Chemical Selection of Plausible Protopolypeptides

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1
00:00:00,820 --> 00:00:08,919
[Music]

2
00:00:11,720 --> 00:00:11,030
so what I'm gonna talk to you about I'm

3
00:00:14,780 --> 00:00:11,730
Martin

4
00:00:17,710 --> 00:00:14,790
I'm from the HUD lab and we're part of

5
00:00:21,230 --> 00:00:17,720
the Center for chemical evolution and

6
00:00:22,910 --> 00:00:21,240
beyond that were in I'm in the proto

7
00:00:25,429 --> 00:00:22,920
polypeptide team so like I work with

8
00:00:27,380 --> 00:00:25,439
Aaron McKie who talked a little bit

9
00:00:30,919 --> 00:00:27,390
earlier and so what I'm gonna talk about

10
00:00:33,049 --> 00:00:30,929
today is a problem in prebiotic

11
00:00:35,720 --> 00:00:33,059
chemistry and and I'm going to talk

12
00:00:37,819 --> 00:00:35,730
about how we are on how we think we're

13
00:00:39,350 --> 00:00:37,829

gonna be able to explore a solution to

14
00:00:43,970 --> 00:00:39,360
this problem some of the work that we've

15
00:00:47,500 --> 00:00:43,980
been doing so as you heard in in the

16
00:00:51,170 --> 00:00:47,510
first talk today by our Nobel laureate

17
00:00:52,760 --> 00:00:51,180
you can make biopolymers okay and so in

18
00:00:56,810 --> 00:00:52,770
this diagram here what I have I have

19
00:00:59,599 --> 00:00:56,820
just general any any kind of monomer you

20
00:01:01,760 --> 00:00:59,609
want to imagine can be these and biology

21
00:01:04,009 --> 00:01:01,770
today and nature as we know it it will

22
00:01:05,810 --> 00:01:04,019
take these monomers and it will assemble

23
00:01:08,890 --> 00:01:05,820
them it will stitch them together into

24
00:01:11,090 --> 00:01:08,900
some type of polymer okay and so

25
00:01:14,120 --> 00:01:11,100
importantly though is that what nature

26
00:01:17,630 --> 00:01:14,130
does is it stitches these in in a very

27
00:01:19,190 --> 00:01:17,640
specific order okay and then once once

28
00:01:21,560 --> 00:01:19,200
these monomers are stitched together in

29
00:01:23,780 --> 00:01:21,570
a specific order then usually what

30
00:01:25,850 --> 00:01:23,790
happens is these are able to fold in

31
00:01:27,770 --> 00:01:25,860
some way or function in some catalytic

32
00:01:29,960 --> 00:01:27,780
ways so you know the example I have here

33
00:01:32,060 --> 00:01:29,970
is these these monomers are all stitched

34
00:01:33,740 --> 00:01:32,070
together in a polymer and here they are

35
00:01:36,440 --> 00:01:33,750
folded together interacting with this

36
00:01:37,730 --> 00:01:36,450
cool little helix guy you know some

37
00:01:38,840 --> 00:01:37,740
interaction you know it could be it

38
00:01:40,870 --> 00:01:38,850

could be anything could be binding

39
00:01:44,569 --> 00:01:40,880
stabilizing interaction for example

40
00:01:46,819 --> 00:01:44,579
however if we try to think about

41
00:01:49,280 --> 00:01:46,829
prebiotic chemistry and you know the

42
00:01:53,660 --> 00:01:49,290
early Earth billions of years ago

43
00:01:56,539 --> 00:01:53,670
billions and billions of years ago we

44
00:01:57,889 --> 00:01:56,549
didn't have enzymes so if you didn't

45
00:01:59,690 --> 00:01:57,899
have enzymes and and if you didn't have

46
00:02:01,630 --> 00:01:59,700
templating mechanisms like a genetic

47
00:02:05,480 --> 00:02:01,640
coding system then how could you have

48
00:02:07,100 --> 00:02:05,490
reliably produced a functional sequence

49
00:02:12,440 --> 00:02:07,110
over and over again that could have led

50
00:02:13,270 --> 00:02:12,450
to biology or biology like processes so

51
00:02:14,830 --> 00:02:13,280
if

52
00:02:16,720 --> 00:02:14,840
we had a random pool of monomers on the

53
00:02:18,760 --> 00:02:16,730
prebiotic er with no enzymes nothing

54
00:02:21,370 --> 00:02:18,770
over this arrow then if you had a way to

55
00:02:23,710 --> 00:02:21,380
stitch them together if there was a good

56
00:02:26,430 --> 00:02:23,720
way to do it what you'd end up with are

57
00:02:31,479 --> 00:02:26,440
a bunch of random sequence polymers and

58
00:02:34,420 --> 00:02:31,489
that's that's fine however once you make

59
00:02:36,520 --> 00:02:34,430
these these random sequence polymers if

60
00:02:39,309 --> 00:02:36,530
unless you can disassemble these

61
00:02:41,949 --> 00:02:39,319
polymers you can't you're gonna use up

62
00:02:44,229 --> 00:02:41,959
most of your monomer material before you

63
00:02:46,240 --> 00:02:44,239

get to a useful sequence before you get

64
00:02:48,009 --> 00:02:46,250
to a sequence that's able to say have a

65
00:02:51,160 --> 00:02:48,019
stabilizing interaction with some other

66
00:02:53,110 --> 00:02:51,170
molecule so really what you need in in

67
00:02:54,729 --> 00:02:53,120
the absence of an enzyme or you know a

68
00:02:57,009 --> 00:02:54,739
biological system is you need a

69
00:02:58,780 --> 00:02:57,019
reversible chemistry so these these

70
00:02:59,979 --> 00:02:58,790
monomers if they're all just floating

71
00:03:01,449 --> 00:02:59,989
around together if they can stitch

72
00:03:03,309 --> 00:03:01,459
together and form a bunch of different

73
00:03:06,610 --> 00:03:03,319
sequences but then they can break apart

74
00:03:08,140 --> 00:03:06,620
and then reef then restage together in a

75
00:03:10,150 --> 00:03:08,150
different way we can sample many

76
00:03:12,309 --> 00:03:10,160
different sequences from the same from

77
00:03:15,009 --> 00:03:12,319
the same pool of monomers we can recycle

78
00:03:17,080 --> 00:03:15,019
them and so here what I've highlighted

79
00:03:19,030 --> 00:03:17,090
here is oh look this is the sequence

80
00:03:21,789 --> 00:03:19,040
that this is that sequence from the last

81
00:03:26,229 --> 00:03:21,799
slide here and so by random chance you

82
00:03:30,520 --> 00:03:26,239
may be able to form it and what's nice

83
00:03:33,400 --> 00:03:30,530
about this is that this idea is that you

84
00:03:35,199 --> 00:03:33,410
can you can reuse the monomers and this

85
00:03:37,539 --> 00:03:35,209
this has been a problem in particular

86
00:03:41,229 --> 00:03:37,549
for peptide chemistry on the prebiotic

87
00:03:43,180 --> 00:03:41,239
earth but recently in the Center for

88
00:03:45,160 --> 00:03:43,190

chemical evolution a lot of

89
00:03:47,890 --> 00:03:45,170
collaborators here have come up with a

90
00:03:50,319 --> 00:03:47,900
way that we think we can we can get a

91
00:03:52,650 --> 00:03:50,329
system like this on the prebiotic earth

92
00:03:54,849 --> 00:03:52,660
okay so you've probably seen this

93
00:03:58,569 --> 00:03:54,859
picture a hundred million times that's

94
00:04:00,340 --> 00:03:58,579
Stan Lee Miller's experiment seminal

95
00:04:03,970 --> 00:04:00,350
experiment where he showed that you can

96
00:04:06,280 --> 00:04:03,980
create amino acids from simple prebiotic

97
00:04:09,069 --> 00:04:06,290
we plausible mixtures and so everybody

98
00:04:12,729 --> 00:04:09,079
knows that and as Erin said earlier and

99
00:04:14,680 --> 00:04:12,739
as is less popularly known you can make

100
00:04:17,349 --> 00:04:14,690
amino acids in these mixtures but you

101
00:04:19,810 --> 00:04:17,359
can also make hydroxy acids so here on

102
00:04:23,710 --> 00:04:19,820
the left there's an amino acid right and

103
00:04:26,080 --> 00:04:23,720
it has this an amine function and then

104
00:04:26,680 --> 00:04:26,090
here is a hydroxyl group for the hydroxy

105
00:04:28,240 --> 00:04:26,690
and

106
00:04:30,460 --> 00:04:28,250
so in this presentation they're always

107
00:04:32,860 --> 00:04:30,470
gonna be blue or red blue amino acid

108
00:04:34,240 --> 00:04:32,870
red hydroxy acid and so you can make

109
00:04:36,550 --> 00:04:34,250
both of these in model prebiotic

110
00:04:38,880 --> 00:04:36,560
experiments and furthermore you can find

111
00:04:40,750 --> 00:04:38,890
these in meteorites you can find these

112
00:04:43,600 --> 00:04:40,760
people people have been you know

113
00:04:45,700 --> 00:04:43,610

analyzing meteoritic samples for many

114
00:04:47,620 --> 00:04:45,710
many years now and you can find lots of

115
00:04:51,570 --> 00:04:47,630
amino acids lots of hydroxy acids so we

116
00:04:54,010 --> 00:04:51,580
know that they were very abundant so

117
00:04:55,600 --> 00:04:54,020
let's suppose that you only had amino

118
00:04:57,130 --> 00:04:55,610
acids because historically what

119
00:04:58,330 --> 00:04:57,140
scientists have done is they said AHA

120
00:04:59,740 --> 00:04:58,340
we're going to take amino acids and

121
00:05:01,240 --> 00:04:59,750
we're gonna try to make a peptide out of

122
00:05:03,760 --> 00:05:01,250
it and that peptide will hopefully have

123
00:05:06,970 --> 00:05:03,770
some function well the problem with that

124
00:05:09,460 --> 00:05:06,980
is that if you have a bunch of monomers

125
00:05:12,730 --> 00:05:09,470
a bunch of amino acid monomers it is

126
00:05:14,470 --> 00:05:12,740
difficult to get these two to stitch

127
00:05:16,960 --> 00:05:14,480
together it's difficult to form a

128
00:05:19,210 --> 00:05:16,970
polymer from these amino acids usually

129
00:05:22,000 --> 00:05:19,220
it requires some kind of activation

130
00:05:24,100 --> 00:05:22,010
chemistry in order to get polymers and

131
00:05:25,510 --> 00:05:24,110
it's difficult to get long polymers and

132
00:05:26,860 --> 00:05:25,520
it's generally thought that if you want

133
00:05:28,360 --> 00:05:26,870
a functional sequence it's gonna have to

134
00:05:30,070 --> 00:05:28,370
be a pretty long polymer think about how

135
00:05:33,520 --> 00:05:30,080
large a protein is you know thousands of

136
00:05:35,260 --> 00:05:33,530
amino acids so if it's difficult to you

137
00:05:38,040 --> 00:05:35,270
know get three amino acids stitched

138
00:05:40,780 --> 00:05:38,050

together then a thousand is unheard of

139
00:05:44,470 --> 00:05:40,790
but beyond that there's another problem

140
00:05:47,020 --> 00:05:44,480
Erin mentioned this as well if you have

141
00:05:49,720 --> 00:05:47,030
two amino acids stitched together as a

142
00:05:52,090 --> 00:05:49,730
dimer they will cyclize very easily and

143
00:05:54,880 --> 00:05:52,100
this actually will will eat up a lot of

144
00:05:56,980 --> 00:05:54,890
the it will eat up a lot of the products

145
00:05:58,510 --> 00:05:56,990
that you would wish to go further along

146
00:06:01,420 --> 00:05:58,520
in the polymerization instead they get

147
00:06:07,360 --> 00:06:01,430
stuck in this cyclic what's called a die

148
00:06:10,210 --> 00:06:07,370
keto piperidine trap so a couple years

149
00:06:13,150 --> 00:06:10,220
ago in the center Center for chemical

150
00:06:15,670 --> 00:06:13,160
evolution a bunch of collaborators got

151
00:06:18,159 --> 00:06:15,680
together and said aha what if we mix

152
00:06:21,220 --> 00:06:18,169
together amino acid and hydroxy amino

153
00:06:24,010 --> 00:06:21,230
and hydroxy acids together and what if

154
00:06:26,040 --> 00:06:24,020
we did like a prebiotic earth kind of

155
00:06:29,290 --> 00:06:26,050
simulation experiment if we had

156
00:06:31,300 --> 00:06:29,300
evaporative conditions so if if we had

157
00:06:33,400 --> 00:06:31,310
amino and hydroxy acids in solution

158
00:06:36,700 --> 00:06:33,410
together and we've heated this up and we

159
00:06:38,170 --> 00:06:36,710
basically boiled that water off or let

160
00:06:40,420 --> 00:06:38,180
the water evaporate off that's

161
00:06:42,400 --> 00:06:40,430
our way of putting it then what will

162
00:06:45,520 --> 00:06:42,410
happen is when that water evaporates off

163
00:06:48,610 --> 00:06:45,530

we're gonna drive condensation reactions

164
00:06:50,379 --> 00:06:48,620
between these and because of an ester

165
00:06:52,270 --> 00:06:50,389
emmett exchange mechanism that I won't

166
00:06:55,439 --> 00:06:52,280
really get into here but Aaron Aaron

167
00:06:58,090 --> 00:06:55,449
mentioned it what you end up forming are

168
00:07:00,580 --> 00:06:58,100
copolymers of the hydroxy and amino

169
00:07:02,890 --> 00:07:00,590
acids and that you can get copolymers of

170
00:07:05,650 --> 00:07:02,900
many different sequences and of many

171
00:07:08,529 --> 00:07:05,660
different lengths now what's important

172
00:07:10,930 --> 00:07:08,539
here is that within this polymer you're

173
00:07:12,550 --> 00:07:10,940
going to have the the peptide bond

174
00:07:13,749 --> 00:07:12,560
that's that's alright that's an amat

175
00:07:15,339 --> 00:07:13,759
that's the one that we're used to seeing

176
00:07:18,339 --> 00:07:15,349
in biology but you're also going to have

177
00:07:24,580 --> 00:07:18,349
an ester in there and that becomes very

178
00:07:28,029 --> 00:07:24,590
important because the ester is way

179
00:07:31,300 --> 00:07:28,039
easier to break using say water by

180
00:07:33,159 --> 00:07:31,310
adding water to this then an amen' so so

181
00:07:36,550 --> 00:07:33,169
we thought okay what maybe we can

182
00:07:38,170 --> 00:07:36,560
explore some of these molecules so what

183
00:07:39,850 --> 00:07:38,180
we did was we cut down a little bit

184
00:07:41,710 --> 00:07:39,860
that's a little bit of a sequence space

185
00:07:43,120 --> 00:07:41,720
of these products so we can form you

186
00:07:44,740 --> 00:07:43,130
know I only have three things here but

187
00:07:47,170 --> 00:07:44,750
you can actually make many more

188
00:07:49,240 --> 00:07:47,180

sequences and many other combinations

189
00:07:52,140 --> 00:07:49,250
and of end of much greater lengths you

190
00:07:56,379 --> 00:07:52,150
know up to I think ten or ten or twelve

191
00:07:58,870 --> 00:07:56,389
amino and hydroxy acids in total and so

192
00:08:01,480 --> 00:07:58,880
what we do here is we say okay what if

193
00:08:06,279 --> 00:08:01,490
we started with this with this hydroxy

194
00:08:08,860 --> 00:08:06,289
and amino acid dimer well if we start

195
00:08:10,330 --> 00:08:08,870
with that then what you'll notice is on

196
00:08:12,159 --> 00:08:10,340
the on what would have been the end

197
00:08:13,689 --> 00:08:12,169
terminus there's a hydroxyl group here

198
00:08:16,360 --> 00:08:13,699
and on the c-terminus that's the

199
00:08:19,029 --> 00:08:16,370
carboxyl group right and if we put these

200
00:08:20,409 --> 00:08:19,039
if we have these molecules okay and

201
00:08:22,659 --> 00:08:20,419
these are groups these could be any

202
00:08:24,159 --> 00:08:22,669
sidechain functionality these are you

203
00:08:26,230 --> 00:08:24,169
know your standard amino acid side

204
00:08:28,120 --> 00:08:26,240
chains and if we have these in a

205
00:08:30,700 --> 00:08:28,130
solution and we evaporate the water off

206
00:08:32,850 --> 00:08:30,710
then the water yet the water is

207
00:08:34,810 --> 00:08:32,860
evaporating up and we actually drive a

208
00:08:37,089 --> 00:08:34,820
condensation reaction between these

209
00:08:38,920 --> 00:08:37,099
monomers and so what you end up with is

210
00:08:40,779 --> 00:08:38,930
they start stitching together using

211
00:08:42,730 --> 00:08:40,789
these esters so here I have them kind of

212
00:08:44,949 --> 00:08:42,740
divided like look we made we put three

213
00:08:46,120 --> 00:08:44,959

of these together but that's what's

214
00:08:47,560 --> 00:08:46,130
happening when we drive the water off

215
00:08:50,800 --> 00:08:47,570
what's cool is that when you add the

216
00:08:51,850 --> 00:08:50,810
water back is that you can take these

217
00:08:53,980 --> 00:08:51,860
polymers and

218
00:08:56,230 --> 00:08:53,990
break them back apart into the monomeric

219
00:08:58,780 --> 00:08:56,240
units or the starting units the the

220
00:09:00,519 --> 00:08:58,790
units that we began with and it's kind

221
00:09:02,829 --> 00:09:00,529
of cool because many of the products of

222
00:09:04,240 --> 00:09:02,839
these of the reactions that I was

223
00:09:06,130 --> 00:09:04,250
talking about that the guys in the

224
00:09:09,670 --> 00:09:06,140
center did a few years ago they're

225
00:09:12,040 --> 00:09:09,680
they're always a peptide that is camped

226
00:09:15,009 --> 00:09:12,050
with the hydroxy acid and that allows

227
00:09:17,350 --> 00:09:15,019
for this chemistry now if I can take

228
00:09:18,730 --> 00:09:17,360
this monomer form a long polymer and

229
00:09:20,319 --> 00:09:18,740
then break that polymer apart that

230
00:09:21,819 --> 00:09:20,329
sounds exactly like what I mentioned in

231
00:09:23,410 --> 00:09:21,829
the beginning doesn't it we have a bunch

232
00:09:25,840 --> 00:09:23,420
of monomers and we can form a bunch of

233
00:09:28,060 --> 00:09:25,850
random sequence polymers here it's it's

234
00:09:30,069 --> 00:09:28,070
very similar now can we do better than

235
00:09:32,620 --> 00:09:30,079
that because remember what we want to do

236
00:09:34,300 --> 00:09:32,630
is we want a very specific sequence so

237
00:09:36,220 --> 00:09:34,310
like this guy here I had it binding and

238
00:09:37,780 --> 00:09:36,230

what an RNA helix or something so can we

239
00:09:42,910 --> 00:09:37,790
can we do better than just random

240
00:09:46,150 --> 00:09:42,920
assembly and I believe that we can so if

241
00:09:49,509 --> 00:09:46,160
we allow this these reversible processes

242
00:09:50,920 --> 00:09:49,519
to occur if we let you know the monomers

243
00:09:56,139 --> 00:09:50,930
form polymers and then back and forth

244
00:09:58,630 --> 00:09:56,149
then if we were to add a molecule or add

245
00:10:01,660 --> 00:09:58,640
something to to our system add something

246
00:10:03,460 --> 00:10:01,670
to our reaction that might stabilize one

247
00:10:07,329 --> 00:10:03,470
of these products like this for example

248
00:10:10,030 --> 00:10:07,339
then what we would expect is that that

249
00:10:12,100 --> 00:10:10,040
product is more stable and therefore

250
00:10:14,019 --> 00:10:12,110
when I add the water back into the

251
00:10:16,720 --> 00:10:14,029
reaction those aren't going to degrade

252
00:10:19,420 --> 00:10:16,730
so we would expect the abundance of say

253
00:10:21,189 --> 00:10:19,430
this guy to increase in time while

254
00:10:24,189 --> 00:10:21,199
everything else kept breaking apart and

255
00:10:26,139 --> 00:10:24,199
reforming and so that is that's what

256
00:10:27,730 --> 00:10:26,149
we're investigating here so I've got a

257
00:10:30,250 --> 00:10:27,740
little bit of change in notation here

258
00:10:32,439 --> 00:10:30,260
but basically what I want you to see

259
00:10:35,290 --> 00:10:32,449
here is that these little red and blue

260
00:10:40,150 --> 00:10:35,300
guy here this is say the starting unit

261
00:10:41,889 --> 00:10:40,160
and what we can do here is we can have

262
00:10:44,710 --> 00:10:41,899
these in solution and we can stitch them

263
00:10:48,189 --> 00:10:44,720

together by by evaporating away the

264
00:10:50,860 --> 00:10:48,199
water and in the presence of a of a of a

265
00:10:52,329 --> 00:10:50,870
template molecule like a cation or you

266
00:10:55,509 --> 00:10:52,339
know some kind of some kind of organic

267
00:10:58,090 --> 00:10:55,519
molecule for example then what we expect

268
00:10:59,980 --> 00:10:58,100
is that if something can bind to say

269
00:11:01,420 --> 00:10:59,990
that cation it will be stabilized or at

270
00:11:04,240 --> 00:11:01,430
least some of those molecules will be

271
00:11:06,280 --> 00:11:04,250
stabilized and we will see there

272
00:11:08,260 --> 00:11:06,290
increase and it will kind of shift the

273
00:11:10,300 --> 00:11:08,270
equilibrium the thermodynamic

274
00:11:12,160 --> 00:11:10,310
equilibrium of this system in their

275
00:11:13,870 --> 00:11:12,170
favor and so that's that's basically

276
00:11:15,100 --> 00:11:13,880
what we're working on and if you want to

277
00:11:17,650 --> 00:11:15,110
talk to me more about it later that's

278
00:11:19,620 --> 00:11:17,660
fine I love talking about this stuff and

279
00:11:22,180 --> 00:11:19,630
that's really all I've got for you guys

280
00:11:25,980 --> 00:11:22,190
yeah thank my lab thank the Center for

281
00:11:27,330 --> 00:11:25,990
chemical evolution any questions

282
00:11:34,890 --> 00:11:27,340
[Music]

283
00:11:39,970 --> 00:11:37,900
what about amyloid forming peptides

284
00:11:41,680 --> 00:11:39,980
they're short and they so select you

285
00:11:43,390 --> 00:11:41,690
don't need to think about the ligands

286
00:11:46,480 --> 00:11:43,400
because a lot of metals will facilitate

287
00:11:48,580 --> 00:11:46,490
hydrolysis also but if instead of

288
00:11:50,650 --> 00:11:48,590

choosing glycine you take peptides that

289
00:11:52,780 --> 00:11:50,660
confirm amyloid sequences such as

290
00:11:55,990 --> 00:11:52,790
Vanille alanine you can have the

291
00:11:58,450 --> 00:11:56,000
selection of the surfaces of structures

292
00:12:00,700 --> 00:11:58,460
of sequences that have already useful

293
00:12:02,830 --> 00:12:00,710
structures yeah just by selecting the

294
00:12:06,130 --> 00:12:02,840
sequence yeah so actually we're

295
00:12:08,590 --> 00:12:06,140
considering several things like that so

296
00:12:12,160 --> 00:12:08,600
if yeah if for example we had phenyl

297
00:12:14,590 --> 00:12:12,170
alanine here as this moiety then and and

298
00:12:15,790 --> 00:12:14,600
some charged moiety here at for the for

299
00:12:18,580 --> 00:12:15,800
the sidechain here what we would expect

300
00:12:20,410 --> 00:12:18,590
is kind of a Nancy philic kind of layer

301
00:12:21,580 --> 00:12:20,420
formation yeah we're definitely looking

302
00:12:22,870 --> 00:12:21,590
into things like that because that would

303
00:12:24,850 --> 00:12:22,880
be a that'll be a very simple way to