1
00:00:01,079 --> 00:00:03,393
>> Dr. Pete Worden: Now he is one of the most frequently cited scientist.

2
00:00:04,545 --> 00:00:07,523
Heís the author of over 250 research articles.

3
00:00:07,758 --> 00:00:12,142
Also the recipient of numerous honorary degrees, public honors and

4
00:00:12,142 --> 00:00:15,759
scientific awards including the 2008 United States National Medal of Science,

5
00:00:16,073 --> 00:00:23,872
The 2002 Gairdner Foundation, International Award
in the 2001 Paul Ehrlich and Ludwig Darmstaedter Prize.

6
00:00:24,198 --> 00:00:29,461
Heís a member of numerous prestigious scientific
organizations including the National Academy of Sciences,

7
00:00:29,773 --> 00:00:33,876
The American Academy of Arts and Sciences,
the American Science Society for Microbiology.

8
00:00:34,169 --> 00:00:37,946
Itís my very great pleasure to welcome you, Craig to

9
00:00:38,379 --> 00:00:43,046
NASA Ames and to all these cool people that are thinking about great stuff.

10
00:00:43,296 --> 00:00:45,779
So, we look forward to hearing what you have to say. Thank you.

11
00:00:46,109 --> 00:00:53,919
[Applause]

12
00:00:54,452 --> 00:00:55,858
>> Dr. J. Craig Venter: Well thank you very much Pete

13
00:00:55,858 --> 00:00:59,801
for the kind introduction and the invitation to come here.

14
00:00:59,801 --> 00:01:05,434
This is not too many things excite my imagination as the implications of

15
00:01:06,179 --> 00:01:17,879
trying to design organisms, even people for long term
space flight and perhaps colonization of other worlds

16
00:01:17,879 --> 00:01:23,094
as we try and use some of these same tools to clean up our own environment.

17
00:01:23,967 --> 00:01:32,206
I understand you all have a wide range of background
so I thought I would get us all on a common wavelength

18
00:01:32,563 --> 00:01:38,072
by putting things in the context of genomics in general

19
00:01:38,299 --> 00:01:42,308
and just some of the kinds of things that Iíve had the privilege of doing.

20
00:01:42,964 --> 00:01:50,685
Perhaps like NASA I get to ask big questions like defining life, trying to digitize it,

21
00:01:50,935 --> 00:01:53,578
which is what weíve been doing for the last 15 years,

22
00:01:53,837 --> 00:01:59,753
how extensive and diverse is it, can we get down to minimal components,

23
00:02:00,032 --> 00:02:06,136
and then can we go the other way, can we start in the digital world and recreate life out of that digital world

24
00:02:06,366 --> 00:02:09,924
not within the computer but outside the computer.

25
00:02:10,139 --> 00:02:14,368
And thatís what we announced earlier this year with the creation of

26
00:02:14,368 --> 00:02:20,389
a bacterial cell controlled by a chemically synthesized chromosome.

27
00:02:20,638 --> 00:02:26,648
So we actually synthesized a million base pair genome starting with four bottles of chemicals.

28
00:02:27,163 --> 00:02:31,279
It was actually assembled in the eukaryotic yeast then

29
00:02:31,512 --> 00:02:35,395
we had to transplant it out of the yeast and to a recipient bacterial cell

30
00:02:35,756 --> 00:02:38,938
where it converted that cell into an entirely new species.

31
00:02:39,750 --> 00:02:45,879
We call that a synthetic cell because everything in the cell was derived from that synthetic chromosome

32
00:02:46,412 --> 00:02:50,795
and all the traces of the original species completely disappeared.

33
00:02:51,090 --> 00:02:57,516
So how did we get here, what sort of the various steps that happened?

34
00:02:57,817 --> 00:03:04,771
And what weíve been doing since the sort of the mid 80ís is what I call digitizing biology.

35
00:03:05,038 --> 00:03:12,556
As we read the genetic code, we go from this analog molecule into the ones and zeroes in the computer.

36
00:03:12,774 --> 00:03:16,067
And so as we read different genomes including the human genome,

37

00:03:16,330 --> 00:03:20,168
itís a key part of digitizing that biology.

38
00:03:20,566 --> 00:03:26,003
Now we can go the other way, we can start with those ones and zeroes and go back.

39
00:03:26,332 --> 00:03:32,672
So in the 1990ís, we developed very rapid ways for discovering genes,

40
00:03:33,101 --> 00:03:38,079
the numbers of these grew quite substantially over time with the EST method,

41
00:03:38,373 --> 00:03:41,979
just pulling out the expressed part of the genome.

42
00:03:42,368 --> 00:03:45,596
Itís amazing these tens of millions of sequences,

43
00:03:45,596 --> 00:03:52,789
most of them are from human trying to understand all the different splice variants(?) in our own genome.

44
00:03:53,319 --> 00:04:00,151
In 1995, the big breakthrough was a new mathematical algorithm, not just sequencing tools

45
00:04:00,546 --> 00:04:08,142
but a way to assemble all the sequences and so we had approached by breaking the DNA down into little piece

46
00:04:08,374 --> 00:04:14,492
sequencing those pieces and then reassembling those computationally in the computer,

47
00:04:14,492 --> 00:04:20,434
we were able to come up with the first sequenced genome of living organism in history.

48
00:04:20,434 --> 00:04:23,774
That was only 15 years ago.

49
00:04:23,989 --> 00:04:29,296
We couldnít get funding for that, government review process said this couldnít possibly work.

50
00:04:29,824 --> 00:04:36,546
We had to use our own money to do it and after we showed it worked, we were given more

51
00:04:36,546 --> 00:04:40,165
money then we knew what to do with all kinds of species

52
00:04:40,633 --> 00:04:44,458
and we had good money from DOE, and NIH looking at diversity,

53
00:04:44,876 --> 00:04:51,212
first in the microbial world and then expanding to plants and working our way up

54
00:04:51,696 --> 00:04:59,839
to in 1998-1999 doing the fruit fly genome and then in 2000, the human genome.

55
00:05:00,328 --> 00:05:08,685
So, the human genome has roughly, each of us have about 6 billion letters of genetic code because we have tw

56
00:05:08,966 --> 00:05:10,664
one from each of our parents.

57
00:05:10,664 --> 00:05:16,209
So you here just pair up numbers or do we have 3 billion letters or 6 billion letters.

58
00:05:16,644 --> 00:05:23,692
And the first draft of this came out in ìScienceî just about 10 years ago.

59
00:05:23,692 --> 00:05:31,632
So in February, weíll be celebrating the 10th anniversary of this publication in a special meeting in San Diego.

60
00:05:31,973 --> 00:05:36,956
But things have progressed first slowly but now a lot faster since then.

61
00:05:36,956 --> 00:05:42,212
So in 2007, we published the first complete diploid genome.

62

00:05:42,459 --> 00:05:47,469
Actually I used my own genome because then I didnít have to go through getting complex permissionsÖ

63
00:05:48,306 --> 00:05:49,260
[Laugh]

64
00:05:49,260 --> 00:05:51,146
and people said of course he used his own genome.

65
00:05:51,634 --> 00:05:58,188
But when we started this project, people were totally afraid of genetics and genomics

66
00:05:58,436 --> 00:06:02,912
and how could we possibly read somebodyís genome and put it on the internet.

67
00:06:03,485 --> 00:06:11,273
Since I did that and published this, and put my genome in the internet, itís now become de rigueur to do that

68
00:06:11,663 --> 00:06:17,106
and I think biology will proceed now in an open fashion instead of a closed fashion.

69
00:06:17,594 --> 00:06:26,344
But looking at my two sets of chromosomes from my parents, they actually differed from each other by about .5

70
00:06:26,575 --> 00:06:33,146
which was much higher than all the announcements in 2000, how we differed out one letter out of genetic code

71
00:06:33,395 --> 00:06:36,765
People just looked at homologous regions, looked at SNIPs,

72
00:06:36,765 --> 00:06:42,362
the single base pair changes and so we only differ by 1 out of a thousand.

73
00:06:43,078 --> 00:06:47,996
When you try to compare any two of us, weíre comparing four sets of chromosomes

74
00:06:48,196 --> 00:06:52,767
and so thatís how we get up to 1 to 3% when we look at all the insertions and deletions

75
00:06:52,767 --> 00:06:56,979
and all the changes other than just the single letter changes.

76
00:06:56,979 --> 00:07:02,656
In fact thereís more rearrangements and changes in the genome, more base pairs involved, in structural chang

77
00:07:02,656 --> 00:07:07,431
insertions, deletions, than there are in the SNIP variation.

78
00:07:07,431 --> 00:07:11,679
So, itís almost 10 times the variation I previously thought.

79
00:07:12,220 --> 00:07:17,950
If you think about that, so 44% of my protein coding genes have

80
00:07:18,210 --> 00:07:23,001
one or more heterozygous variants in the protein sequence.

81
00:07:23,407 --> 00:07:29,446
So if we all have that same sort of percentage differences, to me itís more amazing that our biology

82
00:07:29,446 --> 00:07:35,079
is closely similar than that things donít work on in every single one of us.

83
00:07:35,529 --> 00:07:39,725
Most drugs work on about third of the population; they have little

84
00:07:39,725 --> 00:07:44,075
or no effect on another third and have toxic effects on another third.

85
00:07:44,720 --> 00:07:47,913
Thatís not surprising when you see these kinds of numbers.

86
00:07:48,135 --> 00:07:52,296
So understanding that variation is going to be key.

87

00:07:52,296 --> 00:07:58,074
When youíre looking at 44% variation with as many of,

88
00:07:58,834 --> 00:08:03,094
you know, millions of changes, thereís an awful lot to look at.

89
00:08:04,027 --> 00:08:07,156
Genomics has expanded very rapidly in the last few years.

90
00:08:07,491 --> 00:08:14,635
Due to technological innovations,
so what was a $5 billion government worldwide program,

91
00:08:15,233 --> 00:08:18,773
that we forced to go a little bit faster,

92
00:08:19,269 --> 00:08:22,998
now you can buy a machine about the size of this podium for a half a million

93
00:08:22,998 --> 00:08:29,613
dollars and sequence a genome in one or two days and that cost has going down substantially.

94
00:08:29,817 --> 00:08:33,683
So genomes are pouring into the databases from around the world,

95
00:08:34,011 --> 00:08:39,881
so looking at that 1 to 3% difference, so hereís looking at a Han Chinese,

96
00:08:40,251 --> 00:08:47,426
Gubi, one of the recent sequence people from Africa done by Vanessa Hayes at my institute

97
00:08:47,426 --> 00:08:54,354
then comparing it as a Northern European Caucasian and you can see the degree of overlap.

98
00:08:54,354 --> 00:08:57,601
What Vanessa did is looked at 3 different populations in Africa,

99
00:08:57,601 --> 00:09:02,824

including Desmond Tutuís genome, and there was more variation

100
00:09:02,824 --> 00:09:10,972
within Africa than between Gubi, myself and the Chinese individual.

101
00:09:11,204 --> 00:09:17,207
We all evolved out of these populations in Africa so itís not surprising thereís more variation there.

102
00:09:18,051 --> 00:09:25,807
But itís sort of turning peopleís thinking on its head. So, if you think about in your field,

103
00:09:26,350 --> 00:09:34,807
some of the reading Iíve done and tried to follow over time, NASAís been doing genetic selection for a long tim

104
00:09:34,807 --> 00:09:40,452
You just didnít call it that, because that seem to have a bad connotation

105
00:09:40,452 --> 00:09:43,979
but people had to pass rigorous tests, they had to be certain sizes.

106
00:09:44,431 --> 00:09:50,270
These are phenotypic selections. So why not get smart and actually really do it

107
00:09:50,546 --> 00:09:56,302
and screen for the things that might be meaningful for allowing space flight?

108
00:09:56,912 --> 00:10:06,869
The study is showing that some inner ear changes allow people to totally escape the effects of disorientation in

109
00:10:06,869 --> 00:10:13,979
things associated with bone regeneration, DNA repair from radiation and on and on.

110
00:10:14,366 --> 00:10:24,089
That, probably this list could be thousands of traits long. All biology works on selection, NASAís worked on sele

111
00:10:24,712 --> 00:10:32,696
measure a few more parameters and what youíve been measuring and you probably can get a better result.

112
00:10:33,232 --> 00:10:38,689
If weíre going to have people travelling for their whole lives and even multiple generations,

113
00:10:38,896 --> 00:10:44,463
we might want to think about engineering these and other traits to enable those purposes.

114
00:10:46,098 --> 00:10:51,329
But weíre not alone even in our own bodies, we actually have more microbes than human cells.

115
00:10:51,996 --> 00:10:54,946
So we have roughly a hundred trillion human cells,

116
00:10:54,946 --> 00:10:59,779
each of you have about 200 trillion of bacteria associated with you right now.

117
00:11:00,450 --> 00:11:01,744
Nothing personal.

118
00:11:02,180 --> 00:11:03,496
[Laugh]

119
00:11:03,765 --> 00:11:04,879
But they can get very personal.

120
00:11:05,099 --> 00:11:11,546
So weíre actually born without these microorganisms and we acquire them quite quickly

121
00:11:12,246 --> 00:11:20,092
and the gene population exceeds our own gene population by orders and magnitude.

122
00:11:20,812 --> 00:11:22,995
So think about right now, maybe the person next to you,

123
00:11:23,212 --> 00:11:28,327
especially if theyíre coughing have about a thousand different bacteria in their mouths right now.

124
00:11:29,529 --> 00:11:37,188

If you look at, weíre talking about maybe 10 million genes in the microbes associated with each one of us.

125
00:11:38,154 --> 00:11:40,402
We donít really know what most of these do.

126
00:11:40,611 --> 00:11:42,507
Thereís new studies now just coming out of it,

127
00:11:42,712 --> 00:11:48,267
these were discovered using the tools we developed for
sequence in the human genome, the shotgun sequencing.

128
00:11:48,779 --> 00:11:55,069
So we can just take samples from different body cavities and sequence at once all the microbes that are there.

129
00:11:55,472 --> 00:12:00,417
This should have been being done by NASA for years now.

130
00:12:01,064 --> 00:12:05,132
Each new person that goes up in the space station is bringing

131
00:12:05,132 --> 00:12:11,039
perhaps 10 million new genes, organisms, pathogens with them on that trip.

132
00:12:12,381 --> 00:12:15,739
Weíve been doing environmental sequencing as Iíll show you in a minute

133
00:12:16,050 --> 00:12:17,996
and some environments such as submarines and others,

134
00:12:18,700 --> 00:12:25,423
and certainly Iím sure the space station create a very unique microbial habitats.

135
00:12:25,923 --> 00:12:30,574
So to understand our biology, we have to understand our own genetic code,

136
00:12:30,945 --> 00:12:35,472
we have to understand the genetic code and the extent of these microbes associated with us.

137
00:12:35,766 --> 00:12:41,230
We have to understand the interactions with our immune system and then with the external environment.

138
00:12:41,508 --> 00:12:49,526
So itís getting more complicated by the minute but the exciting thing for me is now we know what the paramete

139
00:12:49,805 --> 00:12:51,118
at least we think we do.

140
00:12:51,412 --> 00:12:55,096
So I think for the first time we actually have a chance of making some progress.

141
00:12:56,341 --> 00:12:59,326
Instead of being ignorant that all these things exist,

142
00:12:59,837 --> 00:13:03,752
we can know about them and even manipulate them and understand them.

143
00:13:04,282 --> 00:13:08,922
Hereís the change in different cancers since 1975.

144
00:13:09,183 --> 00:13:12,851
Esophageal cancer is the fastest growing one.

145
00:13:13,101 --> 00:13:19,322
And if we look at the microbiome in these individuals with the esophageal cancer,

146
00:13:19,667 --> 00:13:24,894
they have a whole unique microbiota associated with them.

147
00:13:25,172 --> 00:13:29,423
Now we donít know yet is that causal or is that the result of the cancer?

148
00:13:30,125 --> 00:13:35,227
It becomes important to determine, but obviously esophageal cancer people think is

149

00:13:35,546 --> 00:13:41,506
clearly environmentally determined and these microbes are key part of that environment.

150
00:13:41,942 --> 00:13:44,506
So what else does this microbiome do?

151
00:13:45,172 --> 00:13:51,832
When we look at physiology, our biochemistry only allows certain things to be made,

152
00:13:52,241 --> 00:13:59,852
our microbes provide a lot of that additional physiology so what is that microbial potential?

153
00:14:00,276 --> 00:14:06,703
So if we have 20,000 somewhat genes, maybe you can get a hundred thousand different transcripts,

154
00:14:06,994 --> 00:14:12,829
maybe 100,000 to 300,000 different proteins depending on splice variants etcetera,

155
00:14:13,470 --> 00:14:16,437
but the best quantitation of our chemistry is

156
00:14:16,651 --> 00:14:23,023
roughly 2,400 different chemical compounds that we can make enzymatically from our gene set.

157
00:14:23,801 --> 00:14:25,112
So what happens with those?

158
00:14:25,871 --> 00:14:29,994
So if weíre to measure your blood stream after a meal,

159
00:14:30,242 --> 00:14:35,312
we find around 500 different chemicals circulating in your blood stream.

160
00:14:35,605 --> 00:14:39,255
Only 60% of those are from human metabolism.

161
00:14:39,538 --> 00:14:46,155
30% or so are derived from all those different species you eat during your meal.

162
00:14:46,155 --> 00:14:53,726
But 10% or on the order of 50 chemicals perhaps circulating
in your blood stream right now are bacterial metabolites.

163
00:14:54,063 --> 00:14:58,803
We have no idea what role they play in human physiology; do they make you feel better?

164
00:14:59,023 --> 00:15:00,956
Do they protect you from disease?

165
00:15:01,175 --> 00:15:01,990
Do they cause disease?

166
00:15:02,283 --> 00:15:04,688
Do they make you depressed?

167
00:15:04,688 --> 00:15:08,804
All the above, any of those things, nobody has any idea.

168
00:15:08,804 --> 00:15:15,151
We just know theyíre there now, and they can be readily measured so we need to measure the genetic code,

169
00:15:15,151 --> 00:15:16,922
we need to measure our microbes,

170
00:15:16,922 --> 00:15:22,785
and we need to know all these different chemicals circulating in our blood in different environments.

171
00:15:22,785 --> 00:15:32,439
This would be great studies to do just on an existing space trips now, let alone try to understand for longer one

172
00:15:32,688 --> 00:15:40,912
So for using our imaginations and I was asked to do that,
why not come up with a synthetic microbiome?

173
00:15:41,859 --> 00:15:47,330
If we had a way with antibiotics or a way to sterilize an astronaut

174
00:15:47,330 --> 00:15:55,089
before going into space and providing them with a synthetically compiled community.

175
00:15:55,378 --> 00:16:02,543
We could eliminate completely disease organisms; maybe have no dental decay for example.

176
00:16:02,870 --> 00:16:11,453
From reading ìPacking for Marsî, I understand methanogens and
sulphur producers are a major problem in space flight,

177
00:16:12,292 --> 00:16:16,769
except for those who want to propel themselves around the cabin.

178
00:16:16,769 --> 00:16:18,826
[Laugh]

179
00:16:19,326 --> 00:16:21,899
But I understand the physics of that doesnít really work.

180
00:16:22,398 --> 00:16:27,425
Body odor is primarily caused by microbes.

181
00:16:27,858 --> 00:16:31,743
The French have tried to cover up things with perfume but the best way

182
00:16:32,085 --> 00:16:39,375
to eliminate smell from your armpits or other areas is to kill the microbes.

183
00:16:39,793 --> 00:16:45,724
So if you use something like the 70% alcohol, you can totally eliminate some of those odors.

184
00:16:45,942 --> 00:16:49,496
So, if we come up with the right set of microbes,

185
00:16:49,779 --> 00:16:56,204
we can eliminate some of these perhaps olfactory and even health problems.

186
00:16:56,659 --> 00:17:03,616
Why not add bac-cells that make specific nutrients or vitamins instead of having to get those from the diet.

187
00:17:04,414 --> 00:17:09,175
Unique metabolisms, so for example if we were making an algae based food,

188
00:17:09,466 --> 00:17:12,727
we could metabolize every part of that algae with

189
00:17:12,727 --> 00:17:17,795
cellulose degradation to sugars perhaps retaining calcium better, etcetera.

190
00:17:18,014 --> 00:17:25,551
So Iím sure many of you come up with far better advantages than I can with the controlled environment.

191
00:17:26,000 --> 00:17:33,818
So if we look at environments, based Carl Woese, who started measuring 16 sRNA,

192
00:17:34,458 --> 00:17:38,480
our view of the world expanded dramatically.

193
00:17:38,480 --> 00:17:44,505
But it turns out even the 16 sRNA was missing things by over an order of magnitude

194
00:17:44,846 --> 00:17:47,393
and just from simple experiments in my spaceship,

195
00:17:47,393 --> 00:17:57,262
itís a 95 foot spaceship that weíve sailed around the world taking samples every 200 miles in diverse environm

196
00:17:57,686 --> 00:17:59,463
Weíve come up with a very different view.

197
00:17:59,714 --> 00:18:05,796
We just finished sampling in the Baltic and the Mediterranean and Black Seas this last summer.

198
00:18:06,014 --> 00:18:11,012

We just simply filter sea water, collect different levels of microorganisms,

199
00:18:11,012 --> 00:18:13,788
then sequence everything thatís on the filters.

200
00:18:13,788 --> 00:18:17,036
We donít even see the organisms; we donít know what they look like.

201
00:18:17,036 --> 00:18:23,726
We know what their genomes look like from compiling all their genetic data.

202
00:18:23,970 --> 00:18:27,423
So itís a simple apparatus, we have a different one for sampling an air.

203
00:18:27,423 --> 00:18:35,207
Weíve been doing the air genome and looking in all kinds of diverse environments.

204
00:18:35,577 --> 00:18:41,037
These are complex plots but basically what youíd expect if there was limited diversity

205
00:18:41,037 --> 00:18:50,303
when we first sampled in the Sargasso Sea in early 2001 through 2003, we were told weíd only find a few micr

206
00:18:51,756 --> 00:18:57,089
So what we can do is put a genome sequence across the top of this and then compare things,

207
00:18:57,386 --> 00:19:02,972
each one of these little bars is roughly 600 base pairs of DNA sequence.

208
00:19:03,317 --> 00:19:10,693
So, if there was a simple set of organisms and not much diversity everything would be up around 100% range.

209
00:19:11,395 --> 00:19:14,109
Instead what we found was this incredible diversity,

210
00:19:14,499 --> 00:19:18,341
where all these organisms have basically the same 16 sRNA sequence

211
00:19:18,788 --> 00:19:22,366
so we thought there was not this kind of diversity underneath.

212
00:19:23,052 --> 00:19:30,598
But instead of being a single organisms or eleven maybe 20,000 different related organisms.

213
00:19:31,539 --> 00:19:36,515
In fact if we look at this broadly of whatís falling out what were thought to be basically

214
00:19:36,515 --> 00:19:42,208
single organisms now are of the major taxa that weíre finding in the ocean.

215
00:19:42,984 --> 00:19:48,184
Some of these were unknown before seeing these clouds of organisms.

216
00:19:48,868 --> 00:19:52,392
So if people talk to you about a single organism from the environment,

217
00:19:52,656 --> 00:19:58,850
itís basically a meaningless concept whether that environment is your gut, the ocean or the atmosphere.

218
00:19:59,976 --> 00:20:02,643
Weíve also looked at deep sea microbes.

219
00:20:03,171 --> 00:20:10,226
So this is the high temperature vent in the Pacific Ocean were Holger Jannasch isolated this organism.

220
00:20:10,492 --> 00:20:18,302
This is the first archaea genome that we sequenced in 1996 and this is a complete anecdote,

221
00:20:18,586 --> 00:20:20,599
it doesnít need any organic compounds.

222
00:20:20,801 --> 00:20:27,156
It makes everything it needs from life from carbon dioxide and hydrogen as an energy source.

223
00:20:27,898 --> 00:20:32,538

So, this is one of the many CO2 utilizers out there in the sense

224
00:20:33,170 --> 00:20:38,835
inspired us to go in directions of capturing CO2 for energy production.

225
00:20:39,098 --> 00:20:46,419
But part of a program we have would be peer looking
for microbes deep on the earth to do unique metabolism of hydrocarbons,

226
00:20:47,058 --> 00:20:52,273
we came up with the same level of diversity deep on the earth that we find in the oceans.

227
00:20:52,658 --> 00:20:57,872
But something is very different about them; perhaps because a mile deep theyíre shielded from radiation,

228
00:20:58,133 --> 00:21:02,175
they certainly donít get any UV radiation there.

229
00:21:02,441 --> 00:21:06,447
Instead of seeing these huge clouds going down to 50% diversity,

230
00:21:06,725 --> 00:21:12,204
you can see things are clustered much more like people expected initially to find in the oceans.

231
00:21:12,453 --> 00:21:14,671
Itís a much smaller set.

232
00:21:14,671 --> 00:21:20,183
We have the diversity in terms of different types of organisms but the depth from all the mutations

233
00:21:20,392 --> 00:21:26,822
you might see are caused by UV radiation in the oceans doesnít occur deep in the Earth.

234
00:21:27,459 --> 00:21:32,280
So we have a whole range of different types of organisms that could be captured.

235
00:21:32,750 --> 00:21:37,473
Now, if you want to discover a more mammalian genes we have to hope

236
00:21:37,683 --> 00:21:40,375
and that thereís going to be strange mammals on different planets

237
00:21:40,734 --> 00:21:47,288
because thereís no point in sequencing more mammals on Earth to discover new genes thatís basically satura

238
00:21:47,555 --> 00:21:53,469
But if weíre looking at viruses, bacteria, archaea, weíre still in the linear phase of discovery

239
00:21:53,469 --> 00:21:59,798
even though weíve exceeded 50 million genes now in our databases. Itís still growing exponentially.

240
00:22:00,064 --> 00:22:08,627
We can take a sample anywhere in the world out of an aqueous system and majority of genes will be new in th

241
00:22:10,018 --> 00:22:13,667
So minimal life is something that came out of our early studies.

242
00:22:13,667 --> 00:22:17,913
In fact, inspired by some NASA scientist.

243
00:22:18,910 --> 00:22:23,437
When we sequenced this genome, itís the second one we did in 1995.

244
00:22:23,728 --> 00:22:34,352
This has the smallest genome of a self replicating organism with only about 482 protein-coding genes and 43 R

245
00:22:34,819 --> 00:22:40,341
Now this was roughly around the time when some NASA scientist claim they found nanobacteria in some Marti

246
00:22:40,876 --> 00:22:44,870
So there was a lot of discussion then about minimal life what it could be.

247
00:22:45,134 --> 00:22:48,844
Turns out the volume of those so called nanobacteria were so small,

248

00:22:48,844 --> 00:22:56,278
you couldnít even get a tiny piece of DNA or RNA in them so I think everybody pretty much concluded those w

249
00:22:57,018 --> 00:22:59,624
These are much larger cells.

250
00:23:00,079 --> 00:23:01,967
Weíre trying to understand minimal life.

251
00:23:01,967 --> 00:23:07,302
So we had two genomes, and we asked how many of these genes are essential for life,

252
00:23:07,507 --> 00:23:11,825
whatís the smallest number of genes required for cellular life,

253
00:23:12,139 --> 00:23:17,615
and ultimately could we design and construct such a minimal genome?

254
00:23:17,818 --> 00:23:21,916
We took a variety of approaches, comparative genomics in the computer.

255
00:23:21,916 --> 00:23:25,566
Trying to knock out genes to see which ones were essential and

256
00:23:25,566 --> 00:23:30,778
we realized we could only get there by making a synthetic chromosome.

257
00:23:31,012 --> 00:23:38,390
When we looked at the first two genomes that we sequenced and this was a study out of NIH from Kooninís lab

258
00:23:38,876 --> 00:23:44,692
you can see a pretty small overlap between the first two genomes.

259
00:23:44,958 --> 00:23:51,687
They actually concluded that gene diversity in our planet must be really small to have this extent of overlap.

260
00:23:52,103 --> 00:23:58,202
If they waited 6 more months till we had the methanococcus

genome they would have come to totally different conclusions.

261
00:23:58,538 --> 00:24:01,712
So comparative genomics could only take us so far.

262
00:24:01,968 --> 00:24:07,567
Clyde Hutchison at the institute developed this technique called whole genome transposon mutagenesis.

263
00:24:07,767 --> 00:24:13,026
So transposons are these small pieces of DNA that jump around in the genetic code.

264
00:24:13,399 --> 00:24:18,672
Over half of our human genome is composed of these transposons.

265
00:24:18,950 --> 00:24:22,868
Theyíre constantly jumping around and if they jump in to the middle of a key gene,

266
00:24:23,226 --> 00:24:28,471
we can get a disease or next generations wonít exist with these.

267
00:24:28,764 --> 00:24:30,685
But because we had the sequence of the genome,

268
00:24:30,685 --> 00:24:33,959
we could put in these transposons which go in randomly and then

269
00:24:33,959 --> 00:24:37,358
you can sequence off those and know exactly where they went in.

270
00:24:37,815 --> 00:24:42,600
So we were able to over the years develop this map of the Mycoplasma genitalium genome.

271
00:24:42,805 --> 00:24:49,466
Every place you see one of these little triangles thatís where a transposon randomly inserted in the cell.

272
00:24:49,859 --> 00:24:53,073
So if the cell could live with one of these transposons in it,

273
00:24:53,442 --> 00:24:58,392
we define that gene that it was in as a non-essential gene.

274
00:24:58,672 --> 00:25:03,573
You know, see thereís some little bars on here with no transposons in them;

275
00:25:03,839 --> 00:25:07,156
basically we define those as essential genes.

276
00:25:07,359 --> 00:25:12,074
But the trouble is the term essential and non-essential is totally context specific.

277
00:25:12,724 --> 00:25:21,726
It turns out this cell will grow nicely on both glucose and fructose and thereís a gene for the transporter for each

278
00:25:22,369 --> 00:25:26,671
If you have both sugars in the media and you knock out the glucose transporter,

279
00:25:26,875 --> 00:25:32,382
the cell keeps living and you say, well that glucose transporter must be a non-essential gene.

280
00:25:32,896 --> 00:25:38,719
But if youíre only growing the cells on glucose and you knock off the glucose transporter gene, the cell dies.

281
00:25:38,988 --> 00:25:46,141
So we can only define the genetics, including our own genetics, in the context of the environment that itís in.

282
00:25:46,342 --> 00:25:51,743
And I think thatís an important concept when you think of these confined or limited environments.

283
00:25:52,118 --> 00:25:58,513
When we look at the metabolic map of the cell and then look at all the genes that could be knocked out one at

284
00:25:58,806 --> 00:26:02,242
we decided this would probably not lead to a viable cell.

285
00:26:02,959 --> 00:26:07,434

So it turns out thereís genes that cover the duplicate function,

286
00:26:07,793 --> 00:26:13,018
you know, they are back up systems like NASA likes to have and so if you knock out one gene,

287
00:26:13,018 --> 00:26:17,858
it doesnít really tell you whether thatís an essential function.

288
00:26:17,858 --> 00:26:19,398
So after spending years doing this,

289
00:26:19,398 --> 00:26:22,693
we decided the only approach was to make a synthetic chromosome

290
00:26:22,908 --> 00:26:26,793
where we could control completely the genetic content.

291
00:26:27,012 --> 00:26:28,495
So then we had new technical questions,

292
00:26:28,495 --> 00:26:34,443
would the chemistry even permit us to be able to make these large pieces of DNA and if we could,

293
00:26:34,443 --> 00:26:38,375
would we just have a large inert chemical or could we boot it up?

294
00:26:39,058 --> 00:26:44,376
So jumping ahead to 2003, we tried a number of approaches.

295
00:26:44,376 --> 00:26:46,793
We underwent some very critical ethical review that

296
00:26:46,793 --> 00:26:50,926
Iíll get back to and we developed some techniques for error correction.

297
00:26:50,926 --> 00:26:56,092
So the DNA synthesizers are not great machines.

298
00:26:56,292 --> 00:26:58,588
They create errors in the DNA as they make one.

299
00:26:58,588 --> 00:27:05,225
Itís an N minus one situation, the longer the piece of DNA you make the more errors.

300
00:27:05,225 --> 00:27:09,959
And because of that, we either need error correction methods like we published here.

301
00:27:09,959 --> 00:27:13,952
And what we did here, we started with the viral sequence in the computer.

302
00:27:13,952 --> 00:27:20,161
We made these small pieces of DNA that we assembled together to make the whole genome.

303
00:27:20,161 --> 00:27:26,673
And the exciting phase came, we inserted this piece of inert chemical in to E. coli

304
00:27:26,673 --> 00:27:33,344
and the E. coli genome system started reading this piece of DNA. Started making all the proteins.

305
00:27:33,344 --> 00:27:38,743
The protein self assembled to make the virus and the virus showed its gratitude by killing the cells

306
00:27:38,743 --> 00:27:43,998
that made it which is how we detected with this clear plaques on a plate.

307
00:27:43,998 --> 00:27:47,838
So we call this a situation where the software is actually building its own hardware.

308
00:27:48,041 --> 00:27:50,737
All we did was put in a chemical piece of software and that

309
00:27:50,939 --> 00:27:56,964
led to making this a physical structure that has biological activity.

310
00:27:57,215 --> 00:28:00,009

But we didnít want to make just a small virus.

311
00:28:00,009 --> 00:28:04,404
We wanted to make an entire bacterial chromosome and there were two aspects as I said,

312
00:28:04,404 --> 00:28:06,483
one, could you boot up the DNA,

313
00:28:06,483 --> 00:28:09,987
it was easy with the viral DNA in E. coli but we didnít think

314
00:28:09,987 --> 00:28:14,483
it would be so easy with trying to boot up an entire bacterial genome.

315
00:28:14,483 --> 00:28:21,594
So this study in 2007 that we published on booting up and transplanting the genome.

316
00:28:21,797 --> 00:28:25,293
I think thatís actually one of the most important ones our teamís ever

317
00:28:25,293 --> 00:28:29,899
published because we actually by changing the genome in a cell,

318
00:28:29,899 --> 00:28:33,942
we completely converted one species into another.

319
00:28:33,942 --> 00:28:37,558
And it seems like alchemy or something to many people until you really understand

320
00:28:37,558 --> 00:28:42,678
the importance of DNA and the importance of genetics and how life actually works.

321
00:28:42,678 --> 00:28:45,812
Because this is so important, I thought Iíd walk you through it.

322
00:28:45,812 --> 00:28:51,049
So we isolated the DNA from M. mycoides.

323
00:28:51,049 --> 00:28:56,228
These are a very simple cells with just plasma membranes.

324
00:28:56,570 --> 00:29:04,404
We needed to know, for example were proteins required to do transplantation because if weíre just making che

325
00:29:04,917 --> 00:29:11,413
we need to know if proteins were involved so we treated it harshly with proteinases and removed all the protein

326
00:29:11,659 --> 00:29:15,198
We added a few gene cassettes so we could select for the chromosome,

327
00:29:15,432 --> 00:29:19,631
and they would turn themselves bright blue if it got activated.

328
00:29:19,831 --> 00:29:26,185
And we worked out ways to insert that genome into a related cell, M. capricolum.

329
00:29:26,665 --> 00:29:28,353
And we thought about this for a long time.

330
00:29:28,353 --> 00:29:35,418
We thought we would have to eliminate the chromosome in the recipient cell before we put in the new one.

331
00:29:36,026 --> 00:29:39,053
And we worked on a lot of ways to do that with radiation damage,

332
00:29:39,339 --> 00:29:42,270
chemical damage and finally after trying a number of things,

333
00:29:42,497 --> 00:29:45,013
we decided maybe we donít have to do that,

334
00:29:45,013 --> 00:29:50,782
and we could use the enzymatic systems in the cell themselves to do this for us.

335
00:29:50,982 --> 00:29:56,102

So we have this very sophisticated movie to show you what we think happened.

336
00:29:56,336 --> 00:29:59,659
So we inserted the new chromosome in the cell and for a brief period

337
00:29:59,659 --> 00:30:04,812
of time now we have a capricolum cell with two different chromosomes in it.

338
00:30:05,058 --> 00:30:11,734
As with the viral piece of DNA, the cell system started reading the new chromosome and started making protei

339
00:30:12,034 --> 00:30:16,876
Some of the early proteins that are made are restriction enzymes.

340
00:30:18,526 --> 00:30:27,606
The restriction enzymes that were made, recognized the capricolum chromosome as foreign DNA and chewed

341
00:30:28,466 --> 00:30:37,116
So now we have a capricolum cell with the information system the chromosome from M. mycoides.

342
00:30:37,446 --> 00:30:43,746
In a very short period of time, we had these bright blue cells and when we looked at these cells,

343
00:30:44,056 --> 00:30:48,116
all the characteristics of the capricolum species were gone.

344
00:30:48,426 --> 00:30:53,856
All the proteins that existed in the cell were those coded for by the M. mycoides chromosome.

345
00:30:54,506 --> 00:30:57,966
So simply by changing the software, all the characteristics of

346
00:30:57,966 --> 00:31:02,896
one species went away and we had an entirely, a new one coded for.

347
00:31:03,216 --> 00:31:05,606
So we knew now we could do transplants.

348
00:31:05,906 --> 00:31:14,456
So jumping ahead to 2008, we had teams working diligently on the chemistry to make these larger pieces of DI

349
00:31:14,456 --> 00:31:20,926
We knew we could make viral pieces accurately so we thought if we made a series of this viral size pieces,

350
00:31:21,166 --> 00:31:24,986
we could perhaps assemble these with homologous recombination.

351
00:31:24,986 --> 00:31:29,696
And thatís where a study of biology certainly helped us with different systems.

352
00:31:29,696 --> 00:31:35,746
So we made 101 of these cassettes that were 5,000 to 7,000 letters each.

353
00:31:35,746 --> 00:31:42,076
And then we went through this assembly process of assembling these pieces together on the lab bench,

354
00:31:42,076 --> 00:31:47,376
first at the 6kb range then going up to 24kb.

355
00:31:47,376 --> 00:31:54,966
And in each stage we cloned these pieces in a coli and sequenced them trying to make sure it was really a vali

356
00:31:54,966 --> 00:31:59,186
but and we kept going until we got up over 100000 base pairs.

357
00:31:59,396 --> 00:32:02,896
An E. coli would only take 2 of the 4 pieces,

358
00:32:02,896 --> 00:32:09,926
so we started looking around for a new system as Mike Montague said earlier and we settled on yeast,

359
00:32:09,926 --> 00:32:14,286
because not only did it happily clone these larger pieces,

360
00:32:14,526 --> 00:32:18,186

the homologous recombination system and yeast assembled those.

361
00:32:18,446 --> 00:32:21,106
Now, weíd spent years studying DInococcus radiodurans.

362
00:32:21,106 --> 00:32:27,556
So, this is one of the earliest genomes we sequenced with the DOE.

363
00:32:27,816 --> 00:32:33,926
This cell has 4 different DNA elements, 3 chromosomes and a plasmid

364
00:32:34,246 --> 00:32:39,306
and it can take up to 3 million rounds or radiation and not be killed.

365
00:32:39,556 --> 00:32:45,556
What happens is you get a couple of hundred double stranded brakes that chromosomes literally get blown ap

366
00:32:45,826 --> 00:32:49,156
but if itís in an aqueous environment, 12 to 24 hours later,

367
00:32:49,576 --> 00:32:54,616
it reassembles its chromosome and the cell starts replicating again.

368
00:32:55,086 --> 00:32:58,146
It could be pretty nice for space traveller if humans could do that,

369
00:32:58,616 --> 00:33:05,556
but itís a much more complex equation where 6 billion letters of genetic code other than a few million.

370
00:33:05,776 --> 00:33:12,806
But we thought we could use these processes and we expended several postdoc year lives on this,

371
00:33:13,076 --> 00:33:17,836
but never got it to work outside the cell and so weíre delighted that we could jump ahead

372
00:33:18,196 --> 00:33:25,676
and use simple brewerís yeast with itís powerful homologous recombination system to do this.

373
00:33:26,496 --> 00:33:31,855
So, we were able to put just the 4 quarter molecules with proper overlaps and this simple vector.

374
00:33:31,856 --> 00:33:38,249
And what this vector has in it, is an artificial yeast centromere.

375
00:33:38,950 --> 00:33:44,492
And so just adding a centromere, a eukaryotic centromere to this bacterial clones,

376
00:33:44,957 --> 00:33:53,651
yeast assembled all these immediately into the entire bacterial chromosome and thatís what we reported on 20

377
00:33:54,230 --> 00:34:00,080
And that was the almost 600,000 base pair genome sequence

378
00:34:00,495 --> 00:34:05,473
assembled from 4 bottles of chemicals and using this assembly process.

379
00:34:05,894 --> 00:34:09,793
The trouble is, as Michael said, these cells grow extremely slowly.

380
00:34:10,151 --> 00:34:13,941
We have still not been able to boot up this chromosome because we think in the

381
00:34:14,223 --> 00:34:18,174
6 weeks that it takes to do that the selection processes arenít adequate.

382
00:34:18,513 --> 00:34:19,949
We also discovered a few other things.

383
00:34:20,171 --> 00:34:26,845
Some of these cells have nucleases on the cell surface and they just chew up the DNA as fast as you expose i

384
00:34:27,266 --> 00:34:30,513
For jumping ahead, we had to solve a number of problems.

385
00:34:30,997 --> 00:34:36,988

Michael mentioned how we could throw in smaller pieces in good assembly and so Dan Gibson

386
00:34:37,293 --> 00:34:43,595
who did all this work wanted to see if we could just throw in tiny DNA fragments in to yeast and get assembly.

387
00:34:43,985 --> 00:34:50,229
So we could just put all simple nucleotides in to yeast and it will assemble those nicely into larger pieces.

388
00:34:50,603 --> 00:34:54,945
But the real breakthrough that Dan came up with after studying these reactions is

389
00:34:55,529 --> 00:35:02,752
this very simple single pot chemical reaction that actually allows us now to automate all these processes.

390
00:35:03,097 --> 00:35:07,205
Itís just three enzymes, one that chewes back the DNA,

391
00:35:07,620 --> 00:35:12,569
another one that ligates it together and then fills in with this fusion polymerase.

392
00:35:12,986 --> 00:35:16,593
So itís a one step reaction at 50 degrees centigrade.

393
00:35:17,078 --> 00:35:23,862
All you do is put in the synthetic pieces of small DNA and it assembles them into larger pieces.

394
00:35:25,346 --> 00:35:42,594
We can go from the digital world to making an entire analogue of molecules potentially even booting them up.

395
00:35:43,752 --> 00:35:47,322
Danny Hillis and I are talking about trying to build a robot,

396
00:35:47,762 --> 00:35:51,424
that's a self-learning robot system that could do these experiments

397
00:35:51,896 --> 00:35:56,169
and learn biology a thousand times faster than any scientist can.

398
00:35:56,809 --> 00:35:58,179
We have a lot of biology to learn,

399
00:35:58,586 --> 00:36:01,720
we don't know what most of these 50 million genes weíve already discovered is.

400
00:36:02,112 --> 00:36:07,045
But if we can automate these processes going from the digital world into creating new life forms,

401
00:36:07,524 --> 00:36:10,254
we have a chance to learn a whole lot faster.

402
00:36:11,722 --> 00:36:17,137
So our problem was, we were assembling the bacterial chromosome inside a eukaryote.

403
00:36:17,790 --> 00:36:25,362
To do the transplants, we have to find a way to isolate the DNA from the eukaryote and get it back into a bacte

404
00:36:26,620 --> 00:36:33,720
And Gwen Binders at the institute cloned entire chromosomes in yeast, adding the simple yeast centromere.

405
00:36:34,168 --> 00:36:37,602
So that gave us the ability to these trial experiments.

406
00:36:37,851 --> 00:36:40,398
But we ran into a problem.

407
00:36:40,696 --> 00:36:41,864
It didn't work.

408
00:36:42,160 --> 00:36:47,227
We couldn't take the chromosome, that native chromosome out of yeast and transplant it.

409
00:36:47,585 --> 00:36:52,125
So it took our team of roughly 25 scientists two years to solve this problem.

410
00:36:52,600 --> 00:36:57,385

It turns out that the DNA, when we isolated it from the bacterial cell was methylated.

411
00:36:57,725 --> 00:37:03,596
And that methylation protected it from the restriction enzymes that the Capricolum cell had.

412
00:37:04,452 --> 00:37:11,484
The genome was using its own restriction enzymes to destroy that enzyme but it was getting destroyed first.

413
00:37:11,737 --> 00:37:15,869
So if we purified the specific methylases and methylated the DNA,

414
00:37:16,185 --> 00:37:23,231
we could then readily do the transplants out of yeast into the bacteria.

415
00:37:23,547 --> 00:37:29,128
So we actually have this circle that allows us to make very rapid changes now genetically.

416
00:37:29,568 --> 00:37:32,593
And for those of you who work with microbes, some of the biggest limitations

417
00:37:32,982 --> 00:37:36,167
working with microbes is that they don't have genetic systems.

418
00:37:36,402 --> 00:37:42,156
So simply isolating the chromosome from the microbe, putting it into yeast,

419
00:37:42,156 --> 00:37:48,147
we can now modify that chromosome using a whole repertoire of yeast eukaryotic genetics.

420
00:37:48,463 --> 00:37:54,899
We can then isolate it, methylate it if necessary, and transplant it into a recipient cell forming a new species.

421
00:37:55,102 --> 00:37:59,269
And we can go around this circle very rapidly.

422
00:37:59,801 --> 00:38:06,433
So we made the decision early on because of the problem with the slow growth of the microplasmic genitalium

423
00:38:07,319 --> 00:38:12,872
to make a leap, knowing that we could transplant the mycoides genome,

424
00:38:13,286 --> 00:38:18,334
to resynthesize that genome, even though it was a much larger project.

425
00:38:18,611 --> 00:38:23,749
And initially we thought DNA synthesis was going to be the limitation of the biology.

426
00:38:23,962 --> 00:38:29,681
So this is what we reported this spring and so the process was again starting with these all of the nucleotides

427
00:38:30,077 --> 00:38:34,201
but now using this new single-part assembly method.

428
00:38:34,572 --> 00:38:37,151
So we could start with 1-kb pieces.

429
00:38:37,370 --> 00:38:43,262
In fact John Mulligan, who is here, made all those for us at Blue Heron.

430
00:38:43,852 --> 00:38:50,749
To speed up the process we then took ten 1-kb pieces; put them together and made 10-kb pieces.

431
00:38:51,109 --> 00:38:58,533
We then took ten of the 10-kb pieces together and made 100-kb pieces.

432
00:38:58,969 --> 00:39:04,967
And then there were eleven 1100-kb pieces that we put together in yeast

433
00:39:05,169 --> 00:39:07,299
to assemble this entire million base pair chromosome.

434
00:39:07,517 --> 00:39:12,169
At this stage I was totally certain that it was now just a matter of simply doing the experiment.

435
00:39:13,138 --> 00:39:19,412

And I boldly predicted that we would have the first synthetic species by Christmas last year.

436
00:39:19,641 --> 00:39:21,736
Obviously I was wrong.

437
00:39:22,595 --> 00:39:26,847
For some reason we could never get a living cell out of it.

438
00:39:27,069 --> 00:39:33,434
So just like software engineers have proof-reading software, we had to developed DNA proof-reading software

439
00:39:33,796 --> 00:39:41,559
And what we did was actually made naturally occurring 100-kb pieces, so we could substitute those.

440
00:39:41,761 --> 00:39:47,129
And so we could get ten synthetic pieces and one natural one, and we could boot that up.

441
00:39:47,440 --> 00:39:50,606
So we knew there was a problem in this one piece.

442
00:39:50,839 --> 00:39:57,051
And part of the problem is that the new sequencing technology is not as accurate as the old Sanger sequencin

443
00:39:57,051 --> 00:40:01,556
So even though we'd sequenced that, it couldnít find this one base pair deletion.

444
00:40:01,556 --> 00:40:06,004
So one error out of a million base pairs and we got no life.

445
00:40:06,252 --> 00:40:12,352
So we re-sequenced it with Sanger sequencing, and found the single base pair deletion in the central gene.

446
00:40:12,352 --> 00:40:20,169
Then remade the piece, and booted it up, and hereís the complete map

447
00:40:20,169 --> 00:40:25,679
and hereís the cells that resulted from the transplant.

448
00:40:26,116 --> 00:40:31,025
Let me go back a minute ëcoz we did some things that when you think about the problems you could have with

449
00:40:31,025 --> 00:40:35,206
you could fool yourself and fool others.

450
00:40:35,424 --> 00:40:41,180
Our biggest concern was a single molecule contamination of the native genome.

451
00:40:41,431 --> 00:40:46,908
With living cells we could think that we actually had made a synthetic genome activated.

452
00:40:46,908 --> 00:40:49,641
That would have been a contaminant.

453
00:40:49,905 --> 00:40:53,661
So we started this concept of watermarking the DNA.

454
00:40:53,934 --> 00:40:57,391
And the first genome we made we just signed our names in it and people thought that was very unimaginative.

455
00:40:57,391 --> 00:41:04,037
So we got a little bit more imaginative with this second genome.

456
00:41:04,037 --> 00:41:10,214
And Mike Montague and Harold Smith and Clyde Hutchison developed a new code within the code within the c

457
00:41:10,618 --> 00:41:16,609
So in the first watermark is the code for actually translating DNA into English

458
00:41:17,003 --> 00:41:21,164
or English into DNA with complete punctuation.

459
00:41:21,369 --> 00:41:27,985
A large number of scientists have now solved this code. And there's an email address built into the genome.

460
00:41:28,277 --> 00:41:35,252

So they solved the code and sent an email to the web address proving that they had adequately decoded it.

461
00:41:35,845 --> 00:41:39,525
But once you decode that it tells you how to read the rest of it.

462
00:41:39,853 --> 00:41:44,724
We have 46 names of all the different scientists that have been involved in this project.

463
00:41:45,147 --> 00:41:49,385
And we tried to get creative and add a few quotations from the literature.

464
00:41:49,886 --> 00:41:56,785
So we had one from James Joyce, one from Oppenheimer's biography and one from Richard Feynman.

465
00:41:56,785 --> 00:42:00,916
And just to show you can never get away for free with anything,

466
00:42:00,916 --> 00:42:06,351
after this was published we got a phone call from James Joyce Estate

467
00:42:06,611 --> 00:42:10,352
saying that we hadn't sought his permission to use this quotation.

468
00:42:10,804 --> 00:42:16,311
And you know I know weíre, we have powerful techniques but I didn't know quite how to do that 'coz he was de

469
00:42:16,877 --> 00:42:20,195
But... So all these is built into the genetic code.

470
00:42:20,428 --> 00:42:26,030
I think the chances of this occurring naturally is pretty close to zero.

471
00:42:26,613 --> 00:42:32,647
So the difference is we can insert all of this, what would appear to nonsense DNA.

472
00:42:32,909 --> 00:42:36,794
In fact, part of our code is to put frequent stop codons into it

473
00:42:37,076 --> 00:42:41,839
so we don't introduce new biology in to the cell by making new fragments.

474
00:42:42,129 --> 00:42:46,933
On the other hand, if we have one error in the central gene, you get no life.

475
00:42:47,168 --> 00:42:51,379
So where it is in the genome and what it is is obviously very critical.

476
00:42:51,379 --> 00:42:53,785
This is the map of the whole genome.

477
00:42:53,785 --> 00:43:02,335
So unlike our genetic code which is only about three percent of our genome codes for protein coding genes,

478
00:43:02,676 --> 00:43:04,421
and this, itís well over 90 percent.

479
00:43:04,625 --> 00:43:07,385
You can see, there's not a lot of gaps between the genes.

480
00:43:07,603 --> 00:43:10,849
So it's a much more efficient system.

481
00:43:11,119 --> 00:43:15,965
Again, when we checked, there were no capricolum proteins left.

482
00:43:16,200 --> 00:43:21,285
It was just the proteins made from this modified genome.

483
00:43:21,743 --> 00:43:29,552
So this is the size range thatís happened over this period of time, now being over a million base pairs.

484
00:43:29,786 --> 00:43:36,297
These techniques are so robust Dan Gibson reassembled the genome for each experiment

485
00:43:36,527 --> 00:43:38,934

instead of trying to use a clone variety of it.

486
00:43:39,134 --> 00:43:42,597
So they're truly robust and now theyíre able to be automated.

487
00:43:43,017 --> 00:43:45,277
I think we're gonna enter into a new era.

488
00:43:45,552 --> 00:43:50,145
So I like to think of all these genes weíve discovered today as design components.

489
00:43:50,628 --> 00:43:58,382
In the electronics industry, people in the 40s and 50s had far fewer design components to work with.

490
00:43:58,761 --> 00:44:02,691
By the time we finished characterizing life on this planet,

491
00:44:02,985 --> 00:44:12,313
this number could be two or three hundred million unique genes or genes that are part of complex gene familie

492
00:44:12,711 --> 00:44:18,491
We actually have software synthetic genomics for designing software of life

493
00:44:18,491 --> 00:44:24,936
to create new organisms where we can modularly build in the type of metabolism.

494
00:44:24,936 --> 00:44:26,728
Is it going to be metabolizing sugars?

495
00:44:26,961 --> 00:44:34,936
Is it gonna take to CO2 to methane etcetera as building a backbone to try and design future organisms?

496
00:44:35,451 --> 00:44:40,893
Because there is so much gene diversity and so few scientists on this planet,

497
00:44:41,252 --> 00:44:46,213
we have to come up with new combinatorial approaches to make some rapid progress here.

498
00:44:46,774 --> 00:44:53,343
So just think if you have a metabolic pathway with only ten genes in it,

499
00:44:53,577 --> 00:44:54,557
and if you have ten versions of each of those ten genes.

500
00:44:54,557 --> 00:44:56,445
That's ten to the tenth combinations.

501
00:44:56,667 --> 00:44:59,069
It would take forever to get there.

502
00:44:59,401 --> 00:45:05,966
So we're trying to build this robot that could make a million chromosomes a day just for one or two scientists to

503
00:45:06,258 --> 00:45:12,643
And if it really is self-learning, those scientist are probably just gonna watch the robot work like it happens with

504
00:45:13,763 --> 00:45:17,417
And then it gets down to what with all biology has been selection.

505
00:45:18,102 --> 00:45:21,733
Can you set up the right assays for selecting what you want out of it?

506
00:45:22,034 --> 00:45:26,743
So, some of my different audience, hopefully not this one ask why do this?

507
00:45:27,008 --> 00:45:29,410
But there's a lot of different reasons.

508
00:45:29,696 --> 00:45:36,435
Obviously burning all these fossil fuels were weíve exceeded the equilibrium of CO2 capture on our planet.

509
00:45:36,681 --> 00:45:38,539
The oceans are the largest sink.

510
00:45:38,974 --> 00:45:46,818

This number keeps changing I think it's up to 3.8 million tons of new CO2 in the atmosphere.

511
00:45:47,339 --> 00:45:57,021
We're making more people faster than we can provide the means to feed them and provide medicine and hous

512
00:45:57,226 --> 00:45:58,752
We're at 6.8 billion now.

513
00:45:58,971 --> 00:46:04,343
Within 35 to 40 years we'll be over 9 billion.

514
00:46:04,649 --> 00:46:06,263
Like any number, I like to put it in context.

515
00:46:06,263 --> 00:46:08,820
So I was born in 1946.

516
00:46:09,039 --> 00:46:14,885
There's now three people alive on the planet for everybody that existed the year that I was born.

517
00:46:15,090 --> 00:46:17,868
Soon there'll be four.

518
00:46:17,868 --> 00:46:23,543
All in almost a single generation do we have these huge changes.

519
00:46:23,809 --> 00:46:26,927
We can't provide all means for feeding the ones now.

520
00:46:26,927 --> 00:46:30,642
So weíd need new approaches for the next generations.

521
00:46:30,952 --> 00:46:34,965
When we look at plants, plants are really not very productive systems.

522
00:46:35,213 --> 00:46:37,081
They're pretty limited.

523
00:46:37,569 --> 00:46:44,025
So we, like others, have looked around and even looking at kind of modest numbers ëcoz we have to greatly e

524
00:46:44,293 --> 00:46:50,295
ten thousand gallons an acre with microalgae to make it truly cost effective for making fuels.

525
00:46:50,985 --> 00:46:55,195
It's orders of magnitude better than any of the plants systems.

526
00:46:55,476 --> 00:46:58,518
We've been working on oil palm and jatropha and others.

527
00:46:59,319 --> 00:47:01,547
Look at the bottom of list - corn.

528
00:47:01,778 --> 00:47:06,457
We have an economy in this country based on trying to make ethanol from corn.

529
00:47:07,145 --> 00:47:13,071
It's only because of thereís a corn lobby, not coz it's a smart thing to do.

530
00:47:13,525 --> 00:47:15,631
So we have to try and move in a different direction.

531
00:47:15,931 --> 00:47:20,750
So we've been trying to work on designing what we call 4th generation of fuels and cells,

532
00:47:21,363 --> 00:47:26,035
where sunlight is the energy source and CO2 is the carbon source.

533
00:47:27,303 --> 00:47:30,077
We can almost go in any direction from CO2.

534
00:47:30,282 --> 00:47:31,277
You can make materials.

535
00:47:31,595 --> 00:47:32,369

You can make food.

536
00:47:32,602 --> 00:47:34,654
You can make fuel.

537
00:47:34,880 --> 00:47:36,506
You can make unique chemicals.

538
00:47:36,738 --> 00:47:38,550
You can make proteins.

539
00:47:38,920 --> 00:47:46,085
And so we've been working on this and our team led by Paul Rustler had a really nice breakthrough in the lab.

540
00:47:46,085 --> 00:47:49,345
By changing some genes and some enzyme systems,

541
00:47:49,606 --> 00:47:54,491
instead of treating algae growth like farming of growing up a lot and trying to squeeze the oil out,

542
00:47:54,770 --> 00:48:00,984
we got the cells to pump the oil out of the cells on a continuous basis.

543
00:48:01,229 --> 00:48:04,928
Here's a cell that makes pure C8 and C10.

544
00:48:05,209 --> 00:48:11,405
By changing anything along the pathway, we can make any size lipid.

545
00:48:11,934 --> 00:48:18,142
This is one of the main reasons why Exxon put 600 million dollars on the line to work with us

546
00:48:18,468 --> 00:48:26,158
to try and scale up the production of carbon compounds from CO2.

547
00:48:26,382 --> 00:48:30,853
I don't say fuel because the goal is just to create a biocrude

548
00:48:31,071 --> 00:48:35,085
from the algae to go into the existing refineries to make gasoline,

549
00:48:35,085 --> 00:48:39,952
diesel and jet A fuel, totally consistent with the existing infrastructure

550
00:48:40,217 --> 00:48:45,176
instead of trying to adapt to burning a different type of lipid.

551
00:48:45,396 --> 00:48:49,032
So we're making some good progress along these lines.

552
00:48:49,386 --> 00:48:55,315
But to get to the billions of gallon scale, these are not short-term projects.

553
00:48:55,752 --> 00:49:01,726
So we think the soonest there would be anything on a substantial economic scale will be ten years.

554
00:49:02,152 --> 00:49:04,689
But itís progressing.

555
00:49:04,954 --> 00:49:10,183
Itís where we need synthetic genomics, synthetic biology, cell engineering to take over.

556
00:49:10,183 --> 00:49:19,436
Because it wouldn't make sense for an algae to evolve to produce as much hydrocarbon as we need from CO2

557
00:49:19,853 --> 00:49:21,476
So we have to change evolution.

558
00:49:21,724 --> 00:49:22,895
We have to take over.

559
00:49:23,178 --> 00:49:26,748
Weíve looked at thousands and thousands of algae strains.

560
00:49:27,031 --> 00:49:32,785

And there is nothing within an order of magnitude naturally to get where one needs to be.

561
00:49:33,331 --> 00:49:41,428
People have obviously looked at algae for producing food for a space flight and other processes.

562
00:49:42,037 --> 00:49:45,237
It's pretty inefficient in terms of what was done before.

563
00:49:45,702 --> 00:49:50,195
So using natural algae like this, I think it would take

564
00:49:50,195 --> 00:49:55,283
a pretty large volume just to produce enough to feed a single astronaut.

565
00:49:55,485 --> 00:50:01,943
Going up exponentially in a production scale and engineering these cells to produce different substances.

566
00:50:02,212 --> 00:50:05,519
I think itís totally within the realm of the next few years.

567
00:50:05,985 --> 00:50:13,459
Ken Nielsen at the Institute has a great electrobiology group thatís working on microbial fuel cells.

568
00:50:14,531 --> 00:50:23,102
That, microbes just naturally select the anode or cathode and we can take complex mixtures including raw sew

569
00:50:23,783 --> 00:50:29,711
generate electricity and convert that into close to drinking water.

570
00:50:30,117 --> 00:50:38,275
Nobody wants to do that final experiment yet, but it takes it a very long way and itís in part due to understandi

571
00:50:38,275 --> 00:50:45,077
The teams discovered that bacteria actually make these nanowires that can live off of metal surfaces,

572
00:50:45,485 --> 00:50:50,634
pulling in electrons out of the metal and using those for metabolism.

573
00:50:51,553 --> 00:50:59,569
We just announced formation of a new vaccine company, to use these synthetic approaches to very rapidly ma

574
00:50:59,773 --> 00:51:04,505
This is based on 15 years of work weíve had with Novartis on the new meningitis vaccine,

575
00:51:04,505 --> 00:51:10,116
which is the first genomic-based vaccine and just finished phase-3 clinical trials in Europe.

576
00:51:11,022 --> 00:51:18,136
Meningitus B is one of those diseases that by the time you diagnose it in young people, it is too late.

577
00:51:18,776 --> 00:51:20,847
They are dead shortly thereafter.

578
00:51:21,101 --> 00:51:23,439
So vaccine is the only preventative approach.

579
00:51:23,925 --> 00:51:28,717
And now we are applying this to making very rapidly new influenza vaccines.

580
00:51:29,167 --> 00:51:34,969
So NIH has funded my Institute to make synthetic fragments of every influenza virus that we and others have e

581
00:51:35,344 --> 00:51:40,052
So, we are going to have all these fragments just on the shelf.

582
00:51:41,552 --> 00:51:48,164
And if there is a new pandemic, we are actually going to be making vaccines with the new emerging ones for n

583
00:51:48,915 --> 00:51:56,915
within less than 24 hours we can make new vaccine candidates that can go right into their new cell production

584
00:51:57,352 --> 00:52:01,866
and get very rapid production of vaccines that we think are going to be far more effective

585
00:52:02,550 --> 00:52:07,352

than our century-old technology we are using today of growing things in chicken eggs.

586
00:52:07,837 --> 00:52:12,566
So, we are trying to apply these tools in a wide variety of areas.

587
00:52:13,140 --> 00:52:16,844
As I said, we asked ethical questions before we started the first experiments.

588
00:52:17,748 --> 00:52:21,179
There is a series of reviews that have been published along the way,

589
00:52:21,752 --> 00:52:28,647
including one that the Sloan foundation has funded my institute along with MIT to look at security concerns.

590
00:52:29,768 --> 00:52:35,150
On our announcement this spring, President Obama has asked the new bioethics committee

591
00:52:35,509 --> 00:52:42,033
to deal with this as their first priority and their report out is due very soon.

592
00:52:42,624 --> 00:52:46,102
This is a report from the Royal Academy of Engineering last year,

593
00:52:46,563 --> 00:52:49,178
saying these synthetic biology,

594
00:52:49,384 --> 00:52:54,088
synthetic genomic tools are likely to be the number one wealth generator for the next century.

595
00:52:54,420 --> 00:52:58,102
For countries, for companies, for individuals,

596
00:52:58,630 --> 00:53:06,102
because they have a chance to completely change how we make everything from food to fuel.

597
00:53:06,897 --> 00:53:09,286
So, we are just at the early stages of this.

598
00:53:09,829 --> 00:53:12,000
The first stage took us 15 years.

599
00:53:12,220 --> 00:53:14,795
We didnít think it would take that long when we started out.

600
00:53:15,447 --> 00:53:21,876
But we developed our own funding to go along with our belief that we will get there.

601
00:53:22,715 --> 00:53:27,052
If we relied on government grants, it would have probably been withdrawn a long time ago.

602
00:53:27,429 --> 00:53:29,720
These are the early stages.

603
00:53:30,052 --> 00:53:32,482
What took us years to do, you can now do in a day.

604
00:53:33,575 --> 00:53:37,785
Hopefully, what we can now do in a day, within a short while we will be able to do millions of times a day.

605
00:53:38,101 --> 00:53:43,498
And just think how that accelerates biology and our understanding.

606
00:53:44,352 --> 00:53:47,662
So, just compiling some things for long term.

607
00:53:47,957 --> 00:53:55,513
Space flight, obviously, we have to start looking at the genetic code of people to understand their range of biolo

608
00:53:55,787 --> 00:54:00,593
how to prevent diseases, to understand and predict what's gonna happen.

609
00:54:00,890 --> 00:54:03,793
Identifying traits compatible for long-term space flight.

610
00:54:04,245 --> 00:54:11,281

With the microbiome, understanding how microbes contribute to health and disease and trying to get positive tr

611
00:54:12,300 --> 00:54:18,485
placing pre-existing ones, and then everything from food to chemicals to materials.

612
00:54:19,269 --> 00:54:24,585
I think this list could be extended indefinitely.

613
00:54:25,340 --> 00:54:33,247
These microbes can be self-correcting with as Deinococcus does, with radiation.

614
00:54:33,747 --> 00:54:36,862
Perhaps the only way to do that with humans is to send up

615
00:54:37,068 --> 00:54:43,002
a set of a lead-covered container for stem cells to do replacement.

616
00:54:43,415 --> 00:54:48,580
But we think we can use synthetic tools to even improve on stem cells to do exactly what we want them to do.

617
00:54:50,015 --> 00:54:54,914
Then ultimately, if it's gonna really be generational space flight,

618
00:54:55,164 --> 00:54:59,827
we might want to go beyond selection ultimately to engineering.

619
00:55:00,109 --> 00:55:01,185
Thank you very much.

620
00:55:01,482 --> 00:55:16,052
[Applause]

621
00:55:16,305 --> 00:55:17,815
>> Moderator: Thank you very much, Craig.

622
00:55:18,082 --> 00:55:19,580
That was great!

623
00:55:19,580 --> 00:55:21,869
If people would like to line up on the microphones over on this side, if they have questions.

624
00:55:21,869 --> 00:55:26,100
If you could identify who you are and where are you from.

625
00:55:26,361 --> 00:55:29,236
If there are any press in the audience that will have questions,

626
00:55:30,153 --> 00:55:33,274
then please also line up here and move to the front of the line.

627
00:55:33,477 --> 00:55:37,625
>> Dr. J. Craig Venter: Pathogens would be amongst the most difficult things to try and deliberately create.

628
00:55:39,484 --> 00:55:43,850
And youíd have to be starting with something pathogenic public to do that,

629
00:55:44,083 --> 00:55:48,253
but biology is still there is a stage of surprising people all the time.

630
00:55:48,565 --> 00:55:53,601
I think doing these experiments;

631
00:55:53,898 --> 00:56:01,139
weíre designing everything where it could not survive outside the laboratory or facility where it was produced.

632
00:56:01,385 --> 00:56:05,520
We can do this with suicide genes, chemical dependencies.

633
00:56:05,738 --> 00:56:12,819
We have almost twenty or so years with this, probably been tens of millions of experiments done in

634
00:56:13,022 --> 00:56:20,452
molecular biology with E. coli, that can't grow outside the lab because of such a chemical dependency.

635
00:56:21,337 --> 00:56:23,294

So we know how to control these things.

636
00:56:24,458 --> 00:56:27,578
I think the ability to rapidly make vaccines,

637
00:56:27,904 --> 00:56:33,119
I think new emerging infections are orders of magnitude greater risks than

638
00:56:33,119 --> 00:56:36,858
humans making anything infecting deliberately or otherwise.

639
00:56:39,558 --> 00:56:45,224
>> Audience 1 (female): If you were to choose chassis environment, chassis microorganism for space environ

640
00:56:45,819 --> 00:56:46,941
what do you think it would be?

641
00:56:47,173 --> 00:56:54,068
So it's a containment organism with minimum genome that you would start modifying and rebooting, for examp

642
00:56:54,569 --> 00:56:58,405
And the second question, I'm sorry for not letting you answer it right away.

643
00:56:58,765 --> 00:57:05,049
And the second question is, what type of space stressors would cause

644
00:57:05,906 --> 00:57:13,614
a colony of multiple organisms to take on the whole chromosome, you think?

645
00:57:14,051 --> 00:57:15,565
Maybe it's radiation?

646
00:57:15,565 --> 00:57:16,770
And how easy it is?

647
00:57:16,770 --> 00:57:17,592
What is the probability?

648
00:57:17,856 --> 00:57:20,211
Thank you very much.

649
00:57:20,619 --> 00:57:22,848
>> Dr. J. Craig Venter: I don't think there is any one type of microbe

650
00:57:23,052 --> 00:57:25,624
right now that we know about that would be any better than others.

651
00:57:25,624 --> 00:57:33,597
In fact diversity is gonna be important if we're gonna try and recreate a microbiome, generate energy, create fo

652
00:57:33,597 --> 00:57:35,469
But they need to be robust.

653
00:57:35,739 --> 00:57:38,325
We obviously like to build in the kinds of things that Deinococcus,

654
00:57:38,325 --> 00:57:46,435
where the endurance has where they can self-repair very robustly from continuous radiation.

655
00:57:46,715 --> 00:57:50,620
So DNA repair is important for us as it is for these microbes.

656
00:57:50,850 --> 00:57:57,842
And there is a wide range of DNA repair systems in microbes going all the way to something like Deinococcus.

657
00:57:58,385 --> 00:58:02,242
In terms of exchange, you and I were talking about this earlier.

658
00:58:02,445 --> 00:58:10,523
I think in the environment on our planet we see not just from our deliberate transplants but when we look back

659
00:58:10,523 --> 00:58:15,005
we see all kinds of organisms that have multiple chromosomes in the microbial world.

660
00:58:15,421 --> 00:58:18,250

The first one we saw was with cholera.

661
00:58:18,825 --> 00:58:26,953
One of the arguments based on 16S RNA, there was no point in sequencing the cholera genome because it's v

662
00:58:27,435 --> 00:58:33,236
But when we sequenced the genome it actually had two chromosomes,

663
00:58:33,236 --> 00:58:35,204
one that was very similar to E. coli and one that was very different.

664
00:58:35,419 --> 00:58:36,823
And so we think we see this all the time.

665
00:58:37,291 --> 00:58:43,986
So Deinococcus has four chromosomal elements, some quite different from the core ones.

666
00:58:44,747 --> 00:58:48,969
So I think many species have acquired entirely new traits.

667
00:58:49,445 --> 00:58:55,083
In a heartbeat, literally, you could add a thousand new traits in evolution to a cell.

668
00:58:55,919 --> 00:58:57,919
We don't understand these mechanisms very well.

669
00:58:58,523 --> 00:59:00,259
We don't know if there's cell fusion.

670
00:59:00,520 --> 00:59:02,849
Some cells take up DNA quite nicely.

671
00:59:03,190 --> 00:59:07,562
So obviously, continued evolution is something we have to understand with the microbes

672
00:59:07,947 --> 00:59:11,369
that we are putting together in stressed environments.

673
00:59:13,800 --> 00:59:15,236
>> Orlando Santos: Hi, Craig.

674
00:59:15,236 --> 00:59:19,913
I'm Orlando Santos from NASA Ames and I wanna ask you about technology development timelines.

675
00:59:20,614 --> 00:59:24,764
Because if you take out your crystal ball, given what you heard all day today,

676
00:59:25,106 --> 00:59:29,181
what do you think would be the first application of synthetic biology to

677
00:59:29,181 --> 00:59:33,205
NASA's mission and how long do you think it will take to get there?

678
00:59:33,484 --> 00:59:34,970
>> Dr. J. Craig Venter: How much money you got?

679
00:59:35,218 --> 00:59:37,685
[Crowd laughs, Venter chuckles]

680
00:59:37,685 --> 00:59:39,240
>> Orlando Santos: Good answer.

681
00:59:39,240 --> 00:59:43,895
>> Dr. J. Craig Venter: I mean, you know, without knowing the level of effort going into it that's impossible to ar

682
00:59:44,095 --> 00:59:49,539
But I think it could change the shape of everything NASA does if you make the commitment to do it.

683
00:59:49,903 --> 00:59:55,762
You know, itís, I found it really hard to predict the future ever when

684
00:59:55,762 --> 00:59:58,724
I'm a month or two away from something that I'm sure will happen.

685
00:59:58,724 --> 01:00:00,689

I've been wrong many times.

686
01:00:01,017 --> 01:00:09,020
But, yeah, we're a small group of scientists that have done this work independently over a fifteen-year period.

687
01:00:09,520 --> 01:00:14,106
The fact that you or anyone else now could take these techniques that we've published and these kits that wou

688
01:00:14,106 --> 01:00:19,753
be available and do what we did in three years and do it in an afternoon

689
01:00:20,209 --> 01:00:24,652
or so means you could move a whole lot faster and learn a whole lot faster.

690
01:00:24,886 --> 01:00:30,552
So, without the financial commitment and the intellectual commitment, yes, it's not just dollars.

691
01:00:30,552 --> 01:00:33,863
It's having the right people doing the right experiments for the right reasons.

692
01:00:34,313 --> 01:00:41,485
I can't think of an organization that has more potential to use synthetic genomics and synthetic biology than NA

693
01:00:41,911 --> 01:00:46,179
I mean, Exxonís doing pretty well but itís trying to stay on this planet, right now?

694
01:00:48,504 --> 01:00:49,661
>> Andrew: Hi. My name is Andrew Bingham.

695
01:00:50,575 --> 01:00:51,622
You mentioned openness a couple of times in your presentation in posting

696
01:00:51,622 --> 01:00:58,755
the human genome online and how that would spur research in the area of biology.

697
01:01:00,076 --> 01:01:05,776
My understanding is that currently up to 20% of the genes in my body have actually

698
01:01:06,005 --> 01:01:10,013
been patented by different companies involved in the area of biology.

699
01:01:10,013 --> 01:01:11,985
>> Dr. J. Craig Venter: You must have some cool genes.

700
01:01:11,985 --> 01:01:13,138
[Crowd laughs, Venter chuckles]

701
01:01:13,138 --> 01:01:14,310
>> Andrew: And Iím wondering,

702
01:01:14,310 --> 01:01:18,738
how did you strike the balance between the need to give private companies incentive to

703
01:01:18,738 --> 01:01:23,123
do this type of research versus the idea of patenting things that are then around

704
01:01:23,123 --> 01:01:24,961
in nature for hundreds of thousands of years.

705
01:01:25,537 --> 01:01:31,089
>> Dr. J. Craig Venter: Well I would urge you to try and understand the patent process and why we have one in

706
01:01:31,448 --> 01:01:34,867
ëcoz itís designed to encourage and force openness.

707
01:01:35,817 --> 01:01:44,397
The Coca-Cola formula was never patented and was kept secret for a very long time ëcoz it was a trade secret

708
01:01:45,269 --> 01:01:52,149
So part of their reasons for having patents is to force people to completely disclose all the information about the

709
01:01:52,479 --> 01:01:56,599
so that somebody else could build on it The trade-off is that our

710
01:01:56,599 --> 01:02:00,093

government makes with inventors is you get a period of exclusivity,

711
01:02:00,809 --> 01:02:06,287
not to own the data, not to block every people from using it, but to commercially develop it.

712
01:02:06,769 --> 01:02:08,608
Itís the basis of our economy.

713
01:02:09,543 --> 01:02:14,303
I doubt that your 20% of your genes have any value rather than to you.

714
01:02:16,095 --> 01:02:17,909
But some of them do, you know.

715
01:02:18,154 --> 01:02:20,093
Thereís millions of diabetics that are...

716
01:02:20,093 --> 01:02:22,589
>> Andrew: Wait. Theyíre not inventing it. I mean look at...

717
01:02:22,589 --> 01:02:23,710
>> Dr. J. Craig Venter: Let me finish, please.

718
01:02:23,710 --> 01:02:31,196
There are millions of diabetics that are very pleased UC San Francisco patented the gene for insulin and Gene

719
01:02:31,432 --> 01:02:33,476
You know, it doesnít matter in this country.

720
01:02:33,476 --> 01:02:38,661
The law is, it treats invention and discovery exactly the same.

721
01:02:38,661 --> 01:02:42,169
If you have an issue with that take it up with a lawyer or a congressman.

722
01:02:42,694 --> 01:02:47,405
But itís the law of the land and thatís how science and industry move forward.

723
01:02:50,109 --> 01:02:52,303
>> Doug Messier from Parabolic Arc.

724
01:02:53,074 --> 01:02:59,139
This is space manufacturing some of us, looking at that, can you see organisms being built to assist with minin

725
01:02:59,418 --> 01:03:06,943
manufacturing life support systems, those types of things?

726
01:03:08,376 --> 01:03:11,243
>> Dr. J. Craig Venter: I am (inaudible name), to what extent are you talking about mining?

727
01:03:11,538 --> 01:03:21,039
There are several groups, companies on this planet trying to see if microbes can enhance mining of copper, mi

728
01:03:21,616 --> 01:03:28,418
Obviously the oil companies weíre working with BP to see if we can use these deep-earth

729
01:03:28,627 --> 01:03:34,121
microbes to enhance oil recovery, change viscosity of oil etc.

730
01:03:34,534 --> 01:03:42,167
So, how and if these things apply to work on Mars is beyond my expertise.

731
01:03:42,167 --> 01:03:44,096
>> Doug Messier: OK. Thank you.

732
01:03:47,298 --> 01:03:52,801
>> Wayne White. You said that some microbes have the ability to self-repair DNA.

733
01:03:53,627 --> 01:03:58,650
It occurs to me that if you could introduce that trait into the human genome,

734
01:03:59,091 --> 01:04:02,440
then one of the consequences of your work would be life extension.

735
01:04:03,455 --> 01:04:07,626

>> Dr. J. Craig Venter: Well, all humans have the ability to repair DNA.

736
01:04:07,626 --> 01:04:13,267
In fact it was a discovery early on that we made with Burt Vogelstein that mutations

737
01:04:13,267 --> 01:04:16,985
and some of these DNA repair enzymes are associated with colon cancer.

738
01:04:17,807 --> 01:04:24,251
So if you canít repair the damage that weíre constantly being subject to, others can increase incidents of cance

739
01:04:24,862 --> 01:04:28,701
Basically, all organisms can repair their DNA.

740
01:04:28,932 --> 01:04:31,817
Not all of them can do what Deinococcus Radiodurans can.

741
01:04:32,050 --> 01:04:35,809
It can be blown apart and reassemble their chromosomes in the same way.

742
01:04:36,327 --> 01:04:40,946
But it turns out there is probably a very large number of organisms on this planet that can do it.

743
01:04:40,946 --> 01:04:44,783
People think it wasnít necessarily evolution to deal with radiation

744
01:04:45,142 --> 01:04:50,337
as much as it was drought resistance, maybe very similar mechanisms.

745
01:04:51,019 --> 01:04:58,960
Being able to completely reassemble our chromosomes like Deinococcus can, would be an interesting phenom

746
01:04:59,319 --> 01:05:03,047
Iím not sure with the biological consequences of that would be.

747
01:05:03,517 --> 01:05:05,623
But itís an intriguing idea.

748
01:05:07,622 --> 01:05:09,197
>> Patrick Fu: Hi. Iím Patrick Fu.

749
01:05:09,617 --> 01:05:18,554
You have shown that chemically synthetic genome is doable and it has been created.

750
01:05:19,287 --> 01:05:25,591
Do you have any plan to design for the synthesis of the membrane proteins

751
01:05:25,886 --> 01:05:32,908
so that those chemically synthetic genome can live inside,

752
01:05:33,157 --> 01:05:41,084
it does not need to just borrow other bacteriaís body to accommodate it.

753
01:05:42,722 --> 01:05:44,418
>> Dr. J. Craig Venter: Weíre not specifically doing that.

754
01:05:44,418 --> 01:05:48,044
It would be, weíre trying to see if we can design sort of a universal

755
01:05:48,044 --> 01:05:53,877
recipient cell that we could put a variety of chromosomes into.

756
01:05:54,312 --> 01:06:00,301
And there would be enough diversity of reading that DNA so it could start making almost

757
01:06:00,301 --> 01:06:03,299
any protein system until it can get its own system going.

758
01:06:03,299 --> 01:06:08,634
It needs to get early life going from DNA, we have to be able to read that DNA.

759
01:06:08,634 --> 01:06:12,473
So we need tRNAs and a few other components.

760
01:06:13,111 --> 01:06:17,725

Weíre trying to see if we can make sort of a basic cell that has diversity of

761
01:06:17,725 --> 01:06:23,126
those that could deal with a wide range of codon usage and other things.

762
01:06:23,465 --> 01:06:30,632
So, I think thatís gonna be essential in terms of standardizing things for the field, but that may not work.

763
01:06:31,240 --> 01:06:36,213
I think what you are talking about in terms of unique membrane protein production;

764
01:06:36,651 --> 01:06:38,600
weíre not doing that per se.

765
01:06:39,272 --> 01:06:45,184
But I think thereís ten million things that we can all think of doing that we alone arenít gonna do.

766
01:06:45,184 --> 01:06:46,467
So hopefully you will.

767
01:06:46,725 --> 01:06:48,551
[Venter chuckles]

768
01:06:49,004 --> 01:06:53,047
>> Audience 2: There are some experiments which should not be done on earth.

769
01:06:53,251 --> 01:06:58,802
For example recent work in high energy physics can make micro black holes

770
01:06:59,035 --> 01:07:04,057
which is they considered safe because Hawking says theyíll evaporate.

771
01:07:04,511 --> 01:07:08,193
But if they donít, the Earth is?

772
01:07:08,409 --> 01:07:15,777
The question is, are there experiments that we would like to do that are so potentially hazardous,

773
01:07:15,777 --> 01:07:20,001
it would be a good idea to do them in some remote laboratory of earth?

774
01:07:20,001 --> 01:07:22,579
And is that a good reason or not a good reason to go into space?

775
01:07:22,918 --> 01:07:25,870
[Venter laughs]

776
01:07:25,870 --> 01:07:28,365
>> Dr. J. Craig Venter: It depends what the legal system in space is, I guess.

777
01:07:28,647 --> 01:07:34,105
Itís a, I was offered an island off of Belize but I read a book about that one too.

778
01:07:34,652 --> 01:07:42,484
So, I donít think that is such a good idea.

779
01:07:42,745 --> 01:07:45,494
I donít think we should have a different ethical system necessarily in space.

780
01:07:45,494 --> 01:07:56,740
But I think human engineering is one of those things that we sort of

781
01:07:56,740 --> 01:07:58,708
all agree on you canít do ëcoz you canít do human experimentation.

782
01:07:58,708 --> 01:08:07,753
You know, that leap from selection to engineering is gonna be a very complex one for society, I mean if it ever

783
01:08:07,753 --> 01:08:12,184
I donít think doing that in space makes it any better, easier.

784
01:08:14,949 --> 01:08:17,493
>> Silvano Columbano: Silvano Columbano from NASA Ames.

785
01:08:17,831 --> 01:08:28,251

To what extent are you able to predict functionality from your designed genome?

786
01:08:28,251 --> 01:08:29,984
And if itís merely trial and error in a computer,

787
01:08:29,984 --> 01:08:35,318
could you do the trial and error in a computer, as a form of simulation?

788
01:08:35,318 --> 01:08:36,347
>> Dr. J. Craig Venter: Yeah.

789
01:08:36,347 --> 01:08:39,951
I wish we could do everything by computer modelling and simulation right now.

790
01:08:40,609 --> 01:08:46,196
But we canít even completely model this very simple 500-gene cell.

791
01:08:46,411 --> 01:08:48,347
It's basic metabolism can be.

792
01:08:48,930 --> 01:08:51,937
But even with that cell 100 of the essential genes for biology.

793
01:08:52,401 --> 01:08:59,116
In other words, if we remove that gene or disrupt it the cell dies out of unknown function.

794
01:08:59,407 --> 01:09:08,048
So, biology is fundamentally in a discovery, not by a first principle method right now.

795
01:09:08,344 --> 01:09:11,082
I mean thatís what these combinatorial methods,

796
01:09:11,082 --> 01:09:19,315
if we can learn rapidly from them we can get to the first principles that there is not a single genome

797
01:09:19,315 --> 01:09:22,680
where a scientific community understands the function of every gene in it.

798
01:09:22,983 --> 01:09:24,993
We are not even close to that.

799
01:09:25,817 --> 01:09:30,357
So, empirical science is a big part of this field for a long time to come.

800
01:09:30,357 --> 01:09:35,363
Thatís why we need good ways to measure, good ways to speed it up.

801
01:09:36,385 --> 01:09:37,485
>> Silvano Columbano: Thank you.