17,039

is you basically start with an enormous

714
00:30:22,549 --> 00:30:20,000
pool of randomized rna molecules

715
00:30:25,669 --> 00:30:22,559
usually on the order of 10 to the 13th

716
00:30:27,990 --> 00:30:25,679
to 10 through the 16th unique sequences

717
00:30:30,710 --> 00:30:28,000
and you subject this pool to some sort

718
00:30:33,190 --> 00:30:30,720
of functional screen

719
00:30:35,669 --> 00:30:33,200
you can also do

720
00:30:38,310 --> 00:30:35,679
reverse transcription and pcr

721
00:30:41,909 --> 00:30:38,320
amplification and transcription again in

722
00:30:43,350 --> 00:30:41,919
order to regenerate the rna pool

723
00:30:44,549 --> 00:30:43,360
and you can do multiple rounds of

724
00:30:46,549 --> 00:30:44,559
selection

725
00:30:48,549 --> 00:30:46,559
and hopefully if you've set up your

726
00:30:50,389 --> 00:30:48,559
selection system well

727
00:30:53,990 --> 00:30:50,399
your pool will then be dominated by

728
00:30:57,830 --> 00:30:56,470
and the specific activity that we were

729
00:31:00,789 --> 00:30:57,840
interested in

730
00:31:03,990 --> 00:31:00,799
was the ability of an rna molecule

731
00:31:06,630 --> 00:31:04,000
to bind cyclic tri-metaphosphate

732
00:31:08,710 --> 00:31:06,640
and thiomodified guanozine

733
00:31:11,990 --> 00:31:08,720
and react them together in order to form

734
00:31:13,590 --> 00:31:12,000
sixth io gtp

735
00:31:16,070 --> 00:31:13,600
we use a second

736
00:31:18,950 --> 00:31:16,080
ribozyme called the polymerase ribozyme

737
00:31:21,990 --> 00:31:18,960
as a sort of detection system and it

738
00:31:23,909 --> 00:31:22,000

would take freshly generated gtp and tag

739
00:31:26,230 --> 00:31:23,919
it on to the end of the active pull

740
00:31:28,870 --> 00:31:26,240
sequence and we could use this thio

741
00:31:32,710 --> 00:31:28,880
modification as a sort of handle to

742
00:31:35,669 --> 00:31:32,720
isolate those active sequences

743
00:31:38,310 --> 00:31:35,679
so there was one major hurdle that we

744
00:31:39,909 --> 00:31:38,320
needed to overcome

745
00:31:41,590 --> 00:31:39,919
in this selection

746
00:31:43,350 --> 00:31:41,600
so if we were to do the selection in

747
00:31:46,230 --> 00:31:43,360
bulk solution you can imagine a

748
00:31:47,830 --> 00:31:46,240
situation in which you have an inactive

749
00:31:49,909 --> 00:31:47,840
pool sequence

750
00:31:52,230 --> 00:31:49,919
and because this molecule can freely

751
00:31:54,630 --> 00:31:52,240
diffuse

752
00:31:56,389 --> 00:31:54,640
it might get tagged by the polymerase

753
00:31:58,230 --> 00:31:56,399
ribozyme

754
00:32:00,149 --> 00:31:58,240
such that you're pulling down inactive

755
00:32:02,230 --> 00:32:00,159
sequences

756
00:32:05,190 --> 00:32:02,240
and the way that we got around this

757
00:32:07,430 --> 00:32:05,200
was to do the selection in emulsion

758
00:32:09,909 --> 00:32:07,440
so that each pool molecule was

759
00:32:11,669 --> 00:32:09,919
sequestered in their own droplet and

760
00:32:14,389 --> 00:32:11,679
inactive sequences

761
00:32:17,110 --> 00:32:14,399
would not be able to form gtp 6th

762
00:32:19,830 --> 00:32:17,120
thiogtp and they would not get tagged by

763
00:32:21,350 --> 00:32:19,840

the polymerase ribozyme

764
00:32:22,710 --> 00:32:21,360
one other important thing that i want to

765
00:32:23,909 --> 00:32:22,720
point out here

766
00:32:25,509 --> 00:32:23,919
is this

767
00:32:28,070 --> 00:32:25,519
selection system

768
00:32:30,630 --> 00:32:28,080
relied on the coupling of the activities

769
00:32:33,110 --> 00:32:30,640
of two ribozymes

770
00:32:36,389 --> 00:32:33,120
through their common metabolite of sixth

771
00:32:40,549 --> 00:32:37,909
so a

772
00:32:42,789 --> 00:32:40,559
previous grad student in our lab

773
00:32:43,990 --> 00:32:42,799
arvin performed the selection in

774
00:32:47,110 --> 00:32:44,000
emulsion

775
00:32:50,470 --> 00:32:47,120
and he made 18 rounds of selection

776
00:32:53,269 --> 00:32:50,480
and observed an increase in pool

777
00:32:55,269 --> 00:32:53,279
activity starting at round 12.

778
00:32:58,230 --> 00:32:55,279
so you might be wondering what this off

779
00:33:00,630 --> 00:32:58,240
inactivity at round 15 is he did one

780
00:33:03,029 --> 00:33:00,640
round of mutagenic pcr in order to

781
00:33:05,269 --> 00:33:03,039
sample the local sequence space

782
00:33:07,830 --> 00:33:05,279
of the pool

783
00:33:10,470 --> 00:33:07,840
he also did high throughput sequencing

784
00:33:12,870 --> 00:33:10,480
of each round of selection and the plot

785
00:33:14,789 --> 00:33:12,880
on the right is showing the last nine

786
00:33:15,830 --> 00:33:14,799
rounds of selection

787
00:33:17,990 --> 00:33:15,840
and

788
00:33:21,590 --> 00:33:18,000

five of the major clusters

789
00:33:23,590 --> 00:33:21,600
of he observed a cluster is just

790
00:33:24,389 --> 00:33:23,600
sequences that are closely related to

791
00:33:26,710 --> 00:33:24,399
each other

792
00:33:28,470 --> 00:33:26,720
so each of these clusters is assigned a

793
00:33:30,310 --> 00:33:28,480
different color in the plot

794
00:33:32,149 --> 00:33:30,320
and the size of the stacked plot

795
00:33:34,230 --> 00:33:32,159
indicates the

796
00:33:38,389 --> 00:33:34,240
abundance of sequences within that

797
00:33:39,110 --> 00:33:38,399
cluster for a given round of selection

798
00:33:41,350 --> 00:33:39,120
so

799
00:33:43,430 --> 00:33:41,360
i next took

800
00:33:45,430 --> 00:33:43,440
candidate sequences from each one of

801
00:33:47,110 --> 00:33:45,440
these rounds of

802
00:33:47,830 --> 00:33:47,120
from each one of these clusters excuse

803
00:33:50,950 --> 00:33:47,840
me

804
00:33:52,389 --> 00:33:50,960
and tested them biochemically

805
00:33:55,669 --> 00:33:52,399
so the biochemical

806
00:33:57,990 --> 00:33:55,679
assay that i used was very similar to

807
00:34:01,269 --> 00:33:58,000
the selection step

808
00:34:03,509 --> 00:34:01,279
except for a couple key differences

809
00:34:05,190 --> 00:34:03,519
so one of them is that we are now

810
00:34:06,389 --> 00:34:05,200
challenging the sequences to use

811
00:34:11,510 --> 00:34:06,399
guanozine

812
00:34:13,990 --> 00:34:11,520
and the polymerase ribozyme is now

813
00:34:15,349 --> 00:34:14,000

taking generated gtp

814
00:34:17,829 --> 00:34:15,359
and adding it to the end of a

815
00:34:20,629 --> 00:34:17,839
radio-labeled oligo instead of to the

816
00:34:22,149 --> 00:34:20,639
end of the sequence

817
00:34:23,589 --> 00:34:22,159
and because of this

818
00:34:25,909 --> 00:34:23,599
radioactivity

819
00:34:29,990 --> 00:34:25,919
we could then monitor the incorporation

820
00:34:32,470 --> 00:34:30,000
of g using gel electrophoresis

821
00:34:33,270 --> 00:34:32,480
so if we look at one of these gels

822
00:34:34,470 --> 00:34:33,280
the

823
00:34:36,550 --> 00:34:34,480
upper band

824
00:34:37,510 --> 00:34:36,560
corresponds to successful incorporation

825
00:34:39,349 --> 00:34:37,520
of g

826
00:34:41,109 --> 00:34:39,359
and our first two lanes are negative and

827
00:34:43,750 --> 00:34:41,119
positive control

828
00:34:45,990 --> 00:34:43,760
and you could see from the

829
00:34:48,629 --> 00:34:46,000
gel and from the quantification

830
00:34:50,790 --> 00:34:48,639
that it appeared that sequences only

831
00:34:52,710 --> 00:34:50,800
from cluster one were able to

832
00:34:55,510 --> 00:34:52,720
successfully incorporate g to the

833
00:34:56,629 --> 00:34:55,520
radio-labeled oligo

834
00:34:59,030 --> 00:34:56,639
and

835
00:35:00,870 --> 00:34:59,040
we next took the

836
00:35:03,910 --> 00:35:00,880
sequence that had the highest percent

837
00:35:05,990 --> 00:35:03,920
ligation sequence number 59 and i don't

838
00:35:09,030 --> 00:35:06,000

have time to go into it but it i did a

839
00:35:11,990 --> 00:35:09,040
number of reaction optimization

840
00:35:14,150 --> 00:35:12,000
and sequence optimization to arrive at

841
00:35:15,750 --> 00:35:14,160
an optimal sequence which we renamed

842
00:35:17,829 --> 00:35:15,760
gtr1

843
00:35:21,430 --> 00:35:17,839
so that's how i'll be referring to it

844
00:35:26,550 --> 00:35:24,310
one limitation with this assay is that

845
00:35:28,550 --> 00:35:26,560
we're not really directly measuring the

846
00:35:31,589 --> 00:35:28,560
formation of gtp

847
00:35:37,430 --> 00:35:31,599
and so to assess whether or not gtr1 was

848
00:35:39,510 --> 00:35:37,440
actually making gtp we used lcms

849
00:35:41,910 --> 00:35:39,520
and i'd like to thank dr sue for help

850
00:35:42,790 --> 00:35:41,920
with these experiments

851
00:35:44,950 --> 00:35:42,800
so

852
00:35:47,910 --> 00:35:44,960
from the lc trace you can see that

853
00:35:49,349 --> 00:35:47,920
there's a peak around two minutes that's

854
00:35:55,030 --> 00:35:49,359
only present when you have nine

855
00:35:58,710 --> 00:35:57,109
and the mass spec data

856
00:36:01,910 --> 00:35:58,720
reveals a

857
00:36:03,670 --> 00:36:01,920
peak around 524 m over z

858
00:36:06,870 --> 00:36:03,680
that's only present in the nine

859
00:36:09,589 --> 00:36:06,880
micromolar gtr1 samples or the six

860
00:36:11,349 --> 00:36:09,599
micromolar gtp samples and it's absent

861
00:36:12,710 --> 00:36:11,359
in the buffer system

862
00:36:15,750 --> 00:36:12,720
and this peak

863
00:36:17,670 --> 00:36:15,760

is indicative of the presence of gtp so

864
00:36:20,390 --> 00:36:17,680
from this data we were reasonably

865
00:36:21,990 --> 00:36:20,400
confident that gtr1 was indeed making

866
00:36:24,710 --> 00:36:22,000
gtp

867
00:36:27,910 --> 00:36:24,720
and i next characterize the reaction

868
00:36:31,990 --> 00:36:27,920
kinetics of gtr1

869
00:36:36,870 --> 00:36:34,390
assay that i showed before as a time

870
00:36:39,750 --> 00:36:36,880
course we observed the rate

871
00:36:40,550 --> 00:36:39,760
of the catalyzed reaction around 1.9 per

872
00:36:42,630 --> 00:36:40,560
hour

873
00:36:44,710 --> 00:36:42,640
and the uncatalyzed reaction was on the

874
00:36:47,030 --> 00:36:44,720
order of 10 to the minus fourth

875
00:36:50,150 --> 00:36:47,040
so that means that the rate enhancement

876
00:36:52,390 --> 00:36:50,160
was around 17 000.

877
00:36:55,510 --> 00:36:52,400
i also measured the turnover number of

878
00:36:57,349 --> 00:36:55,520
the reaction by titrating the ribozyme

879
00:36:59,270 --> 00:36:57,359
concentration and holding everything

880
00:37:02,550 --> 00:36:59,280
else constant

881
00:37:05,670 --> 00:37:02,560
and i use the saturation point of these

882
00:37:09,030 --> 00:37:05,680
type of these curves to estimate the

883
00:37:11,750 --> 00:37:09,040
concentration of gtp formed and compared

884
00:37:13,829 --> 00:37:11,760
that to the concentration of ribozyme to

885
00:37:15,430 --> 00:37:13,839
determine that the turnover number was

886
00:37:17,190 --> 00:37:15,440
quite low for the ribozyme it's only

887
00:37:21,270 --> 00:37:17,200
around 1.7

888
00:37:22,390 --> 00:37:21,280

and we'll return to that at the end

889
00:37:24,790 --> 00:37:22,400
um so

890
00:37:25,829 --> 00:37:24,800
we also wanted to know

891
00:37:26,550 --> 00:37:25,839
if

892
00:37:32,470 --> 00:37:26,560
the

893
00:37:33,910 --> 00:37:32,480
now be incorporated into a growing rna

894
00:37:37,270 --> 00:37:33,920
polymer

895
00:37:39,109 --> 00:37:37,280
again

896
00:37:42,790 --> 00:37:39,119
and so this time

897
00:37:44,310 --> 00:37:42,800
we are feeding the polymerase ribozyme

898
00:37:46,790 --> 00:37:44,320
in the negative control we're only

899
00:37:48,710 --> 00:37:46,800
feeding it atp and ctp

900
00:37:51,670 --> 00:37:48,720
in the positive control we're giving it

901
00:37:54,390 --> 00:37:51,680
atp ctp and gtp

902
00:37:57,270 --> 00:37:54,400
and in our sample we're feeding it atp

903
00:38:00,390 --> 00:37:57,280
and ctp and then the reaction products

904
00:38:03,190 --> 00:38:00,400
of a gtr1 reaction to see if it can

905
00:38:05,750 --> 00:38:03,200
extend a primer on a template

906
00:38:09,190 --> 00:38:05,760
and what we observe is if you compare

907
00:38:11,109 --> 00:38:09,200
the no gtr1 condition to the plus gtr1

908
00:38:13,109 --> 00:38:11,119
condition you can see that there's

909
00:38:15,109 --> 00:38:13,119
measurably more extension at the plus

910
00:38:17,190 --> 00:38:15,119
two position which corresponds to

911
00:38:19,030 --> 00:38:17,200
incorporation of gtp

912
00:38:21,829 --> 00:38:19,040
suggesting that there is indeed

913
00:38:27,430 --> 00:38:21,839

successful incorporation of ribozyme

914
00:38:33,030 --> 00:38:30,550
and finally i wanted to examine the

915
00:38:36,069 --> 00:38:33,040
secondary structure of gt01

916
00:38:39,190 --> 00:38:36,079
using shape chemical probing

917
00:38:41,349 --> 00:38:39,200
so basically the way this re this assay

918
00:38:43,990 --> 00:38:41,359
works is

919
00:38:46,069 --> 00:38:44,000
high reactivity to the chemical probe

920
00:38:47,670 --> 00:38:46,079
indicates flexibility and single

921
00:38:50,790 --> 00:38:47,680
strandedness

922
00:38:53,750 --> 00:38:50,800
and low reactivity indicates rigidity

923
00:38:55,430 --> 00:38:53,760
and is more likely to be double-stranded

924
00:38:58,230 --> 00:38:55,440
so by measuring the

925
00:38:59,510 --> 00:38:58,240
chemical reactivity at each position

926
00:39:00,710 --> 00:38:59,520
of the

927
00:39:02,390 --> 00:39:00,720
ribozyme

928
00:39:04,390 --> 00:39:02,400
you can use that information to

929
00:39:05,589 --> 00:39:04,400
construct the secondary structure shown

930
00:39:06,790 --> 00:39:05,599
on the right

931
00:39:09,589 --> 00:39:06,800
and i'll just point out a few

932
00:39:11,670 --> 00:39:09,599
interesting features of the structure

933
00:39:12,790 --> 00:39:11,680
it appears to show this tri-helical

934
00:39:14,790 --> 00:39:12,800
junction

935
00:39:17,030 --> 00:39:14,800
and there's an interesting

936
00:39:19,750 --> 00:39:17,040
region in the loop on the right that

937
00:39:23,190 --> 00:39:19,760
appears to be protected and we believe

938
00:39:25,829 --> 00:39:23,200

that that is making tertiary con context

939
00:39:29,270 --> 00:39:25,839
with either this stem here or this loop

940
00:39:34,630 --> 00:39:32,230
so to summarize

941
00:39:37,270 --> 00:39:34,640
we used a selection in emulsion to

942
00:39:39,349 --> 00:39:37,280
identify gtr1

943
00:39:42,390 --> 00:39:39,359
and we coupled the activity of that

944
00:39:44,069 --> 00:39:42,400
ribozyme to a polymerase ribozyme

945
00:39:45,870 --> 00:39:44,079
through gtp

946
00:39:48,550 --> 00:39:45,880
and we believe that these

947
00:39:51,270 --> 00:39:48,560
triphosphorylation ribozymes strengthen

948
00:39:54,630 --> 00:39:51,280
the case for a central role of rna in an

949
00:39:59,750 --> 00:39:56,790
the turnover number of the ribozyme was

950
00:40:00,870 --> 00:39:59,760
a little low 1.7 so that's the subject

951
00:40:03,109 --> 00:40:00,880
of

952
00:40:05,750 --> 00:40:03,119
some ongoing studies

953
00:40:06,950 --> 00:40:05,760
which i'll share a little bit

954
00:40:10,870 --> 00:40:06,960
about

955
00:40:13,109 --> 00:40:10,880
we want to try to do a dope selection

956
00:40:15,349 --> 00:40:13,119
in order to identify sequences with

957
00:40:16,309 --> 00:40:15,359
higher variance

958
00:40:19,589 --> 00:40:16,319
and

959
00:40:22,710 --> 00:40:19,599
dope selection simply means that we are

960
00:40:23,670 --> 00:40:22,720
starting with a partially mutagenized

961
00:40:25,510 --> 00:40:23,680
pool

962
00:40:27,990 --> 00:40:25,520
from the parental sequence and the

963
00:40:30,870 --> 00:40:28,000

starting sequence we're going to use is

964
00:40:32,630 --> 00:40:30,880
a slightly shorter variant of gtr1 and

965
00:40:36,470 --> 00:40:32,640
that's to enable higher sequence

966
00:40:41,430 --> 00:40:39,349
and i'd finally like to thank

967
00:40:44,309 --> 00:40:41,440
um some important people who contributed

968
00:40:46,710 --> 00:40:44,319
to this work of course my pioli

969
00:40:49,190 --> 00:40:46,720
arvin this was his main thesis project

970
00:40:51,910 --> 00:40:49,200
and he spent a lot of time and effort

971
00:40:53,990 --> 00:40:51,920
working on the pilot experiment for the

972
00:40:55,030 --> 00:40:54,000
emulsion selection doing the selection

973
00:40:57,750 --> 00:40:55,040
itself

974
00:40:59,990 --> 00:40:57,760
and analyzing the sequencing data i'd

975
00:41:02,550 --> 00:41:00,000
also like to thank dr shu from the mass

976
00:41:06,069 --> 00:41:02,560
spec facility at ucsd

977
00:41:09,109 --> 00:41:06,079
sophie for help with analyzing the hts

978
00:41:11,430 --> 00:41:09,119
data and doug magdy for help

979
00:41:14,950 --> 00:41:11,440
tuning the droplet sizes for the

980
00:41:28,950 --> 00:41:16,710
and i'll take any questions if you're

981
00:41:31,109 --> 00:41:29,829
um

982
00:41:33,349 --> 00:41:31,119
so one

983
00:41:35,030 --> 00:41:33,359
hypothesis of course for the low

984
00:41:36,510 --> 00:41:35,040
turnover number

985
00:41:39,349 --> 00:41:36,520
is that the right enzyme is

986
00:41:40,630 --> 00:41:39,359
stoichiometric rather than catalytic so

987
00:41:43,510 --> 00:41:40,640
have you guys

988
00:41:44,870 --> 00:41:43,520

done any analysis to see if the ribozyme

989
00:41:47,030 --> 00:41:44,880
is itself

990
00:41:50,309 --> 00:41:47,040
modified or spent

991
00:41:52,390 --> 00:41:50,319
by the reaction of the metaphosphate

992
00:41:56,069 --> 00:41:52,400
um that's a good thought

993
00:41:58,309 --> 00:41:56,079
we haven't tested anything yet

994
00:42:00,309 --> 00:41:58,319
i think to your point what we believe is

995
00:42:02,790 --> 00:42:00,319
happening is

996
00:42:03,750 --> 00:42:02,800
when we were doing the selection

997
00:42:06,470 --> 00:42:03,760
we

998
00:42:11,270 --> 00:42:06,480
progressively reduced the concentration

999
00:42:15,430 --> 00:42:12,950
so that by the end of the selection they

1000
00:42:18,390 --> 00:42:15,440
were quite low and we believe that the

1001
00:42:20,870 --> 00:42:18,400
ribozyme is just really holding on to

1002
00:42:23,270 --> 00:42:20,880
the product

1003
00:42:25,190 --> 00:42:23,280
so we're hoping that with the dope

1004
00:42:27,430 --> 00:42:25,200
selection we'll be able to identify

1005
00:42:32,710 --> 00:42:27,440
sequences that can help release the

1006
00:42:37,349 --> 00:42:35,270
uh chris mayer bacon university of

1007
00:42:38,790 --> 00:42:37,359
maryland baltimore county a very

1008
00:42:42,790 --> 00:42:38,800
interesting talk

1009
00:42:45,030 --> 00:42:42,800
i'm curious if you've

1010
00:42:47,109 --> 00:42:45,040
with the gtr1

1011
00:42:49,030 --> 00:42:47,119
uh sequence if

1012
00:42:51,030 --> 00:42:49,040
that's capable of

1013
00:42:51,829 --> 00:42:51,040

uh adding other

1014
00:42:53,349 --> 00:42:51,839
uh

1015
00:42:57,349 --> 00:42:53,359
other

1016
00:42:58,710 --> 00:42:57,359
ntps besides quantizing or

1017
00:43:01,510 --> 00:42:58,720
that

1018
00:43:04,230 --> 00:43:01,520
addition of other ntps would require

1019
00:43:06,470 --> 00:43:04,240
slightly different sequences of rna

1020
00:43:09,030 --> 00:43:06,480
yeah i think that's a great

1021
00:43:10,950 --> 00:43:09,040
question it's definitely

1022
00:43:14,390 --> 00:43:10,960
a subject for future studies in our lab

1023
00:43:17,910 --> 00:43:14,400
we are definitely interested in

1024
00:43:21,990 --> 00:43:17,920
identifying other sequences that can use

1025
00:43:23,990 --> 00:43:22,000
atp ctp utp

1026
00:43:25,750 --> 00:43:24,000
we haven't actually directly tested it

1027
00:43:26,470 --> 00:43:25,760
using gtr1

1028
00:43:28,230 --> 00:43:26,480
but

1029
00:43:29,430 --> 00:43:28,240
maybe i'll jump in the lab next week and

1030
00:43:31,349 --> 00:43:29,440
try it

1031
00:43:34,309 --> 00:43:31,359
it will be very interesting yeah thank

1032
00:43:39,109 --> 00:43:34,319
you for the question chris

1033
00:43:43,430 --> 00:43:41,349
did you ever test um all those other

1034
00:43:47,030 --> 00:43:43,440
clusters that ended up not working if it

1035
00:43:49,750 --> 00:43:48,950
derivative

1036
00:43:52,390 --> 00:43:49,760
or

1037
00:43:54,470 --> 00:43:52,400
um was there probably just an issue like

1038
00:43:55,829 --> 00:43:54,480

leakiness in the

1039
00:43:57,349 --> 00:43:55,839
uh

1040
00:44:01,190 --> 00:43:57,359
selection

1041
00:44:06,790 --> 00:44:04,550
one thought that i had about that is

1042
00:44:09,109 --> 00:44:06,800
the activity of those

1043
00:44:12,150 --> 00:44:09,119
so sorry let me back up

1044
00:44:14,550 --> 00:44:12,160
we also tested the activity of those

1045
00:44:16,710 --> 00:44:14,560
ribozymes using six thiaguenozine i was

1046
00:44:18,630 --> 00:44:16,720
just showing the guanozine reactions and

1047
00:44:21,270 --> 00:44:18,640
some of those other clusters are active

1048
00:44:23,910 --> 00:44:21,280
for six thiaguanosine but not guanozine

1049
00:44:25,030 --> 00:44:23,920
so cluster one actually had i believe

1050
00:44:27,109 --> 00:44:25,040
the

1051
00:44:29,670 --> 00:44:27,119
reverse phenotype where it wasn't as

1052
00:44:34,790 --> 00:44:29,680
active with six thiaguanosine but it was

1053
00:44:40,550 --> 00:44:37,349
thank you okay

1054
00:44:43,030 --> 00:44:40,560
and uh let's move on to the next speaker

1055
00:44:45,430 --> 00:44:43,040
um roy black from university of

1056
00:44:47,030 --> 00:44:45,440
washington who will provide the details

1057
00:44:49,670 --> 00:44:47,040
on how deep

1058
00:44:51,910 --> 00:44:49,680
the peptides bind to vehicles composed

1059
00:44:53,750 --> 00:44:51,920
of a prebiotic fatty acids and are

1060
00:45:12,550 --> 00:44:53,760
compatible with vehicle stability and

1061
00:45:12,560 --> 00:45:18,150
so just use this

1062
00:45:23,750 --> 00:45:20,950
okay thanks to the organizers for the

1063
00:45:24,630 --> 00:45:23,760

opportunity to speak

1064
00:45:27,109 --> 00:45:24,640
it's

1065
00:45:29,829 --> 00:45:27,119
uh late uh in the

1066
00:45:32,790 --> 00:45:29,839
last day of the conference so

1067
00:45:34,470 --> 00:45:32,800
i'm going to be a bit provocative

1068
00:45:38,950 --> 00:45:34,480
um

1069
00:45:38,960 --> 00:45:42,069
over here

1070
00:45:47,349 --> 00:45:45,109
if i can get the slides going i guess

1071
00:45:51,349 --> 00:45:47,359
okay

1072
00:45:55,030 --> 00:45:51,359
so i'm going to uh suggest that

1073
00:45:56,630 --> 00:45:55,040
the big question in the origin of

1074
00:45:58,950 --> 00:45:56,640
cells

1075
00:46:00,069 --> 00:45:58,960
is the following

1076
00:46:02,710 --> 00:46:00,079
do

1077
00:46:05,910 --> 00:46:02,720
generic oligomers that is with

1078
00:46:09,430 --> 00:46:05,920
relatively non-specific sequence

1079
00:46:13,109 --> 00:46:09,440
confer a selective advantage to

1080
00:46:20,150 --> 00:46:13,119
fatty acid vesicles

1081
00:46:27,109 --> 00:46:23,109
a quick reminder of what fatty acid

1082
00:46:30,950 --> 00:46:28,710
fatty acids

1083
00:46:33,030 --> 00:46:30,960
such as

1084
00:46:33,829 --> 00:46:33,040
decanoic acid

1085
00:46:36,870 --> 00:46:33,839
are

1086
00:46:39,470 --> 00:46:36,880
prebiotic amphiphiles

1087
00:46:41,430 --> 00:46:39,480
that when placed in water

1088
00:46:43,750 --> 00:46:41,440

spontaneously

1089
00:46:46,710 --> 00:46:43,760
form micelles

1090
00:46:49,190 --> 00:46:46,720
and bi-layered structures called

1091
00:46:53,270 --> 00:46:49,200
vesicles

1092
00:46:56,870 --> 00:46:53,280
so what i'm proposing is that including

1093
00:47:00,150 --> 00:46:56,880
analgamer in this system would

1094
00:47:04,550 --> 00:47:00,160
increase the stability or growth of

1095
00:47:04,560 --> 00:47:08,390
and if that's the case

1096
00:47:14,150 --> 00:47:10,309
i'm arguing that these effects could

1097
00:47:16,390 --> 00:47:14,160
have been a key driver of the evolution

1098
00:47:19,190 --> 00:47:16,400
toward complexity

1099
00:47:22,790 --> 00:47:19,200
prior to the advent of replication of

1100
00:47:24,390 --> 00:47:22,800
specific sequences

1101
00:47:25,349 --> 00:47:24,400
so we've focused

1102
00:47:28,950 --> 00:47:25,359
on

1103
00:47:31,670 --> 00:47:28,960
whether peptides have such effects

1104
00:47:33,829 --> 00:47:31,680
uh because peptides are the simplest

1105
00:47:36,630 --> 00:47:33,839
biological oligomer

1106
00:47:38,549 --> 00:47:36,640
uh resulting simply from the joining

1107
00:47:42,710 --> 00:47:38,559
of

1108
00:47:50,829 --> 00:47:46,549
so another way to put it is

1109
00:47:54,230 --> 00:47:50,839
does simply joining two amino

1110
00:47:55,750 --> 00:47:54,240
acids in the context of a fatty acid

1111
00:47:59,829 --> 00:47:55,760
vesicle

1112
00:48:03,190 --> 00:47:59,839
have evolutionary consequences

1113
00:48:04,950 --> 00:48:03,200

and i'll give you my answer up front

1114
00:48:07,750 --> 00:48:04,960
uh yes

1115
00:48:10,069 --> 00:48:07,760
we found that unmodified simple

1116
00:48:11,270 --> 00:48:10,079
unmodified dipeptides

1117
00:48:12,470 --> 00:48:11,280
increase

1118
00:48:14,230 --> 00:48:12,480
vesicle

1119
00:48:16,870 --> 00:48:14,240
stability

1120
00:48:19,109 --> 00:48:16,880
as measured by resistance to salt

1121
00:48:22,390 --> 00:48:19,119
induced flocculation

1122
00:48:26,710 --> 00:48:22,400
and increase vesicle growth

1123
00:48:30,790 --> 00:48:26,720
as monitored by the increase in size

1124
00:48:33,910 --> 00:48:30,800
upon addition of of micelles

1125
00:48:35,510 --> 00:48:33,920
and that the dipeptides do this to a

1126
00:48:39,030 --> 00:48:35,520
greater extent

1127
00:48:41,829 --> 00:48:39,040
than unjoined amino acids

1128
00:48:45,670 --> 00:48:41,839
so why is this important

1129
00:48:46,790 --> 00:48:45,680
it means that a population of fatty acid

1130
00:48:50,390 --> 00:48:46,800
vesicles

1131
00:48:53,670 --> 00:48:50,400
would change over time that is evolve

1132
00:48:56,069 --> 00:48:53,680
as those associated with peptides

1133
00:48:57,990 --> 00:48:56,079
outcompeted others

1134
00:48:59,829 --> 00:48:58,000
for fatty acids

1135
00:49:04,230 --> 00:48:59,839
due to their greater

1136
00:49:08,630 --> 00:49:06,710
okay i'm going to go over the data in

1137
00:49:09,589 --> 00:49:08,640
three parts

1138
00:49:12,470 --> 00:49:09,599

first

1139
00:49:16,230 --> 00:49:12,480
do amino acids and dipeptides

1140
00:49:19,910 --> 00:49:16,240
bind to fatty acid vesicles

1141
00:49:21,430 --> 00:49:19,920
using diffusion nmr we've found that

1142
00:49:24,230 --> 00:49:21,440
all the

1143
00:49:28,069 --> 00:49:24,240
amino acids that we've tested

1144
00:49:31,109 --> 00:49:28,079
do bind to somewhat variable extent

1145
00:49:34,549 --> 00:49:31,119
here we're plotting the percent bound to

1146
00:49:37,829 --> 00:49:34,559
the fatty acid vesicle

1147
00:49:41,750 --> 00:49:37,839
and the dimers of these amino acids

1148
00:49:42,829 --> 00:49:41,760
also bind uh with somewhat altered

1149
00:49:46,309 --> 00:49:42,839
relative

1150
00:49:50,309 --> 00:49:46,319
affinities now one complication with

1151
00:49:51,950 --> 00:49:50,319
these data is that our nmr signal may be

1152
00:49:55,109 --> 00:49:51,960
detecting

1153
00:49:59,030 --> 00:49:55,119
encapsulation as well as

1154
00:50:01,750 --> 00:49:59,040
binding but either way the key point the

1155
00:50:05,589 --> 00:50:01,760
key question now is does such

1156
00:50:08,630 --> 00:50:05,599
association have any beneficial effects

1157
00:50:14,470 --> 00:50:08,640
on uh the vesicles

1158
00:50:19,109 --> 00:50:16,069
when

1159
00:50:21,510 --> 00:50:19,119
decanoic acid vesicles are exposed to a

1160
00:50:23,270 --> 00:50:21,520
high concentration of salt

1161
00:50:25,030 --> 00:50:23,280
they aggregate

1162
00:50:28,150 --> 00:50:25,040
into these large

1163
00:50:31,430 --> 00:50:28,160

structures called flocks

1164
00:50:34,710 --> 00:50:31,440
and this is bad for the vesicles

1165
00:50:36,790 --> 00:50:34,720
they can't grow and divide in this state

1166
00:50:38,630 --> 00:50:36,800
so you could say they're they're they're

1167
00:50:40,470 --> 00:50:38,640
dormant

1168
00:50:43,510 --> 00:50:40,480
the flocks

1169
00:50:45,990 --> 00:50:43,520
scatter light to a much greater extent

1170
00:50:49,190 --> 00:50:46,000
than vesicles do

1171
00:50:50,470 --> 00:50:49,200
so we can use the extent of light

1172
00:50:52,710 --> 00:50:50,480
scattering

1173
00:50:55,910 --> 00:50:52,720
as a quantitative measure of

1174
00:51:01,030 --> 00:50:57,910
and with this assay

1175
00:51:02,710 --> 00:51:01,040
we find that a number

1176
00:51:07,270 --> 00:51:02,720
of simple

1177
00:51:09,510 --> 00:51:07,280
unmodified dipeptides do inhibit salt

1178
00:51:13,190 --> 00:51:09,520
induced flocculation

1179
00:51:17,510 --> 00:51:13,200
preserving the ability of the vesicles

1180
00:51:24,390 --> 00:51:19,829
now there is some specificity to this

1181
00:51:28,230 --> 00:51:24,400
phenomenon all the effective dipeptides

1182
00:51:30,390 --> 00:51:28,240
include a leucine residue

1183
00:51:32,230 --> 00:51:30,400
and we think part of the explanation for

1184
00:51:34,309 --> 00:51:32,240
that specificity

1185
00:51:35,670 --> 00:51:34,319
is the hydrophobicity

1186
00:51:39,589 --> 00:51:35,680
of leucine

1187
00:51:42,150 --> 00:51:39,599
leucine contains a relatively long

1188
00:51:44,150 --> 00:51:42,160

hydrophobic side chain

1189
00:51:46,390 --> 00:51:44,160
which could actually fit into the

1190
00:51:48,470 --> 00:51:46,400
hydrophobic core

1191
00:51:51,670 --> 00:51:48,480
of the bilayer

1192
00:51:53,750 --> 00:51:51,680
thereby anchoring the peptide uh to the

1193
00:51:56,069 --> 00:51:53,760
membrane

1194
00:51:58,150 --> 00:51:56,079
in any event the key take them here is

1195
00:51:59,829 --> 00:51:58,160
that whatever the mechanism

1196
00:52:03,109 --> 00:51:59,839
a number of

1197
00:52:06,790 --> 00:52:03,119
uh simple unmodified dipeptides

1198
00:52:09,750 --> 00:52:06,800
do inhibit salt-induced flocculation

1199
00:52:12,950 --> 00:52:09,760
and that sets up the critical question

1200
00:52:16,069 --> 00:52:12,960
are these effective peptides

1201
00:52:17,270 --> 00:52:16,079
more effective than their unjoined amino

1202
00:52:20,069 --> 00:52:17,280
acids

1203
00:52:22,470 --> 00:52:20,079
and the answer is yes

1204
00:52:30,230 --> 00:52:22,480
unjoined leucine

1205
00:52:33,190 --> 00:52:30,240
do not inhibit salt induced flocculation

1206
00:52:36,710 --> 00:52:33,200
so the amino acids do have to be joined

1207
00:52:40,470 --> 00:52:39,030
so vesicles that

1208
00:52:42,950 --> 00:52:40,480
acquired

1209
00:52:45,750 --> 00:52:42,960
and eventually made

1210
00:52:47,750 --> 00:52:45,760
dipeptides would have an advantage in

1211
00:52:53,030 --> 00:52:47,760
salty environments

1212
00:53:01,910 --> 00:52:56,630
so do the dipeptides actually affect the

1213
00:53:08,870 --> 00:53:03,990

by way of background

1214
00:53:10,790 --> 00:53:08,880
if you add a bolus of of my cells to

1215
00:53:13,109 --> 00:53:10,800
fatty acid vesicles

1216
00:53:16,790 --> 00:53:13,119
the vesicles will grow

1217
00:53:17,670 --> 00:53:16,800
by incorporating micellar fatty acids

1218
00:53:22,470 --> 00:53:17,680
and

1219
00:53:28,470 --> 00:53:26,069
so zoe todd with whom we collaborate at

1220
00:53:31,430 --> 00:53:28,480
the university of washington

1221
00:53:35,270 --> 00:53:31,440
asked whether including

1222
00:53:37,910 --> 00:53:35,280
a dipeptide in this system would affect

1223
00:53:40,870 --> 00:53:37,920
the rate of growth upon the addition of

1224
00:53:46,790 --> 00:53:44,309
she used fret analysis to measure the

1225
00:53:47,750 --> 00:53:46,800
increase in surface area

1226
00:53:49,349 --> 00:53:47,760
and

1227
00:53:54,630 --> 00:53:49,359
from that we can

1228
00:54:00,309 --> 00:53:58,069
so here we're plotting the radius as a

1229
00:54:03,109 --> 00:54:00,319
function of time

1230
00:54:05,109 --> 00:54:03,119
following the addition of micelles

1231
00:54:08,390 --> 00:54:05,119
and you can see clearly that with the

1232
00:54:11,589 --> 00:54:08,400
addition of the lulu dipeptide

1233
00:54:14,630 --> 00:54:11,599
we get a greater rate of growth

1234
00:54:15,829 --> 00:54:14,640
than in the case with the control

1235
00:54:19,190 --> 00:54:15,839
vesicles

1236
00:54:20,710 --> 00:54:19,200
without added dipeptide

1237
00:54:22,870 --> 00:54:20,720
in contrast

1238
00:54:25,990 --> 00:54:22,880

unjoined leucine

1239
00:54:28,710 --> 00:54:26,000
does not affect the rate of growth of

1240
00:54:31,069 --> 00:54:28,720
the vesicles

1241
00:54:33,910 --> 00:54:31,079
and zoe found that other

1242
00:54:35,910 --> 00:54:33,920
leucine-containing dipeptides

1243
00:54:39,109 --> 00:54:35,920
also increase

1244
00:54:41,829 --> 00:54:39,119
the rate of growth and

1245
00:54:43,190 --> 00:54:41,839
as we saw when we were looking at

1246
00:54:46,870 --> 00:54:43,200
effects on

1247
00:54:46,880 --> 00:54:50,789
sorry

1248
00:54:59,109 --> 00:54:54,870
a peptide that does not contain leucine

1249
00:55:01,589 --> 00:54:59,910
so

1250
00:55:04,710 --> 00:55:01,599
in conclusion

1251
00:55:07,990 --> 00:55:04,720
simple unmodified dipeptides

1252
00:55:09,430 --> 00:55:08,000
increase fatty acid vesicle

1253
00:55:10,950 --> 00:55:09,440
stability

1254
00:55:11,990 --> 00:55:10,960
and growth

1255
00:55:14,150 --> 00:55:12,000
and

1256
00:55:17,030 --> 00:55:14,160
they do so to a greater extent than

1257
00:55:19,670 --> 00:55:17,040
unjoined amino acids

1258
00:55:22,950 --> 00:55:19,680
so what are the implications of this

1259
00:55:25,270 --> 00:55:22,960
well this is what i suggest

1260
00:55:27,349 --> 00:55:25,280
as i said i'd be a bit provocative to

1261
00:55:30,390 --> 00:55:27,359
try to keep people awake

1262
00:55:31,910 --> 00:55:30,400
evolution began with the simple joining

1263
00:55:33,829 --> 00:55:31,920

of

1264
00:55:37,750 --> 00:55:33,839
amino acids

1265
00:55:39,589 --> 00:55:37,760
in association with fatty acid vesicles

1266
00:55:43,030 --> 00:55:39,599
this led to the emergence of a

1267
00:55:44,549 --> 00:55:43,040
population of vesicles associated with

1268
00:55:47,109 --> 00:55:44,559
dipeptides

1269
00:55:50,630 --> 00:55:47,119
because those vesicles could out-compete

1270
00:55:53,030 --> 00:55:50,640
others for free fatty acids

1271
00:55:56,150 --> 00:55:53,040
and i further suggest that vesicles

1272
00:55:58,710 --> 00:55:56,160
bearing nucleotides as well

1273
00:56:00,230 --> 00:55:58,720
may have been most favored

1274
00:56:02,390 --> 00:56:00,240
but that would have been because

1275
00:56:05,750 --> 00:56:02,400
nucleotides can actually

1276
00:56:07,670 --> 00:56:05,760
activate amino acids for peptide bond

1277
00:56:10,549 --> 00:56:07,680
synthesis

1278
00:56:12,069 --> 00:56:10,559
not because the nucleotides polymerized

1279
00:56:15,510 --> 00:56:12,079
and started

1280
00:56:19,349 --> 00:56:15,520
replicating from the get-go

1281
00:56:23,910 --> 00:56:19,359
and so this scheme suggests that

1282
00:56:25,990 --> 00:56:23,920
this trinity of membranes peptides and

1283
00:56:28,390 --> 00:56:26,000
nucleotides

1284
00:56:30,950 --> 00:56:28,400
emerged at the very beginning

1285
00:56:31,829 --> 00:56:30,960
of the origin of

1286
00:56:32,710 --> 00:56:31,839
life

1287
00:56:36,710 --> 00:56:32,720
and

1288
00:56:40,309 --> 00:56:36,720

indeed actually drove the progression

1289
00:56:45,510 --> 00:56:41,990
and so i'd like to recognize in

1290
00:56:49,910 --> 00:56:45,520
particular zoe for all the work on the

1291
00:56:52,069 --> 00:56:49,920
growth and ming zhenjua did all the

1292
00:56:53,109 --> 00:56:52,079
the nmr work

1293
00:57:00,630 --> 00:56:53,119
thank you

1294
00:57:05,430 --> 00:57:02,789
hello anthony burnett here from georgia

1295
00:57:07,589 --> 00:57:05,440
tech and i was wondering you you were

1296
00:57:09,750 --> 00:57:07,599
speaking of testing different

1297
00:57:12,069 --> 00:57:09,760
dipeptides to see how they worked with

1298
00:57:13,910 --> 00:57:12,079
these different lipid vesicles have you

1299
00:57:15,109 --> 00:57:13,920
given any thought to selection in the

1300
00:57:17,589 --> 00:57:15,119
other direction could there be

1301
00:57:19,190 --> 00:57:17,599
particular lipids that would be selected

1302
00:57:21,270 --> 00:57:19,200
because they would

1303
00:57:23,670 --> 00:57:21,280
grow better in an environment that had

1304
00:57:26,069 --> 00:57:23,680
dipeptides

1305
00:57:28,309 --> 00:57:26,079
uh yeah very interesting question i mean

1306
00:57:31,430 --> 00:57:28,319
i think this this is a

1307
00:57:34,789 --> 00:57:31,440
a simplified system using just pure

1308
00:57:37,589 --> 00:57:34,799
one one particular uh fatty acid

1309
00:57:41,589 --> 00:57:37,599
and uh yeah that would be a good good

1310
00:57:47,030 --> 00:57:44,309
very interesting talk over here

1311
00:57:49,230 --> 00:57:47,040
um i'm curious about whether or not you

1312
00:57:51,270 --> 00:57:49,240
have any quantitative information on

1313
00:57:53,829 --> 00:57:51,280

stoichiometry so how many of these

1314
00:57:55,990 --> 00:57:53,839
dipeptides might you need for amphiphyl

1315
00:57:58,549 --> 00:57:56,000
molecule or per

1316
00:58:00,710 --> 00:57:58,559
uh surface area of the

1317
00:58:01,829 --> 00:58:00,720
vesicle just to have the stabilizing

1318
00:58:04,230 --> 00:58:01,839
effect

1319
00:58:06,789 --> 00:58:04,240
yeah no that that's a great question and

1320
00:58:08,710 --> 00:58:06,799
uh i've been conferring with jason

1321
00:58:11,589 --> 00:58:08,720
greenwald here at the conference about

1322
00:58:15,030 --> 00:58:11,599
how you really interpret the nmr data so

1323
00:58:17,510 --> 00:58:15,040
it's it's it's not easy to to really

1324
00:58:18,870 --> 00:58:17,520
again for one thing to distinguish

1325
00:58:22,309 --> 00:58:18,880
what's bound

1326
00:58:24,789 --> 00:58:22,319
from what's encapsulated so a short

1327
00:58:28,069 --> 00:58:24,799
answer no but yes that would be very

1328
00:58:30,789 --> 00:58:29,510
okay

1329
00:58:32,390 --> 00:58:30,799
so

1330
00:58:35,589 --> 00:58:32,400
for the sake of keeping up with the

1331
00:58:38,560 --> 00:58:35,599
schedule i would like to move on to the

1332
00:58:40,390 --> 00:58:38,570
next speakers let's thank dr uh

1333
00:58:43,430 --> 00:58:40,400
[Music]

1334
00:58:47,829 --> 00:58:46,150
please stay after this

1335
00:58:51,829 --> 00:58:47,839
the last speaker

1336
00:58:54,870 --> 00:58:51,839
we will have a 15 minute q a session

1337
00:58:56,230 --> 00:58:54,880
so you will still have chance to ask

1338
00:58:58,789 --> 00:58:56,240

your questions

1339
00:59:01,829 --> 00:58:58,799
so our last but not least speakers of

1340
00:59:04,710 --> 00:59:01,839
this session is kavita matanesh

1341
00:59:06,789 --> 00:59:04,720
from georgia tech and she will be

1342
00:59:09,430 --> 00:59:06,799
talking about molecular memory of

1343
00:59:23,670 --> 00:59:09,440
chemical systems

1344
00:59:28,549 --> 00:59:26,710
hello uh good afternoon everyone um

1345
00:59:30,230 --> 00:59:28,559
i am going to be talking about memory

1346
00:59:34,230 --> 00:59:30,240
and molecules today

1347
00:59:36,549 --> 00:59:34,240
um and um just to get us started

1348
00:59:39,510 --> 00:59:36,559
i would like to present a framework

1349
00:59:40,710 --> 00:59:39,520
within which biochemists see the origin

1350
00:59:44,069 --> 00:59:40,720
of life

1351
00:59:47,430 --> 00:59:44,079
uh we typically see very small molecules

1352
00:59:49,910 --> 00:59:47,440
or monomers going to slightly larger

1353
00:59:52,549 --> 00:59:49,920
uh groups of monomers and oligomers

1354
00:59:56,309 --> 00:59:52,559
which then go to slightly even larger

1355
00:59:58,950 --> 00:59:56,319
oligomers and then much much much later

1356
01:00:00,789 --> 00:59:58,960
things get much much much more complex

1357
01:00:03,829 --> 01:00:00,799
to give you life

1358
01:00:06,630 --> 01:00:03,839
and um i guess

1359
01:00:08,549 --> 01:00:06,640
um i really i really liked what roy said

1360
01:00:11,109 --> 01:00:08,559
uh in terms of provocative statements on

1361
01:00:14,630 --> 01:00:11,119
a friday afternoon so i'm gonna go ahead

1362
01:00:19,589 --> 01:00:16,309
we in the williams lab are trying to

1363
01:00:22,630 --> 01:00:19,599

define this idea of molecular memory at

1364
01:00:24,710 --> 01:00:22,640
prebiotic chemistry

1365
01:00:27,030 --> 01:00:24,720
we believe that the origin and evolution

1366
01:00:29,750 --> 01:00:27,040
of life is the origin and evolution of

1367
01:00:31,109 --> 01:00:29,760
sophisticated molecular memory

1368
01:00:32,390 --> 01:00:31,119
now i believe

1369
01:00:34,230 --> 01:00:32,400
very

1370
01:00:36,150 --> 01:00:34,240
i believe many many people in this

1371
01:00:38,470 --> 01:00:36,160
community will agree with the statement

1372
01:00:42,069 --> 01:00:38,480
but very very few people would agree on

1373
01:00:43,589 --> 01:00:42,079
what constitutes molecular memory and we

1374
01:00:45,510 --> 01:00:43,599
are going to try to define it in the

1375
01:00:48,230 --> 01:00:45,520
next few slides

1376
01:00:50,789 --> 01:00:48,240
in order to do that

1377
01:00:52,950 --> 01:00:50,799
we are going to ask two main questions

1378
01:00:56,230 --> 01:00:52,960
the first one being what are the

1379
01:00:58,870 --> 01:00:56,240
strategies that biology uses to record

1380
01:01:00,710 --> 01:00:58,880
the environmental information

1381
01:01:03,430 --> 01:01:00,720
and of these strategies what are the

1382
01:01:04,630 --> 01:01:03,440
strategies that can be

1383
01:01:06,230 --> 01:01:04,640
extended

1384
01:01:08,549 --> 01:01:06,240
to chemical systems what are the

1385
01:01:11,109 --> 01:01:08,559
strategies that chemical systems can use

1386
01:01:11,990 --> 01:01:11,119
to record environmental information

1387
01:01:13,510 --> 01:01:12,000
the

1388
01:01:15,270 --> 01:01:13,520

presumption being that environmental

1389
01:01:17,109 --> 01:01:15,280
information was one of the driving

1390
01:01:19,270 --> 01:01:17,119
factors of evolution

1391
01:01:20,870 --> 01:01:19,280
and it's important for systems to

1392
01:01:24,230 --> 01:01:20,880
respond to the environment to

1393
01:01:26,069 --> 01:01:24,240
continuously change and evolve

1394
01:01:27,910 --> 01:01:26,079
with that premise in mind and with those

1395
01:01:29,510 --> 01:01:27,920
questions in mind i'm just going to go

1396
01:01:31,750 --> 01:01:29,520
ahead and show you our ideas of

1397
01:01:33,510 --> 01:01:31,760
molecular memory

1398
01:01:36,870 --> 01:01:33,520
and we believe that these are the

1399
01:01:39,990 --> 01:01:36,880
chemical strategies in place in biology

1400
01:01:42,069 --> 01:01:40,000
today that help biological systems

1401
01:01:43,349 --> 01:01:42,079
record environmental information and

1402
01:01:46,870 --> 01:01:43,359
we're going to go through some of them

1403
01:01:50,150 --> 01:01:46,880
i'm going to talk about why we think so

1404
01:01:54,309 --> 01:01:50,160
the first one the first strategy that

1405
01:01:58,870 --> 01:01:54,319
we believe conferred memory two systems

1406
01:02:03,670 --> 01:02:01,589
all right the first strategy is we

1407
01:02:07,670 --> 01:02:03,680
believe chemical identity

1408
01:02:08,950 --> 01:02:07,680
now we have redefined chemical identity

1409
01:02:09,750 --> 01:02:08,960
to mean

1410
01:02:13,589 --> 01:02:09,760
these

1411
01:02:16,630 --> 01:02:13,599
specific structures of molecules used in

1412
01:02:19,190 --> 01:02:16,640
biochemistry or biology today

1413
01:02:22,069 --> 01:02:19,200

typically they would be the structure of

1414
01:02:24,150 --> 01:02:22,079
adenosine thymine cytosine and guanine

1415
01:02:25,109 --> 01:02:24,160
in terms of dna

1416
01:02:27,589 --> 01:02:25,119
and

1417
01:02:29,190 --> 01:02:27,599
biology has used these molecules has

1418
01:02:32,630 --> 01:02:29,200
used the chemical identity of these

1419
01:02:35,750 --> 01:02:32,640
molecules in very complicated structures

1420
01:02:38,230 --> 01:02:35,760
over time fantastically to record memory

1421
01:02:41,029 --> 01:02:38,240
over 4 billion years and that's that's

1422
01:02:42,789 --> 01:02:41,039
amazing biology is great at recording

1423
01:02:46,710 --> 01:02:42,799
memory in these specifically in these

1424
01:02:49,109 --> 01:02:46,720
molecules over a huge period of time

1425
01:02:50,150 --> 01:02:49,119
but it extends beyond that so it's it

1426
01:02:52,870 --> 01:02:50,160
extends

1427
01:02:55,910 --> 01:02:52,880
um chemical identity goes much beyond ac

1428
01:02:58,150 --> 01:02:55,920
and gnt and it goes

1429
01:03:00,789 --> 01:02:58,160
uh beyond that in terms of dna

1430
01:03:03,750 --> 01:03:00,799
modifications uh in terms of chromatin

1431
01:03:06,069 --> 01:03:03,760
modifications biology responds to the

1432
01:03:07,829 --> 01:03:06,079
environment epigenetic modifications are

1433
01:03:09,109 --> 01:03:07,839
the ways in which biology responds to

1434
01:03:11,990 --> 01:03:09,119
the environment

1435
01:03:15,029 --> 01:03:12,000
and in and incorporates changes or

1436
01:03:17,430 --> 01:03:15,039
alterations into the chemical identity

1437
01:03:19,910 --> 01:03:17,440
of the genetic code

1438
01:03:21,190 --> 01:03:19,920

to respond to the environment and adapt

1439
01:03:22,069 --> 01:03:21,200
or evolve

1440
01:03:24,069 --> 01:03:22,079
and

1441
01:03:27,430 --> 01:03:24,079
this is what we

1442
01:03:30,150 --> 01:03:27,440
believe is one molecular strategy also

1443
01:03:33,270 --> 01:03:30,160
we what we call molecular memory that

1444
01:03:35,190 --> 01:03:33,280
biology uses to record information

1445
01:03:36,789 --> 01:03:35,200
the problem with chemical identity the

1446
01:03:38,870 --> 01:03:36,799
problem with tying ourselves to the

1447
01:03:41,750 --> 01:03:38,880
identity of these molecules

1448
01:03:43,990 --> 01:03:41,760
is that they can only take us so far

1449
01:03:46,150 --> 01:03:44,000
one of the earlier papers in our lab

1450
01:03:49,029 --> 01:03:46,160
actually talks about how many of these

1451
01:03:51,510 --> 01:03:49,039
small molecules even polymers

1452
01:03:54,150 --> 01:03:51,520
are heavily accepted and heavily adapted

1453
01:03:56,390 --> 01:03:54,160
after the origin of life they have been

1454
01:03:57,990 --> 01:03:56,400
changed they have changed their function

1455
01:03:59,750 --> 01:03:58,000
and they are doing very different things

1456
01:04:01,750 --> 01:03:59,760
from what they did

1457
01:04:05,190 --> 01:04:01,760
when life started

1458
01:04:06,789 --> 01:04:05,200
so it's it's tricky to um understand

1459
01:04:09,990 --> 01:04:06,799
chemical identity

1460
01:04:12,549 --> 01:04:10,000
in this space which is way way uh which

1461
01:04:14,230 --> 01:04:12,559
predates the origin of life

1462
01:04:16,470 --> 01:04:14,240
so what else can we

1463
01:04:17,829 --> 01:04:16,480

learn from or what else can we look at

1464
01:04:19,910 --> 01:04:17,839
and one other

1465
01:04:22,789 --> 01:04:19,920
strategy that we can look at is

1466
01:04:25,349 --> 01:04:22,799
conformational changes of biopolymers in

1467
01:04:27,270 --> 01:04:25,359
biology today

1468
01:04:29,430 --> 01:04:27,280
this is not specific to proteins

1469
01:04:31,910 --> 01:04:29,440
although in this case i've used the

1470
01:04:34,309 --> 01:04:31,920
example of protein because phenotypic

1471
01:04:36,230 --> 01:04:34,319
plasticity and prion-based inheritance

1472
01:04:38,230 --> 01:04:36,240
is something that

1473
01:04:40,309 --> 01:04:38,240
is uh that has

1474
01:04:41,990 --> 01:04:40,319
given us a lot of information about the

1475
01:04:44,150 --> 01:04:42,000
way biology records environmental

1476
01:04:46,789 --> 01:04:44,160
information responses to temperature

1477
01:04:49,829 --> 01:04:46,799
changes have been fantastically recorded

1478
01:04:52,630 --> 01:04:49,839
in prions and um

1479
01:04:55,670 --> 01:04:52,640
and actually the transverse generations

1480
01:04:58,470 --> 01:04:55,680
they have been prion sometimes

1481
01:04:59,510 --> 01:04:58,480
last up to 10 to the five generations

1482
01:05:01,510 --> 01:04:59,520
which was

1483
01:05:03,109 --> 01:05:01,520
very very interesting to us when we came

1484
01:05:04,870 --> 01:05:03,119
up when we

1485
01:05:06,630 --> 01:05:04,880
discovered this idea

1486
01:05:08,630 --> 01:05:06,640
and this is independent of the genetic

1487
01:05:09,990 --> 01:05:08,640
code this is independent of the identity

1488
01:05:12,309 --> 01:05:10,000

of these molecules and this is

1489
01:05:14,470 --> 01:05:12,319
independent of

1490
01:05:17,029 --> 01:05:14,480
the structure of the

1491
01:05:19,829 --> 01:05:17,039
small of the organism itself so this is

1492
01:05:21,190 --> 01:05:19,839
found in yeast and bacteria in multiple

1493
01:05:23,109 --> 01:05:21,200
different organisms but the

1494
01:05:25,510 --> 01:05:23,119
conformational changes

1495
01:05:28,150 --> 01:05:25,520
are ways in which molecules can record

1496
01:05:29,270 --> 01:05:28,160
information and pass it on to generation

1497
01:05:31,750 --> 01:05:29,280
for

1498
01:05:33,990 --> 01:05:31,760
variable amounts of time

1499
01:05:36,150 --> 01:05:34,000
although this one is a long-term memory

1500
01:05:38,309 --> 01:05:36,160
of molecules of course we can also

1501
01:05:40,789 --> 01:05:38,319
account for short-term memory in terms

1502
01:05:43,430 --> 01:05:40,799
of conformational changes of signaling

1503
01:05:45,190 --> 01:05:43,440
proteins conformational changes

1504
01:05:48,230 --> 01:05:45,200
which will then connect downstream

1505
01:05:49,910 --> 01:05:48,240
pathways for um

1506
01:05:52,230 --> 01:05:49,920
for detecting the environment and

1507
01:05:53,910 --> 01:05:52,240
recording it for any period of time so

1508
01:05:55,829 --> 01:05:53,920
hence we believe that conformational

1509
01:05:57,349 --> 01:05:55,839
changes in biopolymers

1510
01:05:59,270 --> 01:05:57,359
are a form of molecular memory in

1511
01:06:01,510 --> 01:05:59,280
biology today and we can definitely

1512
01:06:04,230 --> 01:06:01,520
learn from them

1513
01:06:06,630 --> 01:06:04,240

the other strategy and in our case the

1514
01:06:09,829 --> 01:06:06,640
last one in our list is chemical

1515
01:06:12,230 --> 01:06:09,839
gradients chemical gradients are a very

1516
01:06:14,309 --> 01:06:12,240
very common strategy used in biology

1517
01:06:15,990 --> 01:06:14,319
independent of the identity of the

1518
01:06:17,270 --> 01:06:16,000
molecule so in here we have the

1519
01:06:19,750 --> 01:06:17,280
potassium

1520
01:06:21,270 --> 01:06:19,760
sodium gradient across a neuron which is

1521
01:06:23,829 --> 01:06:21,280
commonly used to respond to

1522
01:06:26,309 --> 01:06:23,839
environmental cues may it be in the

1523
01:06:28,950 --> 01:06:26,319
first ever neuron formed where that was

1524
01:06:31,990 --> 01:06:28,960
that just gave a survival advantage to

1525
01:06:34,870 --> 01:06:32,000
the organism or in very complex

1526
01:06:37,589 --> 01:06:34,880
mammalian brains where we have um

1527
01:06:39,190 --> 01:06:37,599
information stored every minute to form

1528
01:06:41,510 --> 01:06:39,200
memories

1529
01:06:43,349 --> 01:06:41,520
uh chemical gradients can also be as i

1530
01:06:47,190 --> 01:06:43,359
said independent of chemical identity

1531
01:06:49,349 --> 01:06:47,200
which can be gradients of nutrients

1532
01:06:55,029 --> 01:06:49,359
which

1533
01:06:57,270 --> 01:06:55,039
are taken advantage of by bacteria and

1534
01:06:59,349 --> 01:06:57,280
by demonstrating tumbling behavior

1535
01:07:03,430 --> 01:06:59,359
or they may be a small molecule

1536
01:07:05,829 --> 01:07:03,440
gradients which bacteria use in a very

1537
01:07:07,829 --> 01:07:05,839
in a fantastic way for quorum sensing

1538
01:07:12,069 --> 01:07:07,839

and responding to the environment going

1539
01:07:15,109 --> 01:07:13,670
independent of the identity again

1540
01:07:17,990 --> 01:07:15,119
chemical gradients we believe are

1541
01:07:19,670 --> 01:07:18,000
molecular memory which uh exist in

1542
01:07:21,349 --> 01:07:19,680
biology today

1543
01:07:24,390 --> 01:07:21,359
uh there are some others which i'm not

1544
01:07:28,390 --> 01:07:24,400
going to go into too much detail about

1545
01:07:30,789 --> 01:07:28,400
but just as uh just to conclude

1546
01:07:32,150 --> 01:07:30,799
although biological memory itself looks

1547
01:07:33,510 --> 01:07:32,160
very different

1548
01:07:36,309 --> 01:07:33,520
these are some of the underlying

1549
01:07:38,230 --> 01:07:36,319
chemical mechanisms which we can take

1550
01:07:40,390 --> 01:07:38,240
into the space that is prebiotic

1551
01:07:42,230 --> 01:07:40,400
chemistry and study them in that space

1552
01:07:44,069 --> 01:07:42,240
without the constraints that biology

1553
01:07:45,829 --> 01:07:44,079
places on memory

1554
01:07:47,510 --> 01:07:45,839
and

1555
01:07:49,510 --> 01:07:47,520
as you see here although chemical

1556
01:07:51,910 --> 01:07:49,520
identity and conformational changes

1557
01:07:53,190 --> 01:07:51,920
might only take us so far back

1558
01:07:55,990 --> 01:07:53,200
we can

1559
01:07:58,069 --> 01:07:56,000
very reliably and very confidently study

1560
01:07:59,910 --> 01:07:58,079
chemical gradients

1561
01:08:02,470 --> 01:07:59,920
in molecules we can study reaction

1562
01:08:04,549 --> 01:08:02,480
cascades we can study feedback loops in

1563
01:08:07,750 --> 01:08:04,559

small molecular system and gain more

1564
01:08:09,990 --> 01:08:07,760
understanding in them about them to

1565
01:08:11,750 --> 01:08:10,000
learn more about prebiotic chemistry

1566
01:08:12,950 --> 01:08:11,760
without worrying about whether they

1567
01:08:14,069 --> 01:08:12,960
might

1568
01:08:16,149 --> 01:08:14,079
not be

1569
01:08:19,590 --> 01:08:16,159
completely replicated in biology today

1570
01:08:23,430 --> 01:08:21,590
with this i want to end the first part

1571
01:08:25,510 --> 01:08:23,440
of my talk which focuses on the

1572
01:08:29,269 --> 01:08:25,520
principles and move on to the

1573
01:08:31,430 --> 01:08:29,279
experimental aspect wherein i say

1574
01:08:35,269 --> 01:08:31,440
we at the williams lab obviously have

1575
01:08:40,390 --> 01:08:37,669
strategy for molecular memory

1576
01:08:43,030 --> 01:08:40,400
which we call your ensemble memory and

1577
01:08:44,789 --> 01:08:43,040
we are studying this in a system that is

1578
01:08:47,829 --> 01:08:44,799
chemically evolving

1579
01:08:49,669 --> 01:08:47,839
and here i would um refer to

1580
01:08:50,789 --> 01:08:49,679
dr moran's talk

1581
01:08:53,269 --> 01:08:50,799
where she

1582
01:08:55,269 --> 01:08:53,279
spoke about the details of this

1583
01:08:58,390 --> 01:08:55,279
chemically evolving system

1584
01:09:00,390 --> 01:08:58,400
for my talk today i'm just gonna as uh

1585
01:09:03,030 --> 01:09:00,400
i'm just going to say that we took a

1586
01:09:06,470 --> 01:09:03,040
bunch of small molecules and wet dry

1587
01:09:07,430 --> 01:09:06,480
cycle them for about 15 cycles at 45

1588
01:09:10,470 --> 01:09:07,440

degrees

1589
01:09:12,390 --> 01:09:10,480
and conducted an hplc analysis on them

1590
01:09:13,749 --> 01:09:12,400
hbl's analysis on them

1591
01:09:15,430 --> 01:09:13,759
for the chemistry i would again

1592
01:09:16,870 --> 01:09:15,440
recommend you see the talk or the

1593
01:09:19,269 --> 01:09:16,880
preprint

1594
01:09:22,070 --> 01:09:19,279
given below

1595
01:09:23,430 --> 01:09:22,080
we found that this group of or a group

1596
01:09:25,669 --> 01:09:23,440
of molecules

1597
01:09:28,950 --> 01:09:25,679
are capable of changing their chemical

1598
01:09:30,870 --> 01:09:28,960
landscape over a period of 15 cycles

1599
01:09:32,950 --> 01:09:30,880
only with the addition of water every

1600
01:09:35,669 --> 01:09:32,960
two days and this was fantastic for us

1601
01:09:37,749 --> 01:09:35,679
we saw a change in chemical level we saw

1602
01:09:40,229 --> 01:09:37,759
change in the chemical landscape we saw

1603
01:09:42,709 --> 01:09:40,239
chemical evolution we saw open-ended

1604
01:09:45,110 --> 01:09:42,719
change in a system that required us to

1605
01:09:47,189 --> 01:09:45,120
do nothing else but add water

1606
01:09:50,229 --> 01:09:47,199
and the chemistry behind this was really

1607
01:09:54,070 --> 01:09:50,239
amazing and the analysis

1608
01:09:57,669 --> 01:09:54,080
uh has been covered in this paper here

1609
01:10:00,550 --> 01:09:57,679
but what i can what we extended this

1610
01:10:03,189 --> 01:10:00,560
into was we use this as a chemically

1611
01:10:06,149 --> 01:10:03,199
evolving system and we decided to study

1612
01:10:08,390 --> 01:10:06,159
memory in this we decided to study how

1613
01:10:09,590 --> 01:10:08,400

in how this system is capable of

1614
01:10:11,990 --> 01:10:09,600
recording

1615
01:10:14,630 --> 01:10:12,000
in our case environmental perturbation

1616
01:10:16,550 --> 01:10:14,640
so if the control we considered the

1617
01:10:19,030 --> 01:10:16,560
original system which changed every

1618
01:10:21,750 --> 01:10:19,040
cycle as the control

1619
01:10:24,790 --> 01:10:21,760
and we introduced a perturbation so just

1620
01:10:27,030 --> 01:10:24,800
at one cycle at cycle two we shocked the

1621
01:10:28,470 --> 01:10:27,040
system at 65 degrees

1622
01:10:30,709 --> 01:10:28,480
and then

1623
01:10:32,550 --> 01:10:30,719
took it back down to its original format

1624
01:10:33,510 --> 01:10:32,560
and treated it exactly the same for the

1625
01:10:35,189 --> 01:10:33,520
next

1626
01:10:37,110 --> 01:10:35,199
um

1627
01:10:39,270 --> 01:10:37,120
next set of cycles

1628
01:10:40,790 --> 01:10:39,280
and we see that we can actually record

1629
01:10:43,830 --> 01:10:40,800
this perturbation in the chemical

1630
01:10:46,470 --> 01:10:43,840
landscape and the perturbation is very

1631
01:10:48,070 --> 01:10:46,480
evident in the hplc spectra

1632
01:10:49,990 --> 01:10:48,080
and we can confidently say that the

1633
01:10:51,669 --> 01:10:50,000
environmental perturbation alters the

1634
01:10:55,030 --> 01:10:51,679
chemical landscape

1635
01:10:56,070 --> 01:10:55,040
and further analysis of the hplc spectra

1636
01:10:58,870 --> 01:10:56,080
can

1637
01:11:01,430 --> 01:10:58,880
tease out some more information about

1638
01:11:03,270 --> 01:11:01,440

the memory of this ensemble but we can

1639
01:11:04,790 --> 01:11:03,280
definitely see how

1640
01:11:06,709 --> 01:11:04,800
studying

1641
01:11:08,790 --> 01:11:06,719
ensemble memory

1642
01:11:11,030 --> 01:11:08,800
in a small system can give us more

1643
01:11:13,590 --> 01:11:11,040
information and can give us

1644
01:11:15,830 --> 01:11:13,600
insights into the origin and evolution

1645
01:11:17,189 --> 01:11:15,840
of molecular memory at prebiotic

1646
01:11:19,030 --> 01:11:17,199
chemistry

1647
01:11:22,070 --> 01:11:19,040
as a conclusion i would just like to

1648
01:11:24,070 --> 01:11:22,080
reiterate that biological systems are

1649
01:11:25,990 --> 01:11:24,080
known to use genetic and non-genetic

1650
01:11:29,189 --> 01:11:26,000
strategies to record environmental

1651
01:11:29,990 --> 01:11:29,199
information study of chemical systems

1652
01:11:31,590 --> 01:11:30,000
uh

1653
01:11:33,590 --> 01:11:31,600
the way that chemical systems use

1654
01:11:35,669 --> 01:11:33,600
non-genetic strategies is definitely

1655
01:11:37,030 --> 01:11:35,679
going to benefit this field i would also

1656
01:11:39,270 --> 01:11:37,040
like to say that i was really happy to

1657
01:11:42,870 --> 01:11:39,280
see a lot of talks in this

1658
01:11:44,790 --> 01:11:42,880
in this space doing that and i think

1659
01:11:46,950 --> 01:11:44,800
i think that's that's great

1660
01:11:49,110 --> 01:11:46,960
um with this i would like to acknowledge

1661
01:11:51,510 --> 01:11:49,120
the williams lab uh specifically dr

1662
01:11:53,669 --> 01:11:51,520
williams moran and varhab uh we've been

1663
01:11:55,510 --> 01:11:53,679

working together on this project and of

1664
01:11:57,550 --> 01:11:55,520
course the williams lab as a whole

1665
01:12:01,750 --> 01:11:57,560
itself thank you

1666
01:12:06,870 --> 01:12:04,390
let's thank felipe for presentation and

1667
01:12:09,350 --> 01:12:06,880
uh so we have time for a couple of

1668
01:12:12,470 --> 01:12:09,360
questions for kavita meanwhile

1669
01:12:15,590 --> 01:12:12,480
all the other speakers please uh come to

1670
01:12:17,590 --> 01:12:15,600
the podium uh so we will have like 15

1671
01:12:19,350 --> 01:12:17,600
minutes q a session

1672
01:12:21,030 --> 01:12:19,360
if you still have all your questions

1673
01:12:24,550 --> 01:12:21,040
there are a few questions online so

1674
01:12:27,270 --> 01:12:24,560
we'll try to cover all of that

1675
01:12:29,189 --> 01:12:27,280
any questions for kavita yes please hi

1676
01:12:31,669 --> 01:12:29,199
lynn rothschild nasa ames kavita that

1677
01:12:33,430 --> 01:12:31,679
was great do you know i really am a

1678
01:12:34,950 --> 01:12:33,440
great believer in what you're getting at

1679
01:12:37,270 --> 01:12:34,960
and i think what you're really getting

1680
01:12:39,510 --> 01:12:37,280
at is very fundamental property of life

1681
01:12:42,229 --> 01:12:39,520
that's even bigger than what you think

1682
01:12:44,470 --> 01:12:42,239
that chemistry and physics is a

1683
01:12:46,550 --> 01:12:44,480
historical i don't care where the water

1684
01:12:47,510 --> 01:12:46,560
molecule i just drank came from it's

1685
01:12:50,229 --> 01:12:47,520
water

1686
01:12:52,070 --> 01:12:50,239
but if you take 100 people and put them

1687
01:12:53,990 --> 01:12:52,080
in a room and ask you know what do you

1688
01:12:56,149 --> 01:12:54,000

think about phosphine on venus you will

1689
01:12:59,110 --> 01:12:56,159
get a range of answers it depends on

1690
01:13:00,790 --> 01:12:59,120
their history and i'm not convinced

1691
01:13:03,110 --> 01:13:00,800
having heard this twice you're not

1692
01:13:05,270 --> 01:13:03,120
actually getting at that very step of

1693
01:13:06,149 --> 01:13:05,280
the difference between chemistry and

1694
01:13:08,390 --> 01:13:06,159
life

1695
01:13:10,310 --> 01:13:08,400
and so i'd really encourage you to think

1696
01:13:12,950 --> 01:13:10,320
even more broadly on it and by the way

1697
01:13:14,709 --> 01:13:12,960
also morphological inheritance

1698
01:13:17,110 --> 01:13:14,719
as an old protozoologist there is

1699
01:13:18,630 --> 01:13:17,120
literature on inheritance of

1700
01:13:20,470 --> 01:13:18,640
reversal of committees and so on

1701
01:13:22,390 --> 01:13:20,480
conciliates so

1702
01:13:23,830 --> 01:13:22,400
you know keep it up

1703
01:13:25,910 --> 01:13:23,840
thank you all right

1704
01:13:27,910 --> 01:13:25,920
absolutely i will definitely look into

1705
01:13:30,149 --> 01:13:27,920
that

1706
01:13:32,870 --> 01:13:30,159
uh chris may or bacon university of

1707
01:13:34,070 --> 01:13:32,880
maryland baltimore county a great good

1708
01:13:38,149 --> 01:13:34,080
great talk

1709
01:13:42,390 --> 01:13:40,229
chemical systems and chemical ensembles

1710
01:13:46,550 --> 01:13:42,400
that

1711
01:13:47,669 --> 01:13:46,560
reconstruct environmental conditions

1712
01:13:49,350 --> 01:13:47,679
from

1713
01:13:52,310 --> 01:13:49,360

those ensembles it

1714
01:13:56,310 --> 01:13:52,320
reminded me a bit of

1715
01:13:58,870 --> 01:13:56,320
some auto catalytic modeling work out of

1716
01:14:01,510 --> 01:13:58,880
david baum's lab so i'm curious if

1717
01:14:03,189 --> 01:14:01,520
you're familiar at all with that work or

1718
01:14:07,270 --> 01:14:03,199
if that has

1719
01:14:12,229 --> 01:14:09,669
chemical ensembles and how they

1720
01:14:15,270 --> 01:14:12,239
grow and evolve

1721
01:14:16,950 --> 01:14:15,280
um yes um so

1722
01:14:19,430 --> 01:14:16,960
did you say david baum

1723
01:14:21,350 --> 01:14:19,440
yeah sorry yes uh i was here for the

1724
01:14:23,830 --> 01:14:21,360
talk in the earlier session i guess lina

1725
01:14:25,669 --> 01:14:23,840
one of his uh phd students gave the talk

1726
01:14:28,470 --> 01:14:25,679
and it was really really interesting to

1727
01:14:29,430 --> 01:14:28,480
me i had uh i did not know about it

1728
01:14:32,149 --> 01:14:29,440
before

1729
01:14:33,910 --> 01:14:32,159
but going ahead uh it would it would be

1730
01:14:35,510 --> 01:14:33,920
very beneficial for us to look into that

1731
01:14:37,189 --> 01:14:35,520
that's for sure

1732
01:14:40,630 --> 01:14:37,199
absolutely

1733
01:14:46,070 --> 01:14:43,350
all right let's thank kavita and let me

1734
01:14:47,350 --> 01:14:46,080
once again invite all speakers from this

1735
01:14:50,870 --> 01:14:47,360
session

1736
01:14:59,350 --> 01:14:50,880
upstairs here bradley

1737
01:15:07,669 --> 01:15:00,470
or

1738
01:15:11,350 --> 01:15:08,550

and

1739
01:15:12,229 --> 01:15:11,360
so you are all welcome to ask

1740
01:15:14,790 --> 01:15:12,239
uh

1741
01:15:17,510 --> 01:15:14,800
questions to any speaker but

1742
01:15:25,030 --> 01:15:17,520
we can start with sketching up

1743
01:15:25,040 --> 01:15:35,189
um

1744
01:15:39,669 --> 01:15:36,870
the first question

1745
01:15:42,229 --> 01:15:39,679
we have from uh clara lauchawa from

1746
01:15:44,070 --> 01:15:42,239
prague uh thank you roy for the

1747
01:15:46,310 --> 01:15:44,080
interesting talk i'm interested in

1748
01:15:49,350 --> 01:15:46,320
whether you have also tried or thought

1749
01:15:51,510 --> 01:15:49,360
about trying longer peptides and include

1750
01:15:55,430 --> 01:15:51,520
other hydrophobic amino acids

1751
01:16:00,709 --> 01:15:58,709
yeah testing a longer peptide is uh the

1752
01:16:03,030 --> 01:16:00,719
first thing i'm going to do when i get

1753
01:16:16,709 --> 01:16:03,040
to get back to seattle

1754
01:16:22,229 --> 01:16:19,510
okay next one we have also um on the

1755
01:16:24,470 --> 01:16:22,239
chat from uli muller that's also for roy

1756
01:16:26,470 --> 01:16:24,480
black so d alanine seemed to help

1757
01:16:29,830 --> 01:16:26,480
vesicles on an earlier

1758
01:16:32,870 --> 01:16:29,840
slide better than dilucine the final

1759
01:16:35,110 --> 01:16:32,880
analysis was focused on dilucine was

1760
01:16:37,669 --> 01:16:35,120
there a reason for choosing leucine over

1761
01:16:40,310 --> 01:16:37,679
the likely more abundant alanine amino

1762
01:16:43,590 --> 01:16:42,550
sorry i could could you repeat that yeah

1763
01:16:45,910 --> 01:16:43,600

so

1764
01:16:48,470 --> 01:16:45,920
the question was that

1765
01:16:50,870 --> 01:16:48,480
in the earlier slides that you showed

1766
01:16:52,630 --> 01:16:50,880
that diane seemed to have a more a

1767
01:16:54,550 --> 01:16:52,640
better effect and then you focus on

1768
01:16:56,709 --> 01:16:54,560
diluting so

1769
01:16:58,950 --> 01:16:56,719
what was the reason and so dialing would

1770
01:17:01,189 --> 01:16:58,960
be more abundant on the periodic earth

1771
01:17:03,669 --> 01:17:01,199
then right yeah no this started

1772
01:17:06,070 --> 01:17:03,679
essentially as a screen i you know

1773
01:17:09,910 --> 01:17:06,080
bought about 20 or whatever

1774
01:17:11,990 --> 01:17:09,920
uh different die peptides and uh

1775
01:17:16,390 --> 01:17:12,000
diluting was the one that had the most

1776
01:17:22,790 --> 01:17:18,870
all right so any other questions you've

1777
01:17:24,950 --> 01:17:22,800
had uh from the audience here yes please

1778
01:17:26,790 --> 01:17:24,960
okay

1779
01:17:28,630 --> 01:17:26,800
yes

1780
01:17:32,470 --> 01:17:28,640
vladimir suborton university of

1781
01:17:35,830 --> 01:17:33,830
question to

1782
01:17:38,310 --> 01:17:35,840
the same presenter

1783
01:17:41,430 --> 01:17:38,320
are these

1784
01:17:43,189 --> 01:17:41,440
dipeptides that appeared inside vesicles

1785
01:17:46,950 --> 01:17:43,199
is it flip flop

1786
01:17:52,149 --> 01:17:49,510
sorry could you repeat that yes you

1787
01:17:55,350 --> 01:17:52,159
mentioned that you have a dipeptide

1788
01:17:57,430 --> 01:17:55,360

appeared inside vesicles

1789
01:18:00,229 --> 01:17:57,440
is it a flip-flop

1790
01:18:05,030 --> 01:18:00,239
in membrane flip-flop from

1791
01:18:07,110 --> 01:18:05,040
outside to inside or they are free

1792
01:18:10,229 --> 01:18:07,120
dipeptide

1793
01:18:12,790 --> 01:18:10,239
so how how do the peptides get in is

1794
01:18:14,950 --> 01:18:12,800
that essentially the question

1795
01:18:17,350 --> 01:18:14,960
yeah is it

1796
01:18:20,070 --> 01:18:17,360
are they still bound to membrane and

1797
01:18:22,950 --> 01:18:20,080
it's just flip-flop from outside

1798
01:18:24,870 --> 01:18:22,960
membrane to inside membrane uh-huh yeah

1799
01:18:26,630 --> 01:18:24,880
no i assume that they are getting

1800
01:18:29,669 --> 01:18:26,640
through again if you look at some of

1801
01:18:32,070 --> 01:18:29,679
jason greenwald's work he's

1802
01:18:36,310 --> 01:18:32,080
looked at the penetration

1803
01:18:37,910 --> 01:18:36,320
of a variety of uh amino acids and and

1804
01:18:39,910 --> 01:18:37,920
peptides and

1805
01:18:42,870 --> 01:18:39,920
these are very leaky membranes right

1806
01:18:45,830 --> 01:18:42,880
it's just a decanoic acid membrane

1807
01:18:47,990 --> 01:18:45,840
so uh we we assume that they are getting

1808
01:18:50,550 --> 01:18:48,000
inside and

1809
01:18:53,030 --> 01:18:50,560
right could be acting from the inside as

1810
01:19:00,870 --> 01:18:54,709
further outside

1811
01:19:06,149 --> 01:19:04,070
sorry i guess i'm still like so they can

1812
01:19:08,870 --> 01:19:06,159
further participate

1813
01:19:12,070 --> 01:19:08,880

in enhancing durability of vehicles

1814
01:19:14,870 --> 01:19:12,080
because if they are bound to inside

1815
01:19:17,430 --> 01:19:14,880
membrane they can flip-flop and appear

1816
01:19:20,830 --> 01:19:17,440
at outside

1817
01:19:24,229 --> 01:19:20,840
i assume they can go in and out

1818
01:19:27,350 --> 01:19:24,239
and uh again we're assuming that the

1819
01:19:29,669 --> 01:19:27,360
mechanism is is the binding

1820
01:19:30,550 --> 01:19:29,679
but you know we haven't even proven that

1821
01:19:31,750 --> 01:19:30,560
so

1822
01:19:33,430 --> 01:19:31,760
thank you

1823
01:19:35,430 --> 01:19:33,440
okay please kim

1824
01:19:37,510 --> 01:19:35,440
hello my name is tim sakolsky university

1825
01:19:39,189 --> 01:19:37,520
wisconsin madison i also have a question

1826
01:19:41,110 --> 01:19:39,199
for professor black

1827
01:19:43,830 --> 01:19:41,120
um and i was wondering if you have

1828
01:19:45,990 --> 01:19:43,840
examined the role of the interactions

1829
01:19:47,510 --> 01:19:46,000
between charged amino acids and because

1830
01:19:49,430 --> 01:19:47,520
it goes out of the example house like

1831
01:19:54,149 --> 01:19:49,440
you gonna cast it or destiny which also

1832
01:19:57,510 --> 01:19:55,830
so could you repeat that

1833
01:19:59,030 --> 01:19:57,520
oh yeah i was wondering if you examine

1834
01:20:00,709 --> 01:19:59,040
the interactions between charged amino

1835
01:20:01,590 --> 01:20:00,719
acids and charged

1836
01:20:05,030 --> 01:20:01,600
um

1837
01:20:07,350 --> 01:20:05,040
vesicles how to charge

1838
01:20:08,310 --> 01:20:07,360

well i mean the decanonic acid vesicles

1839
01:20:11,590 --> 01:20:08,320
will

1840
01:20:13,110 --> 01:20:11,600
at this is a neutral ph bear a negative

1841
01:20:17,590 --> 01:20:13,120
charge

1842
01:20:19,030 --> 01:20:17,600
so

1843
01:20:22,550 --> 01:20:19,040
that's

1844
01:20:25,430 --> 01:20:22,560
one direction we really want to go in is

1845
01:20:27,750 --> 01:20:25,440
uh the is there interaction between the

1846
01:20:29,990 --> 01:20:27,760
amine groups of the

1847
01:20:33,350 --> 01:20:30,000
peptides or amino acids

1848
01:20:34,950 --> 01:20:33,360
with the carboxylates of the uh

1849
01:20:35,990 --> 01:20:34,960
the head groups

1850
01:20:38,470 --> 01:20:36,000
um

1851
01:20:39,910 --> 01:20:38,480
the uh you know that that's one

1852
01:20:41,590 --> 01:20:39,920
possibility

1853
01:20:43,350 --> 01:20:41,600
uh

1854
01:20:45,030 --> 01:20:43,360
it i it's a really interesting question

1855
01:20:47,910 --> 01:20:45,040
why why would the dye peptides have

1856
01:20:49,510 --> 01:20:47,920
these effects that the unjoined amino

1857
01:20:54,070 --> 01:20:49,520
acids don't

1858
01:20:56,470 --> 01:20:54,080
uh the pka of the amine is different

1859
01:20:59,590 --> 01:20:56,480
in a peptide as

1860
01:21:02,229 --> 01:20:59,600
compared to an unjoined amino acid

1861
01:21:04,070 --> 01:21:02,239
whether that's significant enough to

1862
01:21:06,950 --> 01:21:04,080
explain it i don't know

1863
01:21:09,510 --> 01:21:06,960

you've got the peptide bond itself

1864
01:21:10,229 --> 01:21:09,520
which could be interacting

1865
01:21:12,229 --> 01:21:10,239
and

1866
01:21:13,350 --> 01:21:12,239
the the other thing i thought about is

1867
01:21:17,430 --> 01:21:13,360
the

1868
01:21:20,070 --> 01:21:17,440
are uh

1869
01:21:22,629 --> 01:21:20,080
further removed from each other in a in

1870
01:21:26,629 --> 01:21:22,639
an amino in a dipeptide

1871
01:21:28,550 --> 01:21:26,639
uh allowing a different range of

1872
01:21:31,110 --> 01:21:28,560
uh

1873
01:21:32,470 --> 01:21:31,120
you know relative positions

1874
01:21:34,470 --> 01:21:32,480
uh

1875
01:21:36,629 --> 01:21:34,480
and that could be critical so those are

1876
01:21:40,149 --> 01:21:36,639
my thoughts about

1877
01:21:42,310 --> 01:21:40,159
how they could be interacting

1878
01:21:43,510 --> 01:21:42,320
next question hey how's it going sean

1879
01:21:45,350 --> 01:21:43,520
brown from the university of maryland

1880
01:21:47,910 --> 01:21:45,360
baltimore county hey another question

1881
01:21:49,590 --> 01:21:47,920
production great talks everyone uh have

1882
01:21:52,950 --> 01:21:49,600
you taken a look

1883
01:22:02,229 --> 01:21:52,960
at possible other amino acids that are a

1884
01:22:06,149 --> 01:22:04,390
yeah actually

1885
01:22:08,390 --> 01:22:06,159
very interestingly

1886
01:22:10,470 --> 01:22:08,400
uh isoleucine

1887
01:22:11,750 --> 01:22:10,480
does not have the effect on the

1888
01:22:12,709 --> 01:22:11,760

stability

1889
01:22:15,830 --> 01:22:12,719
uh

1890
01:22:19,189 --> 01:22:15,840
at least at the concentrations we tested

1891
01:22:21,590 --> 01:22:19,199
so that suggests that uh

1892
01:22:24,229 --> 01:22:21,600
isoleucine of course has the uh methyl

1893
01:22:25,750 --> 01:22:24,239
group coming off right at the beginning

1894
01:22:28,310 --> 01:22:25,760
of the side chain

1895
01:22:29,510 --> 01:22:28,320
and so that might block uh

1896
01:22:31,669 --> 01:22:29,520
this uh

1897
01:22:34,229 --> 01:22:31,679
notion that the side chain is actually

1898
01:22:35,910 --> 01:22:34,239
has to penetrate into the hydrophobic

1899
01:22:39,189 --> 01:22:35,920
core of the bilayer

1900
01:22:44,229 --> 01:22:39,199
so uh yeah that was very striking

1901
01:22:48,550 --> 01:22:46,470
hi justin boomin from georgia tech my

1902
01:22:50,310 --> 01:22:48,560
question is for bradley i was um this is

1903
01:22:52,390 --> 01:22:50,320
the first time i've tried bradley first

1904
01:22:54,390 --> 01:22:52,400
time i've heard of these terrans i was

1905
01:22:56,310 --> 01:22:54,400
wondering if you could comment on the

1906
01:22:57,590 --> 01:22:56,320
you know the probiotic relevance and

1907
01:22:59,669 --> 01:22:57,600
their potential for uses and

1908
01:23:01,430 --> 01:22:59,679
informational followers from

1909
01:23:04,070 --> 01:23:01,440
informational parliament

1910
01:23:07,590 --> 01:23:04,080
so you wanted to comment on the terrans

1911
01:23:09,270 --> 01:23:07,600
in what regards um they're i guess

1912
01:23:11,350 --> 01:23:09,280
they're clear if you could clarify their

1913
01:23:13,510 --> 01:23:11,360

prebiotic relevance and potential for

1914
01:23:14,709 --> 01:23:13,520
incorporation into an informational

1915
01:23:18,870 --> 01:23:14,719
polymer

1916
01:23:21,910 --> 01:23:18,880
uh well i don't think the the terrans

1917
01:23:25,510 --> 01:23:21,920
are important necessarily for the

1918
01:23:27,910 --> 01:23:25,520
informational problems so they don't

1919
01:23:30,229 --> 01:23:27,920
exhibit the same sort of like

1920
01:23:32,390 --> 01:23:30,239
hydrogen bonding that we see and what we

1921
01:23:33,350 --> 01:23:32,400
like for modern

1922
01:23:36,149 --> 01:23:33,360
um

1923
01:23:37,270 --> 01:23:36,159
pyrimidines and purines or protonucleic

1924
01:23:39,830 --> 01:23:37,280
acids

1925
01:23:42,310 --> 01:23:39,840
uh but what we do see in modern

1926
01:23:45,350 --> 01:23:42,320
biochemistry they play a really large

1927
01:23:47,270 --> 01:23:45,360
part in supportive biochemistry and as

1928
01:23:48,550 --> 01:23:47,280
cofactors for a lot of important

1929
01:23:50,310 --> 01:23:48,560
reactions

1930
01:23:52,550 --> 01:23:50,320
and so

1931
01:23:54,709 --> 01:23:52,560
we're really

1932
01:23:57,430 --> 01:23:54,719
intrigued by how they could have

1933
01:24:00,149 --> 01:23:57,440
supported the nascent biochemistry

1934
01:24:02,390 --> 01:24:00,159
during the prebiotic

1935
01:24:04,470 --> 01:24:02,400
the the prebiotic chemistry of the early

1936
01:24:07,750 --> 01:24:04,480
earth as well and so that's how i look

1937
01:24:10,070 --> 01:24:07,760
at it there um

1938
01:24:12,470 --> 01:24:10,080

yeah so i don't see any um hydrogen

1939
01:24:13,590 --> 01:24:12,480
bonding necessarily capabilities that

1940
01:24:15,270 --> 01:24:13,600
would make them

1941
01:24:16,790 --> 01:24:15,280
competitive with the other options

1942
01:24:20,709 --> 01:24:16,800
available at the time

1943
01:24:23,270 --> 01:24:20,719
so that's what really excites us because

1944
01:24:25,270 --> 01:24:23,280
if you're looking in the prebiotic world

1945
01:24:27,669 --> 01:24:25,280
it's not just like

1946
01:24:30,709 --> 01:24:27,679
each polymer or each type of

1947
01:24:33,669 --> 01:24:30,719
biochemistry operating in isolation

1948
01:24:36,149 --> 01:24:33,679
there's a lot of unexplored chemistry

1949
01:24:39,030 --> 01:24:36,159
with the cooperation between them

1950
01:24:40,470 --> 01:24:39,040
that we really have to uncover and so we

1951
01:24:42,550 --> 01:24:40,480
view this as

1952
01:24:45,030 --> 01:24:42,560
like one step in

1953
01:24:46,709 --> 01:24:45,040
helping us to

1954
01:24:48,870 --> 01:24:46,719
view the different associations that

1955
01:24:51,270 --> 01:24:48,880
could have happened to know what could

1956
01:24:53,590 --> 01:24:51,280
be present and then the next steps would

1957
01:24:55,510 --> 01:24:53,600
be to figure out how prebiotic chemistry

1958
01:24:57,990 --> 01:24:55,520
could utilize them compared to modern

1959
01:24:58,790 --> 01:24:58,000
biochemistry

1960
01:25:01,830 --> 01:24:58,800
you

1961
01:25:05,830 --> 01:25:03,910
hi i'm mark ditzler from the nasa ames

1962
01:25:08,390 --> 01:25:05,840
research center and i just

1963
01:25:09,830 --> 01:25:08,400

had a comment related to roy's talk

1964
01:25:12,950 --> 01:25:09,840
uh it is

1965
01:25:15,030 --> 01:25:12,960
it is interesting that um the

1966
01:25:17,350 --> 01:25:15,040
the most hydrophobic

1967
01:25:20,550 --> 01:25:17,360
hydrophobic difference

1968
01:25:22,870 --> 01:25:20,560
is actually it's very similar to

1969
01:25:24,149 --> 01:25:22,880
kate alamado when she was in jackson i

1970
01:25:27,990 --> 01:25:24,159
had shown

1971
01:25:31,030 --> 01:25:28,000
uh growth of fatty acid specifically um

1972
01:25:32,229 --> 01:25:31,040
by taking up my cells uh in a system

1973
01:25:33,629 --> 01:25:32,239
where they were generating a

1974
01:25:35,830 --> 01:25:33,639
phenylalanine

1975
01:25:37,030 --> 01:25:35,840
beneficial diet

1976
01:25:39,030 --> 01:25:37,040
and so that's also you know it's a very

1977
01:25:40,550 --> 01:25:39,040
hydrophobic diet peptide and

1978
01:25:43,189 --> 01:25:40,560
uh there's actually a paper that just

1979
01:25:44,950 --> 01:25:43,199
came out last year from a

1980
01:25:46,390 --> 01:25:44,960
android really and

1981
01:25:48,950 --> 01:25:46,400
cheney way

1982
01:25:50,070 --> 01:25:48,960
did some simulations looking at that

1983
01:25:52,390 --> 01:25:50,080
peptide and a couple of other

1984
01:25:54,149 --> 01:25:52,400
hypothetical peptides and they saw in

1985
01:25:56,310 --> 01:25:54,159
their simulations that the more

1986
01:25:57,990 --> 01:25:56,320
hydrophobic it was the faster the uptake

1987
01:25:59,270 --> 01:25:58,000
was and they actually have a it's an

1988
01:26:00,950 --> 01:25:59,280

interesting paper they they have a

1989
01:26:02,950 --> 01:26:00,960
mechanism where the hydrophobic

1990
01:26:04,550 --> 01:26:02,960
dipeptides cluster together from a

1991
01:26:06,310 --> 01:26:04,560
hydrophobic patch

1992
01:26:08,790 --> 01:26:06,320
and that allows a stock to form between

1993
01:26:10,550 --> 01:26:08,800
the micellar and vegetables so it seems

1994
01:26:13,270 --> 01:26:10,560
like this is consistent with that and

1995
01:26:15,510 --> 01:26:13,280
that likely the diamond scene was

1996
01:26:17,189 --> 01:26:15,520
establishing uh is probably doing the

1997
01:26:20,229 --> 01:26:17,199
same thing making a hydrophobic patch

1998
01:26:23,990 --> 01:26:20,239
and supporting the uptake of myself

1999
01:26:25,590 --> 01:26:24,000
right yeah i looked at that and that may

2000
01:26:28,149 --> 01:26:25,600
be true but

2001
01:26:29,430 --> 01:26:28,159
with that peptide they had both ends

2002
01:26:33,590 --> 01:26:29,440
blocked

2003
01:26:35,590 --> 01:26:33,600
so it was a very hydrophobic molecule

2004
01:26:37,990 --> 01:26:35,600
and with the the amine and the

2005
01:26:41,430 --> 01:26:38,000
carboxylate both blocked

2006
01:26:43,990 --> 01:26:41,440
that precluded some interactions that

2007
01:26:45,030 --> 01:26:44,000
i suspect are going on here too

2008
01:26:45,750 --> 01:26:45,040
yeah uh

2009
01:26:51,990 --> 01:26:45,760
so

2010
01:26:54,310 --> 01:26:52,000
there was clear correlation between

2011
01:26:55,189 --> 01:26:54,320
hydropurposity and activity i suspect

2012
01:26:56,470 --> 01:26:55,199
it's

2013
01:26:58,470 --> 01:26:56,480

telling us that

2014
01:27:03,669 --> 01:26:58,480
even with the non-block that it's the

2015
01:27:07,110 --> 01:27:05,590
hi my name is

2016
01:27:09,189 --> 01:27:07,120
from university of arizona and i also

2017
01:27:11,430 --> 01:27:09,199
have a question to avoid blog it's kind

2018
01:27:13,590 --> 01:27:11,440
of any of all the questions that have

2019
01:27:15,830 --> 01:27:13,600
been asked but i specifically was

2020
01:27:18,390 --> 01:27:15,840
wondering um

2021
01:27:21,669 --> 01:27:18,400
the kind of bias towards certain amino

2022
01:27:22,470 --> 01:27:21,679
acids this kind of mechanism

2023
01:27:24,870 --> 01:27:22,480
does

2024
01:27:26,870 --> 01:27:24,880
and if that bias towards certain types

2025
01:27:29,910 --> 01:27:26,880
that are better encapsulated or selected

2026
01:27:30,950 --> 01:27:29,920
for by this mechanism if it's consistent

2027
01:27:32,870 --> 01:27:30,960
with the

2028
01:27:35,669 --> 01:27:32,880
sort of trends we see in amino acid

2029
01:27:36,870 --> 01:27:35,679
composition of very very early protein

2030
01:27:39,430 --> 01:27:36,880
per se

2031
01:27:41,910 --> 01:27:39,440
right yeah great question and

2032
01:27:43,110 --> 01:27:41,920
i've looked at that very very casually

2033
01:27:44,550 --> 01:27:43,120
and uh

2034
01:27:46,629 --> 01:27:44,560
don't see it

2035
01:27:48,390 --> 01:27:46,639
readily but uh the the next session

2036
01:27:49,830 --> 01:27:48,400
we're going to hear more about there's a

2037
01:27:50,950 --> 01:27:49,840
three-class session we're going to hear

2038
01:27:53,110 --> 01:27:50,960

more about

2039
01:27:54,790 --> 01:27:53,120
what amino acids were incorporated or

2040
01:27:57,430 --> 01:27:54,800
utilized early on

2041
01:27:59,430 --> 01:27:57,440
uh but uh

2042
01:28:03,189 --> 01:27:59,440
no it doesn't pop out right

2043
01:28:07,350 --> 01:28:05,110
okay we're almost done but there's just

2044
01:28:08,870 --> 01:28:07,360
one more question for bradley on the

2045
01:28:10,149 --> 01:28:08,880
chat so

2046
01:28:13,350 --> 01:28:10,159
uh that's from

2047
01:28:14,709 --> 01:28:13,360
that's from molly muller so are the um

2048
01:28:17,350 --> 01:28:14,719
pterydines

2049
01:28:21,350 --> 01:28:17,360
as photostable as the canonical nuclear

2050
01:28:27,750 --> 01:28:22,470
that

2051
01:28:30,550 --> 01:28:27,760
i did a lot of work on the analytical

2052
01:28:32,149 --> 01:28:30,560
aspects of it and cesar is the one who

2053
01:28:35,750 --> 01:28:32,159
did a lot of the

2054
01:28:37,990 --> 01:28:35,760
reaction synthesis and those pathways

2055
01:28:39,590 --> 01:28:38,000
for that i know

2056
01:28:40,790 --> 01:28:39,600
he did

2057
01:28:43,830 --> 01:28:40,800
uv

2058
01:28:45,910 --> 01:28:43,840
for part of the reactions early on but i

2059
01:28:48,550 --> 01:28:45,920
cannot comment on

2060
01:28:50,870 --> 01:28:48,560
the relative stability between them i

2061
01:28:54,470 --> 01:28:50,880
think that's in our paper

2062
01:28:57,189 --> 01:28:54,480
but i'm not 100 sure so if it's

2063
01:28:58,950 --> 01:28:57,199

important i suggest emailing cesar on

2064
01:29:01,270 --> 01:28:58,960
that i wish i could speak to it so i

2065
01:29:03,990 --> 01:29:01,280
apologize all right thanks

2066
01:29:06,080 --> 01:29:04,000
so let's thank all speakers and thank