WEBVTT

1 00:00:00.000 --> 00:00:09.519 Support for Yale Cancer Answers comes from AstraZeneca, working to change how cancer is treated with personalized medicine.

2 00:00:09.519 --> 00:00:11.179 Learn more at

3 00:00:11.179 --> 00:00:13.400 astrazeneca-us.com. Welcome

4 00:00:13.400 --> 00:00:17.829 to Yale Cancer Answers. With doctor Anees Chagpar.

5 00:00:17.829 --> 00:00:27.379 Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week,

6 00:00:27.379 --> 00:00:32.159 it's a conversation about how CRISPR is transforming cancer research with Dr. Jun Lu.

7 00:00:32.159 --> 00:00:36.590 Doctor Lu is an associate professor of genetics at the Yale School of Medicine

9 00:00:41.549 --> 00:00:48.159 Dr. Lu, maybe you can start by telling us a little bit about your research and some of the new technologies

10 00:00:48.159 --> 00:00:51.259 that you're using. It's a very interesting question.

11 00:00:51.259 --> 00:00:57.820 Basically we are very interested in cancer in general and we have two major interests.

12 00:00:57.820 --> 00:00:59.869 One is to understand leukemia,

13 00:00:59.869 --> 00:01:04.790 which is a special cancer that's originating from the lymph system.

14 00:01:04.790 --> 00:01:07.659 We are also interested in immune responses.

15 00:01:07.659 --> 00:01:10.530 against normal types of cancers,

16 00:01:10.530 --> 00:01:12.989 what you normally hear about,

17 00:01:12.989 --> 00:01:16.269 what wel call solid cancers like breast cancer,

18 00:01:16.269 --> 00:01:18.319 prostate cancer, colon cancer, etc.

19 00:01:18.319 --> 00:01:21.239 And we have been working with melanoma

20 00:01:21.239 --> 00:01:23.150 as well as colon cancer ourselves.

21 00:01:23.150 --> 00:01:26.650 It sounds like you've been doing a lot of work.

22 00:01:26.650 --> 00:01:31.099 Tell us a little bit more about some of the unique aspects of your

23 00:01:31.099 --> 00:01:37.459 cancer research.

24 00:01:37.459 --> 00:01:46.040 We have been very interested in several types of questions, and we are particularly interested in understanding how cancers work, and one thing that we're trying to understand is how does a normal cell go weird and become bad

25 00:01:46.040 --> 00:01:51.450 and become cancer cells. Number two is, we're trying to understand the wiring, the molecular wiring within cancer cells and the molecular wiring

26 00:01:51.450 --> 00:01:53.079 we are particularly interested in

27 00:01:53.079 --> 00:01:57.219 are what we call non coding regions of the genome.

28 00:01:57.219 --> 00:02:07.569 You may have heard, the human genome consists of important pieces of DNA that we call the coding piece of DNA that encode so-called protein genes and these

29 00:02:07.569 --> 00:02:10.330 account for roughly 2% or less than 2%

30 00:02:10.330 --> 00:02:13.090 of the genome, and the rest of the 98%

31 00:02:13.090 --> 00:02:15.509 of the genome is so called non coding parts of the genome.

32 00:02:15.509 --> 00:02:21.030 They are on the DNA and initially we didn't recognize much out of it.

33 00:02:21.030 --> 00:02:23.110 We think they are less important.

34 00:02:23.110 --> 00:02:26.460 It turns out that they are there for a reason.

35 00:02:26.460 --> 00:02:33.830 They're not just junk, and so we have been particularly interested in the non coding parts of genome and how they control

36 00:02:33.830 --> 00:02:35.509 the coding parts of the genome.

37 00:02:35.509 --> 00:02:45.560 So tell us a little bit more about that because intuitively one would think that the coding parts of the genome are the ones that make the proteins

38 00:02:45.560 --> 00:02:48.569 and the proteins are the things that make functions,

39 00:02:48.569 --> 00:02:50.919 but the non coding parts, they control

40 00:02:50.919 --> 00:02:52.930 the coding parts. Tell us more

41 00:02:52.930 --> 00:02:54.599 about that.

42 00:02:54.599 --> 00:02:56.770 Absolutely right, so the noncoding parts of the genome,

43 00:02:56.770 --> 00:02:58.939 at least through what we currently understand,

44 00:02:58.939 --> 00:03:02.969 one part of their function is to control the protein coding genes themselves,

45 00:03:02.969 --> 00:03:06.069 and they can have many different ways to do that.

46 00:03:06.069 --> 00:03:11.340 For example, one of the types that we work with are so called non coding RNA.

47 00:03:11.340 --> 00:03:16.300 So these are RNAs that are produced in the cells and these are ones that

48 00:03:16.300 --> 00:03:18.780 control how much proteins are made.

49 00:03:18.780 --> 00:03:21.569 So this is one way they can show that,

50 00:03:21.569 --> 00:03:26.530 but there are many other ways non coding parts of genome can control non coding protein genes,

51 00:03:26.530 --> 00:03:30.349 so that's one way the non coding parts of genome can be important.

52 00:03:30.349 --> 00:03:33.460 Another part

53 00:03:33.460 --> 00:03:36.259 is that they can control themselves.

54 00:03:36.259 --> 00:03:41.539 There are so-called non coding genes themselves that can be controlled by non coding parts of genome.

55 00:03:41.539 --> 00:03:46.830 So it's sort of layer by layer that can have very sophisticated control of the human genome.

56 00:03:46.830 --> 00:03:53.050 And you mentioned that another part of your research is to figure out what makes a normal cell go rogue.

57 00:03:53.050 --> 00:03:56.159 What makes a normal cell mutate into a cancer cell?

58 00:03:56.159 --> 00:03:59.319 Do the non coding parts of the genome have

59 00:03:59.319 --> 00:04:01.050 a role to play in doing that?

60 00:04:01.050 --> 00:04:02.780 That's a very,

61 00:04:02.780 --> 00:04:10.389 very good question. Currently our understanding in human cancer perception has been more heavily focused on the printing parts of genome.

62 00:04:10.389 --> 00:04:13.509 We know that when the cancers initially go around,

63 00:04:13.509 --> 00:04:15.930 for example, in the case of leukemia,

64 00:04:15.930 --> 00:04:19.730 it's occurs initially in the stem cells of normal stem cells,

65 00:04:19.730 --> 00:04:25.959 and these normal stem cells that normally give rise to the blood cells in the blood producing system.

66 00:04:25.959 --> 00:04:30.529 And when the protein coding genes are mutated they will allow themselves to

67 00:04:30.529 --> 00:04:33.449 become bad in some sense and eventually become,

68 00:04:33.449 --> 00:04:44.399 for example, leukemia. And there are now more and more research in the non coding parts of genome because many times we cannot completely explain the phenomena of how does

69 00:04:44.399 --> 00:04:53.889 a normal cell go from a normal cell to become a cancer cell and they have to rely potentially on the non coding parts of genome.

70 00:04:53.889 --> 00:04:59.370 And as a matter of fact the new sequencing technologies have been helping science,

71 00:04:59.370 --> 00:05:01.980 especially biomedical science.

72 00:05:01.980 --> 00:05:08.019 Mutations in the negative parts of genome and some of them do seem to contribute to the initiation of cancer.

73 00:05:08.019 --> 00:05:17.600 Let's talk a little bit more about new technologies because certainly one would think that after the explosion with the human genome project,

74 00:05:17.600 --> 00:05:19.379 when that was finally revealed,

75 00:05:19.379 --> 00:05:27.540 everyone thought that this would be the great discovery that would help us to find the cures to all cancers.

76 00:05:27.540 --> 00:05:32.550 How has the Human Genome Project and understanding the genome really helped us and

77 00:05:32.550 --> 00:05:36.660 where do we still have to go in terms of finding those cures?

78 00:05:36.660 --> 00:05:40.449 Because a lot of people thought once the human genome was decoded,

79 00:05:40.449 --> 00:05:46.769 we would have all of the answers and then we would be able to find the cure for cancer and everything

80 00:05:46.769 --> 00:05:48.980 else. That's again a very interesting question.

81 00:05:48.980 --> 00:05:51.189 Actually, I still remember very early on,

82 00:05:51.189 --> 00:06:00.670 actually the government had declared that we're going to have a cancer cure quite a number of years ago and apparently up

83 00:06:00.670 --> 00:06:04.149 to now we still have some success against cancer,

84 00:06:04.149 --> 00:06:07.319 but there's still other things that we don't have success with.

85 00:06:07.319 --> 00:06:11.540 But from the understanding of how cancer works,

86 00:06:11.540 --> 00:06:15.000 the human genome project has to play this very,

87 00:06:15.000 --> 00:06:19.220 very important, and I would say it's a complete prolific role.

88 00:06:19.220 --> 00:06:26.519 And remember that time when the cancer genome of the human genome was initially revealed roughly around year 2000,

89 00:06:26.519 --> 00:06:28.819 I was a student at the time,

90 00:06:28.819 --> 00:06:33.819 and I remember there was a sort of guessing game among scientists saying,

91 00:06:33.819 --> 00:06:41.879 how many genes there are in the human genome and the guesses ranged widely from probably 100,000 genes to,

92 00:06:41.879 --> 00:06:44.220 maybe millions of genes,

93 00:06:44.220 --> 00:06:47.689 but it turns out that after the human genome has been sequenced,

94 00:06:47.689 --> 00:06:51.779 we start to realize that there are much fewer genes in the genome.

95 00:06:51.779 --> 00:06:59.029 According to protein coding we recognize there are somewhere around 20,000 protein coding gene's in the genome.

96 00:06:59.029 --> 00:07:01.550 But now of course we understand that again,

97 00:07:01.550 --> 00:07:04.069 it's a very initial understanding of the problem,

98 00:07:04.069 --> 00:07:07.850 because now we know there are many non coding parts of genome.

99 00:07:07.850 --> 00:07:12.339 They actually play a very important role to control the protein coding parts of genome

100 00:07:12.339 --> 00:07:19.069 which is only 2%, so it's has dramatically enhanced our understanding on a global scale of how things work,

101 00:07:19.069 --> 00:07:22.610 and some of these things are starting to bear fruits,

102 00:07:22.610 --> 00:07:24.730 and we are now seeing many,

103 00:07:24.730 --> 00:07:27.209 many new findings in the cancer field.

104 00:07:27.209 --> 00:07:33.230 For example, now we have a much better catalog of what genes can contribute to cancers.

105 00:07:33.230 --> 00:07:35.000 Some genes can be mutated.

106 00:07:35.000 --> 00:07:37.470 They are called oncogenes.

107 00:07:37.470 --> 00:07:40.310 Some genes are not mutated, called tumor suppressors.

108 00:07:40.310 --> 00:07:42.079 One is to enhance cancer

109 00:07:42.079 --> 00:07:43.850 and one is to block cancer.

110 00:07:43.850 --> 00:07:49.160 If you gain extra copies or extra activity of so called oncogenes,

111 00:07:49.160 --> 00:07:59.120 then you can have a chance for a normal cell to go to a cancer cell or you can lose the function of tumor suppressor gene and they can be reduced and

112 00:07:59.120 --> 00:08:07.089 this has contributed a lot to our ability now to map things back to the human genome and see the cause of

113 00:08:07.089 --> 00:08:14.149 which genes are mutated and we have a better understanding of the cancer genome now in terms of

114 00:08:14.149 --> 00:08:17.699 which genes got mutated compared to 20 years ago.

115 00:08:17.699 --> 00:08:25.779 And it seems like although we've learned a lot and we've gained our knowledge and we now know about oncogenes and tumor suppressor genes,

116 00:08:25.779 --> 00:08:32.879 we also know that they are far more complex than what we initially thought in terms of how these genes are regulated,

117 00:08:32.879 --> 00:08:34.822 how they are packaged, and so on.

118 00:08:34.875 --> 00:08:44.975 That's absolutely right, yeah.

119 00:08:45.042 --> 00:08:52.610 Tell us a little bit more about the technology that we're now using to look at genes and how they control cancer. If we know that gaining an oncogene increases your risk of cancer, and losing a tumor suppressor gene increases your risk of cancer,

120 00:08:52.610 --> 00:08:54.620 what are we doing about that?

121 00:08:54.620 --> 00:08:59.980 Or do we have technology that can actually help us in terms of correcting the problem?

122 00:08:59.980 --> 00:09:03.330 There are several things being done,

124 00:09:03.669 --> 00:09:13.049 and one thing, of course, we need to understand and have a catalog where you can say,

125 00:09:13.049 --> 00:09:18.120 look at this gene, it is doing this and this kind of tissue

126 00:09:18.120 --> 00:09:20.649 can potentially contribute to this kind of cancer,

127 00:09:20.649 --> 00:09:28.159 and that's basically creeping down by sequencing the genomes of the cancer specimens that we can collect.

128 00:09:28.159 --> 00:09:35.990 There you can sequence to see which changed and then you can compare that to the human genome and say Ok,

129 00:09:35.990 --> 00:09:38.129 these are genes that potentially got mutated,

130 00:09:38.129 --> 00:09:45.250 so once you have a catalog like this then the question is, is it important or not?

131 00:09:45.250 --> 00:09:49.879 So these require specific experiments to start to manipulate and change those genes.

132 00:09:49.879 --> 00:09:53.850 We can increase activity or decrease activity

133 00:09:53.850 --> 00:09:56.690 and the technology is called CRISPR,

134 00:09:56.690 --> 00:10:04.879 to basically allow us as a tool to change things around and start to see whether these genes in the catalog,

135 00:10:04.879 --> 00:10:08.970 are they important or are some more important than the others.

136 00:10:08.970 --> 00:10:13.700 And once we have that then we can move on to potential therapies and say,

137 00:10:13.700 --> 00:10:15.269 OK, this looks very important as a

138 00:10:15.269 --> 00:10:24.720 gene and the cancer seems to be dependent on it and if we can find either a small molecule like normal drugs you normally hear about or other ways

139 00:10:24.720 --> 00:10:34.080 of using immune therapies to attack tumors so that allowed us to pave the ground to go from research side

140 00:10:34.080 --> 00:10:37.799 to bedside.

141 00:10:37.799 --> 00:10:44.120 Tell us more about this CRISPR technology because it seems to me that this is a technology that people may have heard about,

142 00:10:44.120 --> 00:10:47.100 but nobody really understands exactly how it works.

143 00:10:47.100 --> 00:10:53.049 Can you tell us a little bit more about how it was developed,

144 00:10:53.049 --> 00:10:56.399 how it works, and how it's being used in

145 00:10:56.399 --> 00:10:58.840 research?

146 00:10:58.840 --> 00:11:05.320 The initial discovery of CRISPR technology was actually from some research in bacteria,

147 00:11:05.320 --> 00:11:14.279 so we think that we are very sophisticated as humans and we have two

148 00:11:14.279 --> 00:11:19.259 immune molecular systems that control immune responses and the bacteria.

149 00:11:19.259 --> 00:11:22.759 We thought they were very primitive

150 00:11:22.759 --> 00:11:28.629 but it turns out that these have all their own immune system as well,

151 00:11:28.629 --> 00:11:32.929 so CRISPR was discovered initially as the immune system of bacteria.

152 00:11:32.929 --> 00:11:38.789 One bacteria got intruded by other bacteria or viruses that's attacking the bacteria.

153 00:11:38.789 --> 00:11:41.529 The bacteria has a very intelligent way,

154 00:11:41.529 --> 00:11:44.659 which is using CRISPR to document their invaders.

155 00:11:44.659 --> 00:11:47.389 They say, OK, these guys invaded me,

156 00:11:47.389 --> 00:11:50.909 so next time I see it, I will destroy it.

157 00:11:50.909 --> 00:11:54.440 CRISPR is basically a way to do that.

158 00:11:54.440 --> 00:12:01.799 And the way it works is they take the intruders DNA as pieces and putt in their own genome.

159 00:12:01.799 --> 00:12:05.850 And next time they see the same piece of DNA start,

160 00:12:05.850 --> 00:12:07.690 they destroy it.

161 00:12:07.690 --> 00:12:15.049 So this is initially discovered as sort of immune response by bacteria to help them to survive against the invaders.

162 00:12:15.049 --> 00:12:18.360 Then roughly around 2012-2013 scientist start to say,

163 00:12:18.360 --> 00:12:25.720 OK, maybe we can utilize this as a way to help us to change cells,

164 00:12:25.720 --> 00:12:27.700 including human cells. Cancer cells,

165 00:12:27.700 --> 00:12:35.639 for example, where we can explicitly design things so we can manipulate and change specific sequences within the human genome,

166 00:12:35.639 --> 00:12:41.200 and this has dramatically allowed us to expand our tool set to change genes.

167 00:12:41.200 --> 00:12:46.759 For example, increasing gene activity or decreasing activity through this kind of approach.

168 00:12:46.759 --> 00:12:53.509 Tell me more. So I get the whole idea of CRISPR being like a bacteria's immune system.

169 00:12:53.509 --> 00:12:57.519 They recognize something and they say I'm going to

170 00:12:57.519 --> 00:13:06.399 understand what this is, incorporate that DNA so that the next time they see it they can kill it

171 00:13:06.399 --> 00:13:08.710 because they know that it's foreign.

172 00:13:08.710 --> 00:13:11.419 Very much like the human immune system.

173 00:13:11.419 --> 00:13:18.750 But how does that help scientists then to increase the number of genes or decrease?

174 00:13:18.750 --> 00:13:21.840 Or change the genes in a particular cell?

175 00:13:21.840 --> 00:13:27.629 How exactly do you translate that bacterial immune system into gene editing?

177 00:13:28.590 --> 00:13:33.730 That is through an engineering process that has been done on the molecular front.

178 00:13:33.730 --> 00:13:36.299 So

179 00:13:36.299 --> 00:13:40.470 let's take the intruders DNA and put some pieces into our genome,

180 00:13:40.470 --> 00:13:43.360 which is probably going to be dangerous to do.

181 00:13:43.360 --> 00:13:46.250 We actually shortcut that step so we just say,

182 00:13:46.250 --> 00:13:52.350 we know that bacteria use their pieces of DNA storing their genome to attack foreign DNA,

183 00:13:52.350 --> 00:13:56.519 but the same machinery can work on whatever piece of DNA as well.

184 00:13:56.519 --> 00:13:59.799 So basically what you can do is you can

185 00:13:59.799 --> 00:14:06.580 take for example, any piece of the human genome you want to change,

186 00:14:06.580 --> 00:14:09.659 and you can design a sequence using CRISPR.

187 00:14:09.659 --> 00:14:15.200 I will go in there and particularly change a sequence within this part of the human genome.

188 00:14:15.200 --> 00:14:18.590 This is basically how CRISPR is used in human

189 00:14:18.590 --> 00:14:20.440 cells.

190 00:14:20.440 --> 00:14:29.679 We're going to have to learn more about how CRISPR works and how this has changed cancer research right after we take a short break for medical minute.

191 00:14:29.679 --> 00:14:33.139 Please stay tuned. For more information with my

192 00:14:33.139 --> 00:14:45.639 guest doctor Jun Lu. Support for Yale Cancer Answers comes from AstraZeneca dedicated to advancing options and providing hope for people living with cancer. More information is available at astrazeneca-us.com.

193 00:14:46.230 --> 00:14:48.470 This is a medical minute about

194 00:14:48.470 --> 00:14:57.080 head and neck cancers, although the percentage of oral and head and neck cancer patients in the United States is only about 5%

195 00:14:57.080 --> 00:15:03.809 of all diagnosed cancers, there are challenging side effects associated with these types of cancer and their treatment.

196 00:15:03.809 --> 00:15:09.789 Clinical trials are currently under way to test innovative new treatments for head and neck cancers,

197 00:15:09.789 --> 00:15:14.279 and in many cases less radical surgeries are able to preserve nerves,

198 00:15:14.279 --> 00:15:16.559 arteries and muscles in the neck

199 00:15:16.559 --> 00:15:19.100 enabling patients to move, speak,

200 00:15:19.100 --> 00:15:22.139 breathe, and eat normally after surgery.

201 00:15:22.139 --> 00:15:25.179 More information is available at yalecancercenter.org.

202 00:15:25.179 --> 00:15:28.220 You're listening to Connecticut Public Radio.

203 00:15:29.500 --> 00:15:32.240 Welcome back to Yale Cancer Answers.

204 00:15:32.240 --> 00:15:38.620 This is Anees Chagpar and I'm joined tonight by my guest doctor,

205 00:15:38.620 --> 00:15:41.809 Jun Lu. We're talking about CRISPR and

206 00:15:41.809 --> 00:15:47.740 how this new technology really is transforming cancer research and essentially doctor Lu,

207 00:15:47.740 --> 00:16:01.419 you were telling us that this is a way of editing genes using bacterial technology that these bacteria have essentially evolved to try to understand foreign invaders into

208 00:16:01.419 --> 00:16:03.980 their own genome. Is that right?

209 00:16:03.980 --> 00:16:12.269 That's right, and so using this technology you can take any gene that you want and you can either amplify it,

210 00:16:12.269 --> 00:16:14.639 make more copies, or mutate it,

211 00:16:14.639 --> 00:16:20.960 or do various things. Tell us how you use that in terms of cancer research?

212 00:16:20.960 --> 00:16:22.539 Yeah, so there are

213 00:16:22.539 --> 00:16:27.279 two different ways that we can change genes.

214 00:16:27.279 --> 00:16:34.450 One way is actually just use directly as you mentioned about in

215 00:16:34.450 --> 00:16:44.860 bacteria what they do is they can use a piece of DNA as the guidance sequence so we can use that guidance sequence and

216 00:16:44.860 --> 00:16:47.980 destroy anything that looks exactly like the guidance sequence.

217 00:16:47.980 --> 00:16:51.799 So this is a way how they destroy the intruder DNA.

218 00:16:51.799 --> 00:17:02.210 So what we can do is utilize this same thing with cancer cells that we can artificially create a piece of DNA that's exactly the same as

219 00:17:02.210 --> 00:17:05.380 the DNA we want to destroy inside the genome.

220 00:17:05.380 --> 00:17:11.789 And then you can put this with the protein machinery,

221 00:17:11.789 --> 00:17:19.259 and this will actually make a cut in the DNA and this cut leads to a short deletion.

222 00:17:19.259 --> 00:17:22.289 Basically you get rid of a few

223 00:17:22.289 --> 00:17:26.940 pieces of sequences within the human genome.

224 00:17:26.940 --> 00:17:29.109 This allows us to do

225 00:17:29.109 --> 00:17:30.660 gene knockouts. Basically

227 00:17:32.829 --> 00:17:36.240 we want to specifically inactivate a particular gene in the genome.

228 00:17:36.240 --> 00:17:42.130 So this is one way we can use it. For the 2nd way we can use it for

229 00:17:42.130 --> 00:17:45.230 we don't make cuts, but we use the same machinery,

230 00:17:45.230 --> 00:17:47.710 but we don't make cuts in the genome,

231 00:17:47.710 --> 00:17:49.259 so the genome is still intact,

232 00:17:49.259 --> 00:17:53.599 but we can modify around the place where the sequence binds to

233 00:17:53.599 --> 00:17:55.410 and say,

234 00:17:55.410 --> 00:18:05.509 we can make a change in the regulatory parts of genome so that once this sequence redesigned guides approaching to that particular place in the genome,

235 00:18:05.509 --> 00:18:07.680 you will lead to increased production.

237 00:18:09.480 --> 00:18:14.900 So then you can basically control copy numbers for whatever you can make proteins for.

238 00:18:14.900 --> 00:18:17.430 There are basically two different ways,

239 00:18:17.430 --> 00:18:21.039 at least two different ways you can use it.

240 00:18:21.039 --> 00:18:23.960 So by doing so you can

241 00:18:23.960 --> 00:18:27.890 increase the gene of interest or decrease changing activity.

242 00:18:27.890 --> 00:18:28.190 So

243 00:18:28.190 --> 00:18:33.619 scientists have worked out how to either cut DNA or amplify DNA in this artificial kind of matrix.

244 00:18:33.619 --> 00:18:35.740 And then what do you do then?

245 00:18:35.740 --> 00:18:43.589 You take this and you put it into a mouse and you see what happens if you amplify a gene or if you knockout a gene.

246 00:18:43.589 --> 00:18:49.329 Yeah, exactly so you can do this in a mouse or you can do this in a dish.

247 00:18:49.329 --> 00:18:53.559 So basically what we talked about many times is

248 00:18:53.559 --> 00:18:56.069 this sequence got mutated in the human cancers.

249 00:18:56.069 --> 00:18:57.569 Does this piece of sequence,

250 00:18:57.569 --> 00:18:59.970 which could be a protein coding gene sequence,

251 00:18:59.970 --> 00:19:02.069 play an important role in the process?

252 00:19:02.069 --> 00:19:05.369 Maybe is it just happened to be mutated and doing nothing?

253 00:19:05.369 --> 00:19:09.569 So first thing we have to tell the difference between

254 00:19:09.569 --> 00:19:18.569 is this a truly so-called functional gene or functional mutation or not and so we have to do experiments in dishes by changing the piece of

255 00:19:18.569 --> 00:19:21.869 DNA and say, OK, does it make a difference or not?

256 00:19:21.869 --> 00:19:27.640 For example, we may see cells proliferate faster or you may see cells die,

257 00:19:27.640 --> 00:19:32.430 or you can see cells migrate better so they can

258 00:19:32.430 --> 00:19:34.980 move from one place to another,

259 00:19:34.980 --> 00:19:38.809 and so there are many different behaviors we can start to see.

260 00:19:38.809 --> 00:19:48.380 Of course you can also do the same thing once you put cancer cells into the mouse to see whether or not you can see differences

261 00:19:48.380 --> 00:19:52.519 in tumor genes, the way by which the tumor is formed.

262 00:19:52.519 --> 00:19:56.029 So there are many different results we can do once we

263 00:19:56.029 --> 00:19:58.609 can manipulate these genes. So if you manipulate

264 00:19:58.609 --> 00:20:04.539 genes in a Petri dish or you can manipulate genes in a mouse,

265 00:20:04.539 --> 00:20:09.099 is there a role for this gene editing in people?

266 00:20:09.099 --> 00:20:17.759 Like if you know thanks to the human genome project and thanks to previous work that's gone on that,

267 00:20:17.759 --> 00:20:22.779 a particular mutation is involved in tumorigenesis of a particular cancer,

268 00:20:22.779 --> 00:20:29.690 is it possible to edit that gene so that it's not mutated anymore and then

269 00:20:29.690 --> 00:20:31.920 reduce people's risk of developing cancer?

271 00:20:33.029 --> 00:20:35.259 That's a great question,

272 00:20:35.259 --> 00:20:38.220 and actually, there are some clinical trials,

273 00:20:38.220 --> 00:20:41.190 so that's ongoing now, not necessarily against cancer,

274 00:20:41.190 --> 00:20:47.500 but in other diseases that have been using CRISPR as a technology, as a potential curative therapy.

275 00:20:47.500 --> 00:20:52.319 And there are a few clinical trials using CRISPR now in the cancer setting,

276 00:20:52.319 --> 00:20:57.519 but the majority of active research currently is in genetic disease,

277 00:20:57.519 --> 00:20:59.789 and one of the prime examples

278 00:20:59.789 --> 00:21:11.299 is sickle cell anemia, you may have heard of sickle cell anemia which is a disease that's caused by a particular mutation in a gene that's producing a protein, that's

279 00:21:11.299 --> 00:21:14.180 very important red blood cells.

280 00:21:14.180 --> 00:21:19.140 And because of this mutation the red blood cells will have some

281 00:21:19.140 --> 00:21:28.759 not normal behaviors, so called sickling behaviors and that causes many different symptoms in humans and we have known this for quite a few decades now,

282 00:21:28.759 --> 00:21:33.569 which genes cause disease and there's a potential strategy to deal with it.

283 00:21:33.569 --> 00:21:39.119 So the gene that's being mutated is a gene called a hemoglobin,

284 00:21:39.119 --> 00:21:42.079 which is probably the most abundant protein

285 00:21:42.079 --> 00:21:44.299 present in red blood cells,

286 00:21:44.299 --> 00:21:46.890 and this protein has several different forms.

287 00:21:46.890 --> 00:21:50.240 There is a form called embryonic form of gene.

288 00:21:50.240 --> 00:21:53.029 And as well as adult form of gene.

289 00:21:53.029 --> 00:21:57.019 So when we are a baby actually still a fetus,

290 00:21:57.019 --> 00:22:01.410 we express the embryonic form of the gene,

291 00:22:01.410 --> 00:22:05.000 and then once we become born and become adults,

292 00:22:05.000 --> 00:22:07.799 we change to a very similar gene, the

293 00:22:07.799 --> 00:22:09.789 adult form of the gene.

294 00:22:09.789 --> 00:22:16.180 The reason for that is because in the uterus as an embryo versus once you're out of mother,

295 00:22:16.180 --> 00:22:18.970 there are different exposures to oxygen.

296 00:22:18.970 --> 00:22:22.829 And as the concentration is very different,

297 00:22:22.829 --> 00:22:25.660 we have to adjust based on that.

298 00:22:25.660 --> 00:22:28.809 However, we know that the embryonic version of the hemoglobin,

299 00:22:28.809 --> 00:22:32.910 although it's not as good as adult form in terms of functions,

300 00:22:32.910 --> 00:22:42.359 is still very good. And if we can change the gene expression within the red blood cells in the sickle cell patients to convert to the embryonic one,

301 00:22:42.359 --> 00:22:45.819 you can actually cure many of the symptoms of the patients.

302 00:22:45.819 --> 00:22:50.869 So this is one area where CRISPR is actively being explored

303 00:22:50.869 --> 00:22:58.430 in research setting as well as a clinical trial setting and this may actually become a

304 00:22:58.430 --> 00:23:01.829 cure for the disease, so that sounds really promising.

305 00:23:01.829 --> 00:23:13.170 My only question though, is given the fact that hemoglobin is so abundant and in all of your red blood cells and you have thousands of red blood cells,

306 00:23:13.170 --> 00:23:18.460 how do you change the genes in every single one of those?

308 00:23:20.730 --> 00:23:25.539 It turns out that you don't have to change every single cell of hemoglobin.

309 00:23:25.539 --> 00:23:29.579 You only need to change a subset of the cells that carry this mutation.

310 00:23:29.579 --> 00:23:31.890 As long as you correct some of them,

311 00:23:31.890 --> 00:23:33.630 you don't have to correct 100%,

312 00:23:33.630 --> 00:23:41.140 so that's really the reason why this is first using diseases where you only need to restore the function of some of those,

313 00:23:41.140 --> 00:23:44.319 but not all cells. This is slightly tougher for cancer.

314 00:23:44.319 --> 00:23:46.059 Of course, if you have cancer,

315 00:23:46.059 --> 00:23:49.519 you have to create almost every single cell and that becomes an issue,

316 00:23:49.519 --> 00:23:51.549 potentially using the same technology against cancer.

317 00:23:51.549 --> 00:23:53.880 However, there is one way

318 00:23:53.880 --> 00:23:59.759 to potentially, using cancer therapies, change the immune system that's basically fighting cancers.

319 00:23:59.759 --> 00:24:04.170 For that you don't have to change every single cell within the immune system.

320 00:24:04.170 --> 00:24:10.640 You only need to change some of the cells within immune system and then we have a better outcome for cancer patients,

321 00:24:10.640 --> 00:24:13.279 and that's being tried right now,

322 00:24:13.279 --> 00:24:15.049 so there are several clinical trials

323 00:24:15.049 --> 00:24:21.809 in the United States, and a few outside of the United States using CRISPR as a technology to change T cells.

324 00:24:21.809 --> 00:24:25.710 T cells are one of the immune cells we have in the body

325 00:24:25.710 --> 00:24:30.069 to help fight against cancer using the T cell therapy.

326 00:24:30.069 --> 00:24:32.886 How exactly does that work?

327 00:24:33.021 --> 00:24:36.609 I don't know if you have heard, but

328 00:24:36.609 --> 00:24:41.839 currently there's one kind of immune therapy called CAR T cell therapy.

329 00:24:41.839 --> 00:24:54.490 Basically we take normal T cells and then we engineer the T cell so that you will have a sort of fighting ability.

330 00:24:54.490 --> 00:25:00.269 Have a recognition. We call a receptor, specifically against a certain type of cancer,

331 00:25:00.269 --> 00:25:04.400 and so we can engineer that to have this special ability,

332 00:25:04.400 --> 00:25:07.839 and then we can put them back into the patients.

333 00:25:07.839 --> 00:25:11.970 And this has shown very good success against a few different kinds of

334 00:25:11.970 --> 00:25:14.029 cancers such as chronic leukemia,

335 00:25:14.029 --> 00:25:18.160 and so it's currently being tested in many other different settings.

336 00:25:18.160 --> 00:25:27.180 But of course one of the things that's happening with the T cells is once you put the so called manipulation of the T cells

337 00:25:27.180 --> 00:25:30.930 called CAR T cells, they can be active against cancer,

338 00:25:30.930 --> 00:25:32.809 but then they get exhausted.

339 00:25:32.809 --> 00:25:37.680 So the question is, can we somehow change it using CRISPR to inactivate

340 00:25:37.680 --> 00:25:43.680 the exhausting capacity or the blocking capacity for T cell to be further useful against cancer?

341 00:25:43.680 --> 00:25:48.930 So this can further enhance the therapeutic outcome and the effectiveness of the cancer.

342 00:25:48.930 --> 00:25:57.630 So the current services using the clinical trials using CRISPR is trying to engineer the T cells so that can have better potency

343 00:25:57.630 --> 00:25:58.700 against cancer.

345 00:26:00.849 --> 00:26:04.069 And how can CRISPR help it not get exhausted?

346 00:26:04.069 --> 00:26:06.940 So if you think about the immune system,

347 00:26:06.940 --> 00:26:13.740 one of the functions carried out by T cells is to recognize specific intruding stuff.

348 00:26:13.740 --> 00:26:16.250 Initially we think that's how it works,

349 00:26:16.250 --> 00:26:19.829 but you don't want this to be active too much.

350 00:26:19.829 --> 00:26:22.329 If you activate T cells too much,

351 00:26:22.329 --> 00:26:26.210 then you can have potential toxicity against yourself,

352 00:26:26.269 --> 00:26:28.480 your own cells.

354 00:26:29.970 --> 00:26:36.529 So you have to control the activity so nature has designed the system in a way that once it's activated,

355 00:26:36.529 --> 00:26:38.309 it will have to be stopped.

356 00:26:38.309 --> 00:26:45.759 And so this kind of exhausting process is one way the system is controlling itself so that once activated,

357 00:26:45.759 --> 00:26:50.230 we don't want to press the gas pedal too much, once you press the gas pedal,

358 00:26:50.230 --> 00:26:53.210 there's naturally something on the back that breaks it down,

359 00:26:53.210 --> 00:26:57.089 so this is basically the natural ability of the T cells.

360 00:26:57.089 --> 00:27:01.039 And basically what CRISPR is currently trying to do is

361 00:27:01.039 --> 00:27:09.900 adjust this feedback control system so that you will have more mileage out of the same gallon of gas.

362 00:27:09.900 --> 00:27:19.750 Are they using CRISPR technology also to kind of edit the genes that the T cells will recognize,

363 00:27:19.750 --> 00:27:24.779 like the bacteria recognizing foreign intruders like you were saying.

364 00:27:24.779 --> 00:27:26.029 Currently talking

365 00:27:26.029 --> 00:27:31.480 about potentially using CRISPR to change the genome of the cancer cells themselves,

367 00:27:32.740 --> 00:27:38.190 In part changing the genome of the cancer cells themselves.

369 00:27:42.009 --> 00:27:51.000 How bacteria use CRISPR to recognize foreign invaders and then attack them like an immune system,

370 00:27:51.000 --> 00:28:05.130 but is there a thought to using that same technology to introduce those genes of cancer cells to the T cells so that the T cells recognize that and fight

371 00:28:05.130 --> 00:28:07.960 just like a bacteria immune

372 00:28:07.960 --> 00:28:10.180 system would?

373 00:28:10.180 --> 00:28:12.990 To my knowledge this hasn't been actively explored at the moment.

374 00:28:12.990 --> 00:28:17.670 I wouldn't say it will never be a possibility because there are many different insights.

375 00:28:17.670 --> 00:28:23.279 We have to open our imagination and there are lots of things that may seem very,

376 00:28:23.279 --> 00:28:27.029 very far from clinics, but turns out that could be very close,

377 00:28:27.029 --> 00:28:31.079 so that's why we have to support many different kinds of cancer research.

378 00:28:31.079 --> 00:28:39.819 The slight difference between the bacterial system and the cancer cell system is that the bacteria have the invading DNA into their own cells.

379 00:28:39.819 --> 00:28:41.509 We want to destroy them.

380 00:28:41.509 --> 00:28:47.240 Whereas in the case of T cells, targeting cancer cells is between the cells,

381 00:28:47.240 --> 00:28:52.250 so you don't have DNA crossing between the two cell types,

382 00:28:52.250 --> 00:28:58.339 as long as the cancer cells have some other protein fragments that T cells can recognize,

383 00:28:58.339 --> 00:29:01.559 that will be allowed to attack some.

384 00:29:02.069 --> 00:29:07.410 Doctor Jun Lu is an Associate Professor of Genetics at Yale School of Medicine.

385 00:29:07.410 --> 00:29:15.599 If you have questions, the address is cancer-answers@yale.edu and past editions of the program are available in audio and written form at Yalecancercenter.org.

386 00:29:15.599 --> 00:29:24.048 We hope you'll join us next week to learn more about the fight against cancer here on Connecticut public radio.