WEBVTT

NOTE duration:"01:01:09"

NOTE recognizability:0.924

NOTE language:en-us

NOTE Confidence: 0.892603132666667

00:00:00.000 --> 00:00:01.810 So my name is Qingyan.

NOTE Confidence: 0.892603132666667

00:00:01.810 --> 00:00:03.620 It's my great pleasure to

NOTE Confidence: 0.892603132666667

00:00:03.702 --> 00:00:06.117 introduce our ground on speaker,

NOTE Confidence: 0.892603132666667

00:00:06.120 --> 00:00:09.036 Doctor Chen Jin from Mountain Sinai.

NOTE Confidence: 0.892603132666667

00:00:09.040 --> 00:00:12.190 Doctor Chen Jin currently is a Mountain

NOTE Confidence: 0.892603132666667

00:00:12.190 --> 00:00:14.441 Sinai endowed Professor in Therapeutic

NOTE Confidence: 0.892603132666667

00:00:14.441 --> 00:00:16.925 Discovery and he also direct the

NOTE Confidence: 0.892603132666667

00:00:16.925 --> 00:00:19.400 Center for Therapeutic Discovery.

NOTE Confidence: 0.892603132666667

00:00:19.400 --> 00:00:22.872 He's also a Co Leader of Cancer

NOTE Confidence: 0.892603132666667

00:00:22.872 --> 00:00:24.360 Clinical Investigation program

NOTE Confidence: 0.892603132666667

00:00:24.440 --> 00:00:26.030 for Tisch Cancer Institute,

NOTE Confidence: 0.892603132666667

00:00:26.030 --> 00:00:28.680 which is an NCI designated cancer.

NOTE Confidence: 0.845238125

00:00:30.730 --> 00:00:32.330 The microphone is on.

NOTE Confidence: 0.9301902

00:00:38.310 --> 00:00:41.695 It's on. It is on.

NOTE Confidence: 0.9301902

00:00:41.695 --> 00:00:45.830 Maybe I need to be closer. OK. OK.

NOTE Confidence: 0.9301902

00:00:45.830 --> 00:00:48.670 So I think I just skipped that part.

NOTE Confidence: 0.9301902

00:00:48.670 --> 00:00:52.070 Now I just want to give you

NOTE Confidence: 0.9301902

00:00:52.070 --> 00:00:53.870 some background of Doc Tianjin.

NOTE Confidence: 0.9301902

00:00:53.870 --> 00:00:55.870 Doc Tianjin received his best

NOTE Confidence: 0.9301902

00:00:55.870 --> 00:00:57.870 degree from the University of

NOTE Confidence: 0.9301902

00:00:57.946 --> 00:01:00.116 Science and Technology of China.

NOTE Confidence: 0.9301902

00:01:00.120 --> 00:01:01.653 Which is one of the best universities

NOTE Confidence: 0.9301902

00:01:01.653 --> 00:01:03.320 in China because I also went there too.

NOTE Confidence: 0.9352219

00:01:06.400 --> 00:01:08.850 And then he did his PhD training

NOTE Confidence: 0.9352219

00:01:08.850 --> 00:01:11.150 at the Penn State and did a

NOTE Confidence: 0.9352219

00:01:11.150 --> 00:01:13.360 one year postal in Ohio State.

NOTE Confidence: 0.9352219

00:01:13.360 --> 00:01:16.040 Then he was recruited to GSK.

NOTE Confidence: 0.9352219

00:01:16.040 --> 00:01:19.924 He stayed there for 10 years before he

NOTE Confidence: 0.9352219

00:01:19.924 --> 00:01:23.920 was recruited by UNC in 2008 as a social

NOTE Confidence: 0.9352219

00:01:23.920 --> 00:01:28.857 professor And then 24 to 14 he moved to.

NOTE Confidence: 0.9352219

00:01:28.860 --> 00:01:32.500 Mountain Sinai as a as a full professor

NOTE Confidence: 0.9352219

00:01:32.500 --> 00:01:36.084 and he stayed there since and he has

NOTE Confidence: 0.9352219

00:01:36.084 --> 00:01:38.388 country or not and he's initially

NOTE Confidence: 0.9352219

00:01:38.388 --> 00:01:40.986 with his discovery in epigenetic drug

NOTE Confidence: 0.9352219

00:01:40.986 --> 00:01:43.281 discovery and more recently he's

NOTE Confidence: 0.9352219

00:01:43.281 --> 00:01:46.700 more interested in doing degraders.

NOTE Confidence: 0.9352219

00:01:46.700 --> 00:01:50.060 He has published more than 200 papers

NOTE Confidence: 0.9352219

00:01:50.060 --> 00:01:53.336 and have more than 70 pattern.

NOTE Confidence: 0.9352219

00:01:53.340 --> 00:01:55.140 Pattern.

NOTE Confidence: 0.9352219

00:01:55.140 --> 00:01:58.008 And he has advanced 5 compounds

NOTE Confidence: 0.9352219

00:01:58.008 --> 00:02:01.079 to clinical trials and one of them

NOTE Confidence: 0.9352219

00:02:01.079 --> 00:02:03.886 it's has been FD has been approved

NOTE Confidence: 0.9352219

00:02:03.886 --> 00:02:06.658 by in the US and Japan.

NOTE Confidence: 0.9352219

00:02:06.660 --> 00:02:10.332 This is a drug called the Dapro to stat

NOTE Confidence: 0.9352219

00:02:10.332 --> 00:02:13.433 Hypoxo inducible factor polyhydrosis

NOTE Confidence: 0.9352219

00:02:13.433 --> 00:02:16.739 inhibitor for treating anemia.

NOTE Confidence: 0.9352219

00:02:16.740 --> 00:02:19.182 He's well funded 50 ones and

NOTE Confidence: 0.9352219

00:02:19.182 --> 00:02:21.732 many other grants and he couldn't

NOTE Confidence: 0.9352219

00:02:21.732 --> 00:02:24.234 count how many counts he has.

NOTE Confidence: 0.9352219

00:02:24.240 --> 00:02:29.235 And he is also currently a member

NOTE Confidence: 0.9352219

00:02:29.235 --> 00:02:33.400 of Dem PB study section for NIH,

NOTE Confidence: 0.9352219

00:02:33.400 --> 00:02:36.888 and he's also a cofounder of a degree

NOTE Confidence: 0.9352219

00:02:36.888 --> 00:02:39.739 the company called the Cogen and

NOTE Confidence: 0.9352219

00:02:39.739 --> 00:02:42.493 he has been inactive to National

NOTE Confidence: 0.9352219

00:02:42.493 --> 00:02:46.320 Academy of Inventors in 2022.

NOTE Confidence: 0.9352219

00:02:46.320 --> 00:02:48.469 He's going to tell us about his

NOTE Confidence: 0.9352219

00:02:48.469 --> 00:02:50.374 discovery of Nova degraders and

NOTE Confidence: 0.9352219

00:02:50.374 --> 00:02:52.664 development of new approaches to

NOTE Confidence: 0.9352219

00:02:52.664 --> 00:02:54.480 target undrugable proteins today.

NOTE Confidence: 0.9352219

00:02:54.480 --> 00:02:55.664 And without further ado,

NOTE Confidence: 0.9352219

00:02:55.664 --> 00:02:57.440 please join me to welcome Dr.

NOTE Confidence: 0.9352219

00:02:57.440 --> 00:02:57.840 Tianjin.

NOTE Confidence: 0.9352219

00:02:57.840 --> 00:02:57.920 All

NOTE Confidence: 0.93773775

00:03:07.820 --> 00:03:09.170 right, So I hope everybody

NOTE Confidence: 0.93773775

00:03:09.170 --> 00:03:11.140 can hear me. OK, bye.

NOTE Confidence: 0.94629164

00:03:13.500 --> 00:03:17.654 OK, Getting closer. Better. OK. All right.

NOTE Confidence: 0.94629164

00:03:17.654 --> 00:03:22.281 So I'm gonna try to use my cursor here, so.

NOTE Confidence: 0.94629164

00:03:22.281 --> 00:03:24.768 People on the zoom can actually see the

NOTE Confidence: 0.94629164

00:03:24.768 --> 00:03:26.567 arrow here and what I'm pointing to.

NOTE Confidence: 0.946446461538462

00:03:28.850 --> 00:03:32.833 Thank you very much team for very

NOTE Confidence: 0.946446461538462

00:03:32.833 --> 00:03:35.606 generous introduction and for inviting

NOTE Confidence: 0.946446461538462

00:03:35.606 --> 00:03:40.420 me and delighted to be here and and so

NOTE Confidence: 0.946446461538462

00:03:40.420 --> 00:03:42.250 very much enjoyed talking to everybody

NOTE Confidence: 0.946446461538462

00:03:42.250 --> 00:03:44.677 so far and pretty much look very much

NOTE Confidence: 0.946446461538462

00:03:44.677 --> 00:03:46.847 look forward to the rest of the day.

NOTE Confidence: 0.946446461538462

00:03:46.850 --> 00:03:50.206 So I'm going to try to be a a rock

NOTE Confidence: 0.946446461538462

00:03:50.206 --> 00:03:54.394 star today. Wearing the dark glasses.

NOTE Confidence: 0.946446461538462

00:03:54.400 --> 00:03:57.376 But seriously, my eyes are a

NOTE Confidence: 0.946446461538462

00:03:57.376 --> 00:03:58.840 little bit sensitive to the light

NOTE Confidence: 0.946446461538462

00:03:58.840 --> 00:04:00.880 and so dark glasses help.

NOTE Confidence: 0.946446461538462

00:04:00.880 --> 00:04:04.000 Hopefully this is okay with everybody.

NOTE Confidence: 0.946446461538462

00:04:04.000 --> 00:04:06.280 So it's my great pleasure,

NOTE Confidence: 0.946446461538462

00:04:06.280 --> 00:04:10.800 a pleasure to talk about my laps,

NOTE Confidence: 0.946446461538462

00:04:10.800 --> 00:04:12.936 recent progress on discovering

NOTE Confidence: 0.946446461538462

00:04:12.936 --> 00:04:14.520 of novel degraders,

NOTE Confidence: 0.946446461538462

00:04:14.520 --> 00:04:19.252 and development of new approaches to Target.

NOTE Confidence: 0.946446461538462

00:04:19.252 --> 00:04:20.876 And drug bar proteins.

NOTE Confidence: 0.928932275

00:04:28.040 --> 00:04:29.160 So I may need a on the outside,

NOTE Confidence: 0.941691228571429

00:04:33.280 --> 00:04:36.395 not quite sure. Click on the sitting

NOTE Confidence: 0.941691228571429

00:04:36.400 --> 00:04:40.720 area here, Okay. All right. Thank you.

NOTE Confidence: 0.953192257142857

00:04:43.200 --> 00:04:46.255 So here's my conflict interest

NOTE Confidence: 0.953192257142857

00:04:46.255 --> 00:04:48.436 disclosure as Jim mentioned.

NOTE Confidence: 0.953192257142857

00:04:48.436 --> 00:04:51.304 I am a cofounder of Cogin,

NOTE Confidence: 0.953192257142857

00:04:51.310 --> 00:04:54.985 a San Diego based biotech which is

NOTE Confidence: 0.953192257142857

00:04:54.985 --> 00:04:58.189 dedicated to developing normal degraders.

NOTE Confidence: 0.92875252

00:05:00.430 --> 00:05:02.789 So as some of you may know,

NOTE Confidence: 0.92875252

00:05:02.790 --> 00:05:05.702 my my labs have taken a target class

NOTE Confidence: 0.92875252

00:05:05.702 --> 00:05:08.383 approach to generating selective

NOTE Confidence: 0.92875252

00:05:08.383 --> 00:05:11.467 inhibitors of histomestal transferases,

NOTE Confidence: 0.92875252

00:05:11.470 --> 00:05:15.600 HM T's, for well over a decade.

NOTE Confidence: 0.92875252

00:05:15.600 --> 00:05:17.655 In collaboration with the Structure

NOTE Confidence: 0.92875252

00:05:17.655 --> 00:05:19.760 Genuine Consortium SGC Toronto,

NOTE Confidence: 0.92875252

00:05:19.760 --> 00:05:23.600 we have discovered a number of

NOTE Confidence: 0.92875252

00:05:23.600 --> 00:05:28.120 novel and selective HMT inhibitors,

NOTE Confidence: 0.92875252

00:05:28.120 --> 00:05:30.920 some of which have been widely used

NOTE Confidence: 0.92875252

00:05:30.920 --> 00:05:34.892 by research community such as the G9A

NOTE Confidence: 0.92875252

00:05:34.892 --> 00:05:38.440 GLP inhibitors UNC638 and UNC642,

NOTE Confidence: 0.92875252

00:05:38.440 --> 00:05:41.787 the easy issue inhibitor UNC1999

NOTE Confidence: 0.92875252

00:05:41.787 --> 00:05:44.589 and the type 1:00 PM T.

NOTE Confidence: 0.92875252

00:05:44.590 --> 00:05:46.665 Inhibitor MS-23,

NOTE Confidence: 0.92875252

00:05:46.665 --> 00:05:49.185 so I will not talk about them today.

NOTE Confidence: 0.947015821052632

00:05:51.670 --> 00:05:55.604 Since 2014, my lab has also been

NOTE Confidence: 0.947015821052632

00:05:55.604 --> 00:05:59.039 active in discovering novel small

NOTE Confidence: 0.947015821052632

00:05:59.039 --> 00:06:01.502 molecule degraders including

NOTE Confidence: 0.947015821052632

00:06:01.502 --> 00:06:04.786 Protex for oncogenic proteins.

NOTE Confidence: 0.947015821052632

00:06:04.790 --> 00:06:06.934 For some of you who are less familiar

NOTE Confidence: 0.947015821052632

00:06:06.934 --> 00:06:09.630 with the field with this field,

NOTE Confidence: 0.947015821052632

00:06:09.630 --> 00:06:12.030 Protag which stands for

NOTE Confidence: 0.947015821052632

00:06:12.030 --> 00:06:13.608 protelysis targeting Chimera.

NOTE Confidence: 0.947015821052632

00:06:13.608 --> 00:06:17.290 Is a hydro a hydro bifunctional small

NOTE Confidence: 0.947015821052632

00:06:17.372 --> 00:06:20.500 molecule with one end that binds

NOTE Confidence: 0.947015821052632

00:06:20.500 --> 00:06:23.592 to ESV light upicane ligas and the

NOTE Confidence: 0.947015821052632

00:06:23.592 --> 00:06:26.811 other moiety binds to the protein of

NOTE Confidence: 0.947015821052632

00:06:26.811 --> 00:06:30.730 interest by simultaneously binding

NOTE Confidence: 0.947015821052632

00:06:30.730 --> 00:06:35.960 the the ESV ligas and protein of

NOTE Confidence: 0.947015821052632

00:06:35.960 --> 00:06:39.032 interest protax induce our brains.

NOTE Confidence: 0.947015821052632

00:06:39.032 --> 00:06:42.644 The the E3 ligas into close proximity

NOTE Confidence: 0.947015821052632

00:06:42.644 --> 00:06:45.164 of the protein of interest,

NOTE Confidence: 0.947015821052632

00:06:45.164 --> 00:06:47.684 leading to selective Poly recognition

NOTE Confidence: 0.947015821052632

00:06:47.684 --> 00:06:51.295 of the protein of interest and its

NOTE Confidence: 0.947015821052632

00:06:51.295 --> 00:06:53.815 subsequent degradation at a proton.

NOTE Confidence: 0.907284136666667

00:06:56.100 --> 00:06:59.568 Since the protect concept was first

NOTE Confidence: 0.907284136666667

00:06:59.568 --> 00:07:05.184 reported by Craig Kuz and Radisha in 2001,

NOTE Confidence: 0.907284136666667

00:07:05.184 --> 00:07:08.310 numerous significant advancements.

NOTE Confidence: 0.907284136666667

00:07:08.310 --> 00:07:10.590 Have been made in this field,

NOTE Confidence: 0.907284136666667

00:07:10.590 --> 00:07:13.476 some of which are highlighted here

NOTE Confidence: 0.907284136666667

00:07:13.476 --> 00:07:16.750 and summarized in this review article.

NOTE Confidence: 0.907284136666667

00:07:16.750 --> 00:07:17.830 In particularly,

NOTE Confidence: 0.953671466666667

00:07:20.350 --> 00:07:23.350 this field have seen explosive

NOTE Confidence: 0.953671466666667

00:07:23.350 --> 00:07:27.934 growth over lot 8 years and

NOTE Confidence: 0.953671466666667

00:07:27.934 --> 00:07:30.478 more than 20 protests have been

NOTE Confidence: 0.953671466666667

00:07:30.478 --> 00:07:32.670 advanced to clinical development

NOTE Confidence: 0.949059075

00:07:34.990 --> 00:07:36.514 so since 2014.

NOTE Confidence: 0.949059075

00:07:36.514 --> 00:07:39.562 My lab has discovered normal degraders

NOTE Confidence: 0.949059075

00:07:39.562 --> 00:07:43.716 of epigenetic targets such as WDR 5 is,

NOTE Confidence: 0.949059075

00:07:43.716 --> 00:07:50.230 H2, PMT 5, NSD 3, NSD 2:00 PM, PRC one.

NOTE Confidence: 0.949059075

00:07:50.230 --> 00:07:54.360 We have also developed novel degraders for

NOTE Confidence: 0.949059075

00:07:54.360 --> 00:07:58.478 other oncogenic proteins such as kinases AKT,

NOTE Confidence: 0.949059075

00:07:58.478 --> 00:08:04.590 CDK 46, EGFR, Mac, and ALK.

NOTE Confidence: 0.949059075

00:08:04.590 --> 00:08:07.626 In addition, we have developed a

NOTE Confidence: 0.949059075

00:08:07.626 --> 00:08:10.370 number of new technologies for

NOTE Confidence: 0.949059075

00:08:10.370 --> 00:08:12.906 advancing the target degradation,

NOTE Confidence: 0.949059075

00:08:12.910 --> 00:08:14.994 target protein degradation field.

NOTE Confidence: 0.949059075

00:08:14.994 --> 00:08:19.042 So today I will talk about our WDR

NOTE Confidence: 0.949059075

00:08:19.042 --> 00:08:21.947 5 and they should the greater work.

NOTE Confidence: 0.949059075

00:08:21.950 --> 00:08:25.726 First to give you a flavor for our

NOTE Confidence: 0.949059075

00:08:25.726 --> 00:08:28.314 protect discovery effort followed by

NOTE Confidence: 0.949059075

00:08:28.314 --> 00:08:31.326 the new technologies we have developed

NOTE Confidence: 0.949059075

00:08:31.326 --> 00:08:33.950 to target and drug ball proteins.

NOTE Confidence: 0.858867632

00:08:36.620 --> 00:08:38.940 So our WDR 5 degree

NOTE Confidence: 0.943608066666667

00:08:41.180 --> 00:08:44.018 work was done in collaboration with

NOTE Confidence: 0.943608066666667

00:08:44.020 --> 00:08:47.035 Greg One's lab at University of

NOTE Confidence: 0.943608066666667

00:08:47.035 --> 00:08:49.285 North Carolina at Chapel Hill and

NOTE Confidence: 0.943608066666667

00:08:49.285 --> 00:08:51.938 a new Agua's lab at Mount Sinai.

NOTE Confidence: 0.943608066666667

00:08:51.940 --> 00:08:55.083 So this work was spearheaded by three

NOTE Confidence: 0.943608066666667

00:08:55.083 --> 00:08:57.300 extremely talented young scientists.

NOTE Confidence: 0.943608066666667

00:08:57.300 --> 00:09:00.936 She Feng Yun, She's a former.

NOTE Confidence: 0.943608066666667

00:09:00.940 --> 00:09:02.700 Instructor in my lab.

NOTE Confidence: 0.943608066666667

00:09:02.700 --> 00:09:05.150 She's currently have independent Pi

NOTE Confidence: 0.943608066666667

00:09:05.150 --> 00:09:08.540 position in Fudan University in China

NOTE Confidence: 0.943608066666667

00:09:08.540 --> 00:09:11.788 and don't really a former post out in

NOTE Confidence: 0.943608066666667

00:09:11.788 --> 00:09:16.740 Greg Von's lab and Jatish Contour.

NOTE Confidence: 0.943608066666667

00:09:16.740 --> 00:09:18.988 He is a former joint post out in

NOTE Confidence: 0.943608066666667

00:09:18.988 --> 00:09:21.581 a news lab and my lab is currently

NOTE Confidence: 0.943608066666667

00:09:21.581 --> 00:09:25.179 a senior post out in a news lab.

NOTE Confidence: 0.943608066666667

00:09:25.180 --> 00:09:28.156 So why do we want to develop a

NOTE Confidence: 0.943608066666667

00:09:28.156 --> 00:09:29.940 WDR 5 degrader?

NOTE Confidence: 0.943608066666667

00:09:29.940 --> 00:09:34.100 And WDR 5 is an important UNCLE protein,

NOTE Confidence: 0.943608066666667

00:09:34.100 --> 00:09:38.980 but it is not an enzyme so it is

NOTE Confidence: 0.943608066666667

00:09:38.980 --> 00:09:41.540 a important scaffolding protein

NOTE Confidence: 0.943608066666667

00:09:41.540 --> 00:09:45.335 and acts as a functional subunit

NOTE Confidence: 0.943608066666667

00:09:45.335 --> 00:09:47.859 of MML mesotransferase complex.

NOTE Confidence: 0.943608066666667

00:09:47.860 --> 00:09:52.582 WDR 5 is critical for a 3K four

NOTE Confidence: 0.943608066666667

00:09:52.582 --> 00:09:56.040 methylation SL as well as MML complex

NOTE Confidence: 0.943608066666667

00:09:56.147 --> 00:09:59.674 mediated regulation of gene transcription.

NOTE Confidence: 0.943608066666667

00:09:59.674 --> 00:10:03.316 WDR Five also interacts with CIMIC.

NOTE Confidence: 0.943608066666667

00:10:03.320 --> 00:10:05.984 The interactions between WDR 5 and

NOTE Confidence: 0.943608066666667

00:10:05.984 --> 00:10:08.554 its binding partners are essential

NOTE Confidence: 0.943608066666667

00:10:08.554 --> 00:10:11.639 for sustained oncogenesis in MML

NOTE Confidence: 0.943608066666667

00:10:11.639 --> 00:10:15.255 range leukemia and in solid tumors

NOTE Confidence: 0.943608066666667

00:10:15.255 --> 00:10:18.060 such as pancreatic, pancreatic,

NOTE Confidence: 0.943608066666667

00:10:18.060 --> 00:10:21.480 ductal adenocarcinoma pedac,

NOTE Confidence: 0.943608066666667

00:10:21.480 --> 00:10:23.826 a number of small molecule inhibitors

NOTE Confidence: 0.943608066666667

00:10:23.826 --> 00:10:26.141 that blocks the protein protein actions

NOTE Confidence: 0.943608066666667

00:10:26.141 --> 00:10:29.240 between WDR 5 and its binding partners.

NOTE Confidence: 0.943608066666667

00:10:29.240 --> 00:10:31.340 Have been developed.

NOTE Confidence: 0.943608066666667

00:10:31.340 --> 00:10:32.140 However,

NOTE Confidence: 0.943608066666667

00:10:32.140 --> 00:10:36.608 this WDR 5 PPI inhibitors exhibit

NOTE Confidence: 0.943608066666667

00:10:36.608 --> 00:10:38.948 modest cancer cell killing effect

NOTE Confidence: 0.943608066666667

00:10:38.948 --> 00:10:42.059 and the lack in vivo efficacy.

NOTE Confidence: 0.943608066666667

00:10:42.060 --> 00:10:45.738 Likely due to this PPI inhibitors

NOTE Confidence: 0.943608066666667

00:10:45.740 --> 00:10:48.848 block only some but not all of

NOTE Confidence: 0.943608066666667

00:10:48.848 --> 00:10:52.099 WDR five's on cogenic functions,

NOTE Confidence: 0.943608066666667

00:10:52.100 --> 00:10:54.508 so we therefore pursuit

NOTE Confidence: 0.943608066666667

00:10:54.508 --> 00:10:57.518 pharmacological degradation of WDR 5.

NOTE Confidence: 0.943608066666667

00:10:57.520 --> 00:11:00.880 As a novel therapeutic strategy for

NOTE Confidence: 0.943608066666667

00:11:00.880 --> 00:11:03.640 treating WDR 5 dependent tumors,

NOTE Confidence: 0.82014676

00:11:05.840 --> 00:11:11.000 So we used O ICR 9429 as the WDR

NOTE Confidence: 0.82014676

00:11:11.000 --> 00:11:14.275 5 binder because O ICR is the

NOTE Confidence: 0.82014676

00:11:14.275 --> 00:11:17.840 best known WDR 5 PPI inhibitor,

NOTE Confidence: 0.82014676

00:11:17.840 --> 00:11:20.876 which is highly potent and selective

NOTE Confidence: 0.82014676

00:11:20.876 --> 00:11:24.164 for WDR 5 O ICR was previously

NOTE Confidence: 0.82014676

00:11:24.164 --> 00:11:26.810 developed by Raymond Olivar's lab at.

NOTE Confidence: 0.82014676

00:11:26.810 --> 00:11:29.480 The Ontario Institute for Cancer Research

NOTE Confidence: 0.82014676

00:11:29.480 --> 00:11:32.861 has the name of OICR in collaboration

NOTE Confidence: 0.82014676

00:11:32.861 --> 00:11:35.809 with Structured Genuine Consortium.

NOTE Confidence: 0.82014676

00:11:35.810 --> 00:11:37.865 Based on the crystal structure

NOTE Confidence: 0.82014676

00:11:37.865 --> 00:11:41.284 of the WDR 5 OICR binary complex,

NOTE Confidence: 0.82014676

00:11:41.284 --> 00:11:45.054 we identified A solving exposed

NOTE Confidence: 0.82014676

00:11:45.054 --> 00:11:48.414 region shown here and design,

NOTE Confidence: 0.82014676

00:11:48.414 --> 00:11:51.819 synthesize and evaluate a initial set

NOTE Confidence: 0.82014676

00:11:51.819 --> 00:11:54.234 of compounds which contain various

NOTE Confidence: 0.82014676

00:11:54.234 --> 00:11:56.737 linkers and E 3 legacy ligans.

NOTE Confidence: 0.82014676

00:11:56.740 --> 00:11:58.468 From this study,

NOTE Confidence: 0.82014676

00:11:58.468 --> 00:12:01.668 we identified MS33 as the initial

NOTE Confidence: 0.82014676

00:12:01.668 --> 00:12:05.322 lead which contained this relatively

NOTE Confidence: 0.82014676

00:12:05.322 --> 00:12:08.232 relatively long linker and this

NOTE Confidence: 0.82014676

00:12:08.232 --> 00:12:10.780 classic Wehl 1 Wehl ligand.

NOTE Confidence: 0.944827872727273

00:12:14.220 --> 00:12:17.377 So we solved a high resolution crystal

NOTE Confidence: 0.944827872727273

00:12:17.377 --> 00:12:21.660 structure of WDR Five MS33 and Wehl Elongan,

NOTE Confidence: 0.944827872727273

00:12:21.660 --> 00:12:25.440 see Elongan B VCB ternary complex.

NOTE Confidence: 0.944827872727273

00:12:25.440 --> 00:12:27.450 Which is the first crystal

NOTE Confidence: 0.944827872727273

00:12:27.450 --> 00:12:30.208 structure of any WDR 5 protect

NOTE Confidence: 0.944827872727273

00:12:30.208 --> 00:12:32.836 history Ligus ternary complexes.

NOTE Confidence: 0.944827872727273

00:12:32.840 --> 00:12:35.440 So as illustrated here,

NOTE Confidence: 0.944827872727273

00:12:35.440 --> 00:12:41.582 the linker of MS33 was relatively

NOTE Confidence: 0.944827872727273

00:12:41.582 --> 00:12:47.176 extended in the ternary structure in

NOTE Confidence: 0.944827872727273

00:12:47.176 --> 00:12:51.380 the ternary complex and MS33 induced

NOTE Confidence: 0.944827872727273

00:12:51.380 --> 00:12:54.220 limited protein protein interactions.

NOTE Confidence: 0.944827872727273

00:12:54.220 --> 00:12:57.460 Between WDR 5 and Wedgel.

NOTE Confidence: 0.944827872727273

00:12:57.460 --> 00:12:59.515 So based on this critical

NOTE Confidence: 0.944827872727273

00:12:59.515 --> 00:13:01.330 structure insights, we design,

NOTE Confidence: 0.944827872727273

00:13:01.330 --> 00:13:04.300 synthesize and evaluate another set of

NOTE Confidence: 0.944827872727273

00:13:04.300 --> 00:13:07.730 compounds which contain much shorter

NOTE Confidence: 0.944827872727273

00:13:07.730 --> 00:13:10.508 linker linkers and simultaneously

NOTE Confidence: 0.944827872727273

00:13:10.508 --> 00:13:16.300 enhanced bonding to both WDR 5 and Wedgel.

NOTE Confidence: 0.944827872727273

00:13:16.300 --> 00:13:20.380 So from this study we identified

NOTE Confidence: 0.944827872727273

00:13:20.380 --> 00:13:23.746 MS-67-A highly effective WDR 5 degrader.

NOTE Confidence: 0.944827872727273

00:13:23.750 --> 00:13:27.314 Which contain this very very short

NOTE Confidence: 0.944827872727273

00:13:27.314 --> 00:13:31.264 linker and this modified WDR 5 binder

NOTE Confidence: 0.944827872727273

00:13:31.264 --> 00:13:34.350 and this mesolated VHL ligand.

NOTE Confidence: 0.944827872727273

00:13:34.350 --> 00:13:40.366 We also developed MS-67N as a negative

NOTE Confidence: 0.944827872727273

00:13:40.366 --> 00:13:45.230 control of MS-67 which contain the

NOTE Confidence: 0.944827872727273

00:13:45.230 --> 00:13:48.440 identical WDR 5 binder and the linker

NOTE Confidence: 0.944827872727273

00:13:48.440 --> 00:13:51.397 for the dyster isomer of the VHL ligand.

NOTE Confidence: 0.944827872727273

00:13:51.400 --> 00:13:55.360 Which abolishes the binding to VHL.

NOTE Confidence: 0.944827872727273

00:13:55.360 --> 00:13:57.572 So we also saw the high revolution

NOTE Confidence: 0.944827872727273

00:13:57.572 --> 00:14:02.248 crystal structure of WDR 5MS67 and VCB

NOTE Confidence: 0.944827872727273

00:14:02.248 --> 00:14:06.728 ternary complex which confirmed MS-67

NOTE Confidence: 0.944827872727273

00:14:06.728 --> 00:14:10.314 induced much more extensive protein

NOTE Confidence: 0.944827872727273

00:14:10.314 --> 00:14:14.358 protein interactions between WDR 5 and

NOTE Confidence: 0.944827872727273

00:14:14.360 --> 00:14:19.360 VHL and enhanced binding productivity.

NOTE Confidence: 0.944827872727273

00:14:19.360 --> 00:14:21.124 The enhanced binding correctivity

NOTE Confidence: 0.944827872727273

00:14:21.124 --> 00:14:24.380 between WDR 5 and which L induced

NOTE Confidence: 0.944827872727273

00:14:24.380 --> 00:14:27.566 by 67 was also confirmed using

NOTE Confidence: 0.944827872727273

00:14:27.566 --> 00:14:29.159 isothermal titration calorimetry

NOTE Confidence: 0.92817752

00:14:31.680 --> 00:14:35.960 and 67 but no not O ICR or 67 N

NOTE Confidence: 0.92817752

00:14:35.960 --> 00:14:38.455 totally and a selectively degraded

NOTE Confidence: 0.92817752

00:14:38.455 --> 00:14:42.560 WDR 5 in number of MML range range,

NOTE Confidence: 0.92817752

00:14:42.560 --> 00:14:44.320 leukemia cell lines and

NOTE Confidence: 0.92817752

00:14:44.320 --> 00:14:46.600 impedex cell lines in a time.

NOTE Confidence: 0.870047993333333

00:14:49.040 --> 00:14:53.276 VHL natilation and prezone dependent manner

NOTE Confidence: 0.887572013333333

00:14:55.480 --> 00:15:00.168 67 but not OSCR or 67 N effectively

NOTE Confidence: 0.887572013333333

00:15:00.168 --> 00:15:03.040 suppressed transcription of WDR 5 regularly.

NOTE Confidence: 0.887572013333333

00:15:03.040 --> 00:15:06.520 Genes in RN6 studies and effect

NOTE Confidence: 0.887572013333333

00:15:06.520 --> 00:15:08.840 of 67 significantly overlapped

NOTE Confidence: 0.887572013333333

00:15:08.938 --> 00:15:11.560 with that of WDR 5 knockdown

NOTE Confidence: 0.858143817142857

00:15:13.960 --> 00:15:17.425 67 but not OSCR or 67 N.

NOTE Confidence: 0.858143817142857

00:15:17.430 --> 00:15:20.182 Effectively reduced chromatin bonds,

NOTE Confidence: 0.858143817142857

00:15:20.182 --> 00:15:23.622 CMIC and MML complex components

NOTE Confidence: 0.858143817142857

00:15:23.630 --> 00:15:29.572 and 67 but not 67 N decreased H3K4

NOTE Confidence: 0.858143817142857

00:15:29.572 --> 00:15:32.282 dimethylation in both Western Black

NOTE Confidence: 0.858143817142857

00:15:32.282 --> 00:15:35.190 analysis and in Chipsique studies.

NOTE Confidence: 0.924178792857143

00:15:37.230 --> 00:15:40.560 Phenotypically 67 but not OACR

NOTE Confidence: 0.924178792857143

00:15:40.560 --> 00:15:43.890 or 67 N effectively suppressed

NOTE Confidence: 0.924178792857143

00:15:44.005 --> 00:15:46.666 in vitro cell growth and.

NOTE Confidence: 0.924178792857143

00:15:46.666 --> 00:15:49.046 Induced cell cycle arrest and

NOTE Confidence: 0.924178792857143

00:15:49.046 --> 00:15:52.012 apoptosis in number of MML range

NOTE Confidence: 0.924178792857143

00:15:52.012 --> 00:15:54.437 leukemia cell lines as illustrated

NOTE Confidence: 0.924178792857143

00:15:54.437 --> 00:15:58.013 here and also in PDEX cell lines and

NOTE Confidence: 0.924178792857143

00:15:58.013 --> 00:16:01.718 not showing here and importantly 67

NOTE Confidence: 0.924178792857143

00:16:01.718 --> 00:16:05.460 but not OACR significantly inhibit

NOTE Confidence: 0.924178792857143

00:16:05.460 --> 00:16:09.240 tumor tumor growth in vivo and

NOTE Confidence: 0.924178792857143

00:16:09.240 --> 00:16:12.216 improved survival in multiple in

NOTE Confidence: 0.924178792857143

00:16:12.216 --> 00:16:14.916 vivo mouse models including this.

NOTE Confidence: 0.924178792857143

00:16:14.920 --> 00:16:18.520 MML re enriched AML PDX model

NOTE Confidence: 0.924178792857143

00:16:18.520 --> 00:16:22.132 even though the much higher drug

NOTE Confidence: 0.924178792857143

00:16:22.132 --> 00:16:25.124 levels were achieved for OICR

NOTE Confidence: 0.924178792857143

00:16:25.124 --> 00:16:27.984 than 67 in tumor samples.

NOTE Confidence: 0.924178792857143

00:16:27.984 --> 00:16:30.964 We also established PKPD relationship

NOTE Confidence: 0.924178792857143

00:16:30.964 --> 00:16:33.678 for MS-67 for this in vivo models

NOTE Confidence: 0.905998806666667

00:16:35.960 --> 00:16:38.702 and Greg Moss lab and my

NOTE Confidence: 0.905998806666667

00:16:38.702 --> 00:16:40.771 lab also discovered MS-40.

NOTE Confidence: 0.905998806666667

00:16:40.771 --> 00:16:44.917 A novel CRBN recruiting WDR 5

NOTE Confidence: 0.905998806666667

00:16:44.917 --> 00:16:47.674 degrader which effectively degraded

NOTE Confidence: 0.905998806666667

00:16:47.674 --> 00:16:51.750 WDR five in a concentration time

NOTE Confidence: 0.905998806666667

00:16:51.750 --> 00:16:55.125 CRBN and UPS dependent manner.

NOTE Confidence: 0.8799052575

00:16:57.410 --> 00:17:01.365 Interestingly we find using a mass back

NOTE Confidence: 0.8799052575

00:17:01.365 --> 00:17:07.330 based global proteomic studies we find MS-40.

NOTE Confidence: 0.8799052575

00:17:07.330 --> 00:17:09.326 Can effectively degrade not

NOTE Confidence: 0.8799052575

00:17:09.326 --> 00:17:12.810 only WDR 5 but also IKZF one,

NOTE Confidence: 0.8799052575

00:17:12.810 --> 00:17:15.050 which is the CRB and new substrate.

NOTE Confidence: 0.8799052575

00:17:15.050 --> 00:17:18.125 We subsequently confirmed using Western

NOTE Confidence: 0.8799052575

00:17:18.125 --> 00:17:22.370 Black analysis that MS-40 and effectively

NOTE Confidence: 0.8799052575

00:17:22.370 --> 00:17:25.640 indeed effectively degraded CRB and

NOTE Confidence: 0.8799052575

00:17:25.640 --> 00:17:28.250 new substrate IKZF one and three,

NOTE Confidence: 0.8799052575

00:17:28.250 --> 00:17:33.569 but not GSPT one in addition to WDR 5.

NOTE Confidence: 0.8799052575

00:17:33.570 --> 00:17:38.064 So next we developed 2 control compounds.

NOTE Confidence: 0.8799052575

00:17:38.070 --> 00:17:41.125 MS-40 and TWO which effectively

NOTE Confidence: 0.8799052575

00:17:41.125 --> 00:17:44.956 degraded IKZF ONE and Three but not

NOTE Confidence: 0.8799052575

00:17:44.956 --> 00:17:50.285 WDR 5 and MS169 which degraded WDR Five

NOTE Confidence: 0.8799052575

00:17:50.285 --> 00:17:54.007 with a similar potency as MS-40 but

NOTE Confidence: 0.8799052575

00:17:54.007 --> 00:17:57.388 did not degrade IKZF ONE and Three.

NOTE Confidence: 0.8799052575

00:17:57.390 --> 00:17:58.203 Interestingly,

NOTE Confidence: 0.8799052575

00:17:58.203 --> 00:18:02.320 we find MS-40 which degrade both WDR

NOTE Confidence: 0.8799052575

00:18:02.320 --> 00:18:06.510 5 and IKZF 1/3 was more effective.

NOTE Confidence: 0.8799052575

00:18:06.510 --> 00:18:08.694 In suppressing the proliferation

NOTE Confidence: 0.8799052575

00:18:08.694 --> 00:18:11.424 of MML range leukemia cells,

NOTE Confidence: 0.8799052575

00:18:11.430 --> 00:18:14.630 then MS-40 and TWO alone,

NOTE Confidence: 0.8799052575

00:18:14.630 --> 00:18:19.790 which degraded IKZF 1 THREE only, ALL,

NOTE Confidence: 0.8799052575

00:18:19.790 --> 00:18:25.390 MS169 alone which degraded WDR five only,

NOTE Confidence: 0.8799052575

00:18:25.390 --> 00:18:26.845 and as expected,

NOTE Confidence: 0.8799052575

00:18:26.845 --> 00:18:31.310 the cold treatment of MS-40 and TWO and

NOTE Confidence: 0.8799052575

00:18:31.310 --> 00:18:36.432 MS169 displaced similar effectness as MS-40.

NOTE Confidence: 0.8799052575

00:18:36.432 --> 00:18:39.078 So in addition,

NOTE Confidence: 0.8799052575

00:18:39.080 --> 00:18:43.068 IMS 40 but not 40 and two all 169

NOTE Confidence: 0.8799052575

00:18:43.068 --> 00:18:46.116 significantly inhibit tumor growth in vivo.

NOTE Confidence: 0.8799052575

00:18:46.120 --> 00:18:49.992 Even though all three compounds were similar,

NOTE Confidence: 0.8799052575

00:18:49.992 --> 00:18:52.056 drug levels were achieved

NOTE Confidence: 0.8799052575

00:18:52.056 --> 00:18:54.120 for all three compounds.

NOTE Confidence: 0.8799052575

00:18:54.120 --> 00:18:56.028 So taken together,

NOTE Confidence: 0.8799052575

00:18:56.028 --> 00:18:58.572 this results suggest pharmacological

NOTE Confidence: 0.8799052575

00:18:58.572 --> 00:19:02.144 degradation of a WD R5 as a

NOTE Confidence: 0.8799052575

00:19:02.144 --> 00:19:03.808 novel serial pedic strategy.

NOTE Confidence: 0.8799052575

00:19:03.810 --> 00:19:06.670 Is superior to pharmacologic logical

NOTE Confidence: 0.8799052575

00:19:06.670 --> 00:19:08.958 inhibition of protein protein

NOTE Confidence: 0.8799052575

00:19:08.958 --> 00:19:11.732 actions between WDR 5 and its

NOTE Confidence: 0.8799052575

00:19:11.732 --> 00:19:14.090 binding partners for treating WDR 5.

NOTE Confidence: 0.8799052575

00:19:14.090 --> 00:19:17.985 Dependent tumors do degradation of

NOTE Confidence: 0.8799052575

00:19:17.985 --> 00:19:21.825 WDR 5 and IKZF 1/3 and could be more

NOTE Confidence: 0.8799052575

00:19:21.825 --> 00:19:24.040 effective than degradation of WDR

NOTE Confidence: 0.8799052575

00:19:24.124 --> 00:19:27.394 5 or IKZF 1/3 alone in suppressing

NOTE Confidence: 0.8799052575

00:19:27.394 --> 00:19:30.574 the proliferation of MML rearranged

NOTE Confidence: 0.8799052575

00:19:30.574 --> 00:19:33.239 leukemia in vitro and in vivo.

NOTE Confidence: 0.8799052575

00:19:33.240 --> 00:19:36.495 Another key take away from this study

NOTE Confidence: 0.8799052575

00:19:36.495 --> 00:19:39.092 is the ternary complex structure

NOTE Confidence: 0.8799052575

00:19:39.092 --> 00:19:41.680 based design which is extremely where

NOTE Confidence: 0.8799052575

00:19:41.680 --> 00:19:44.520 in the protect field is a powerful

NOTE Confidence: 0.8799052575

00:19:44.520 --> 00:19:47.340 approach and can lead to highly

NOTE Confidence: 0.8799052575

00:19:47.340 --> 00:19:49.820 effective protect degradation and

NOTE Confidence: 0.8799052575

00:19:49.820 --> 00:19:53.395 lastly the degradation of CRBN new

NOTE Confidence: 0.8799052575

00:19:53.395 --> 00:19:56.364 substrates by CRBN recruiting protects

NOTE Confidence: 0.8799052575

00:19:56.364 --> 00:19:59.988 needs to be monitored very carefully.

NOTE Confidence: 0.8799052575

00:19:59.990 --> 00:20:01.350 And such NEO, St.

NOTE Confidence: 0.8799052575

00:20:01.350 --> 00:20:02.030 neo St.

NOTE Confidence: 0.8799052575

00:20:02.030 --> 00:20:04.782 degradation could potentially be

NOTE Confidence: 0.8799052575

00:20:04.782 --> 00:20:07.182 exploited to yield more effective

NOTE Confidence: 0.8799052575

00:20:07.182 --> 00:20:08.466 anti cancer therapeutics.

NOTE Confidence: 0.94276935

00:20:10.750 --> 00:20:12.934 So now I'm going to talk about

NOTE Confidence: 0.94276935

00:20:12.934 --> 00:20:14.909 discovery of easy two inhibition.

NOTE Confidence: 0.94276935

00:20:14.910 --> 00:20:17.934 So canonically easy two is the

NOTE Confidence: 0.94276935

00:20:17.934 --> 00:20:20.597 main catalyst subunit of Hollycomb

NOTE Confidence: 0.94276935

00:20:20.597 --> 00:20:24.470 repressive complex 2P R C2 which

NOTE Confidence: 0.94276935

00:20:24.470 --> 00:20:27.070 catalyzes A3K27 trimethylation

NOTE Confidence: 0.94276935

00:20:27.070 --> 00:20:30.030 and mediating gene repression.

NOTE Confidence: 0.94276935

00:20:30.030 --> 00:20:31.930 An easy issue is overexpressed

NOTE Confidence: 0.94276935

00:20:31.930 --> 00:20:34.316 in many cancers including TNB or

NOTE Confidence: 0.94276935

00:20:34.316 --> 00:20:35.988 triple negative breast cancer.

NOTE Confidence: 0.94276935

00:20:35.990 --> 00:20:39.868 TNBC and it's a high expression level,

NOTE Confidence: 0.94276935

00:20:39.870 --> 00:20:44.286 correlates with the poor prognosis and

NOTE Confidence: 0.94276935

00:20:44.286 --> 00:20:46.534 knocked out easy issue effectively

NOTE Confidence: 0.94276935

00:20:46.534 --> 00:20:50.610 inhibit the growth of breast cancer cells,

NOTE Confidence: 0.94276935

00:20:50.610 --> 00:20:52.998 including TNBC cells. However,

NOTE Confidence: 0.94276935

00:20:52.998 --> 00:20:56.714 all easy issue inhibits are ineffective.

NOTE Confidence: 0.94276935

00:20:56.714 --> 00:21:00.086 In suppressing the provision of TNBC

NOTE Confidence: 0.94276935

00:21:00.086 --> 00:21:03.658 cells even though they effectively

NOTE Confidence: 0.94276935

00:21:03.658 --> 00:21:06.768 reduced H3K27 trimesolation mark,

NOTE Confidence: 0.94276935

00:21:06.770 --> 00:21:09.450 we therefore pursued development of

NOTE Confidence: 0.94276935

00:21:09.450 --> 00:21:13.040 easy shoot degraders to Pheno copy anti

NOTE Confidence: 0.94276935

00:21:13.040 --> 00:21:15.924 tumor effect of easy to knock down.

NOTE Confidence: 0.94427896

00:21:18.850 --> 00:21:20.430 So in collaboration with Roman

NOTE Confidence: 0.94427896

00:21:20.430 --> 00:21:22.010 Parsons Lab at Mount Sinai,

NOTE Confidence: 0.94427896

00:21:22.010 --> 00:21:25.175 we discovered the first easy

NOTE Confidence: 0.94427896

00:21:25.175 --> 00:21:27.074 shoot selective degrader.

NOTE Confidence: 0.94427896

00:21:27.080 --> 00:21:29.360 MS1943 So this project

NOTE Confidence: 0.94427896

00:21:29.360 --> 00:21:31.640 was spearheaded by Anjima,

NOTE Confidence: 0.94427896

00:21:31.640 --> 00:21:33.638 a former poster in my lab

NOTE Confidence: 0.94427896

00:21:33.640 --> 00:21:36.034 alias a former poster in Ramon

NOTE Confidence: 0.94427896

00:21:36.034 --> 00:21:38.000 Parsons lab and Kwongsu park

NOTE Confidence: 0.94427896

00:21:38.000 --> 00:21:39.480 instructor in my lab currently.

NOTE Confidence: 0.86911847

00:21:43.800 --> 00:21:48.376 So in in contrast to the WDR 5 protax

NOTE Confidence: 0.86911847

00:21:48.376 --> 00:21:50.920 degraders I just talked about it,

NOTE Confidence: 0.86911847

00:21:50.920 --> 00:21:53.730 MS1943 is not a protag.

NOTE Confidence: 0.86911847

00:21:53.730 --> 00:21:56.510 Is the hydrophobic tag based

NOTE Confidence: 0.86911847

00:21:56.510 --> 00:21:59.290 degrader which links a selective

NOTE Confidence: 0.91470316

00:22:01.370 --> 00:22:05.426 easy issue. Remember with this bulky

NOTE Confidence: 0.91470316

00:22:05.426 --> 00:22:09.170 hydrophobic hydrophobic elementing group.

NOTE Confidence: 0.91470316

00:22:09.170 --> 00:22:13.118 OK and as illustrated here MS1943 is

NOTE Confidence: 0.91470316

00:22:13.118 --> 00:22:15.540 highly selective for easy issue and

NOTE Confidence: 0.91470316

00:22:15.540 --> 00:22:18.978 some of you probably know Craig Ku.

NOTE Confidence: 0.91470316

00:22:18.978 --> 00:22:22.520 Craig Kus is also a pioneer of.

NOTE Confidence: 0.91470316

00:22:22.520 --> 00:22:26.960 The hydrophobic tag based degrader approach.

NOTE Confidence: 0.91470316

00:22:26.960 --> 00:22:30.976 His lab published the first hydrophobic

NOTE Confidence: 0.91470316

00:22:30.976 --> 00:22:34.672 tag tag based small molecule degraders

NOTE Confidence: 0.91470316

00:22:34.672 --> 00:22:38.026 of helo tag fusion proteins in

NOTE Confidence: 0.91470316

00:22:38.026 --> 00:22:42.320 Nature Chemical Biology in 2011.

NOTE Confidence: 0.91470316

00:22:42.320 --> 00:22:48.045 So back to EH2M S 1943 an effectively

NOTE Confidence: 0.91470316

00:22:48.045 --> 00:22:50.493 degraded EH2IN multiple TMPC

NOTE Confidence: 0.91470316

00:22:50.493 --> 00:22:53.248 cell lines as illustrate here.

NOTE Confidence: 0.91470316

00:22:53.250 --> 00:22:54.813 And in contrast,

NOTE Confidence: 0.91470316

00:22:54.813 --> 00:22:57.418 two is issue inhibitors which

NOTE Confidence: 0.91470316

00:22:57.418 --> 00:22:59.464 were ineffective in inhibiting

NOTE Confidence: 0.91470316

00:22:59.464 --> 00:23:01.764 the growth of TNBC cells.

NOTE Confidence: 0.91470316

00:23:01.770 --> 00:23:05.280 Our issue DEGRADER MS1943 effectively

NOTE Confidence: 0.91470316

00:23:05.280 --> 00:23:09.084 suppressed the growth of the growth

NOTE Confidence: 0.91470316

00:23:09.084 --> 00:23:14.290 in multiple TNBC cell lines and 1943

NOTE Confidence: 0.91470316

00:23:14.290 --> 00:23:18.118 was hourly by available in mice and in

NOTE Confidence: 0.91470316

00:23:18.118 --> 00:23:21.572 TNBC cell line xenograph model 1943.

NOTE Confidence: 0.91470316

00:23:21.572 --> 00:23:23.500 Significantly inhibit tumor growth

NOTE Confidence: 0.91470316

00:23:23.500 --> 00:23:27.369 in vivo and had no effect on the on

NOTE Confidence: 0.91470316

00:23:27.369 --> 00:23:29.532 the body weight of the treaty mice

NOTE Confidence: 0.91470316

00:23:29.532 --> 00:23:31.860 with PKPD relationship established.

NOTE Confidence: 0.950316941428571

00:23:34.060 --> 00:23:37.259 So recently our collaborator Greg Wong's lab,

NOTE Confidence: 0.950316941428571

00:23:37.260 --> 00:23:41.012 Greg Wong at University of North

NOTE Confidence: 0.950316941428571

00:23:41.012 --> 00:23:43.316 Carolina at Chapel Hill and his

NOTE Confidence: 0.950316941428571

00:23:43.316 --> 00:23:45.524 post out June Wong discovered his

NOTE Confidence: 0.950316941428571

00:23:45.524 --> 00:23:47.962 issue have a novel non canonical

NOTE Confidence: 0.950316941428571

00:23:47.962 --> 00:23:51.390 function in activation of uncle genes.

NOTE Confidence: 0.950316941428571

00:23:51.390 --> 00:23:57.102 By binding CMIC and P300 through its

NOTE Confidence: 0.950316941428571

00:23:57.102 --> 00:24:01.402 hidden transactivation domain and so

NOTE Confidence: 0.950316941428571

00:24:01.402 --> 00:24:04.832 this non canonical oncogenic function

NOTE Confidence: 0.950316941428571

00:24:04.832 --> 00:24:09.151 differs from the well known canonical

NOTE Confidence: 0.950316941428571

00:24:09.151 --> 00:24:13.429 gene repression function of PRC two.

NOTE Confidence: 0.950316941428571

00:24:13.430 --> 00:24:17.622 So to target both canonical and the non

NOTE Confidence: 0.950316941428571

00:24:17.622 --> 00:24:20.357 canonical oncogenic function of is H2.

NOTE Confidence: 0.950316941428571

00:24:20.360 --> 00:24:23.522 SharePoint used you know that in

NOTE Confidence: 0.950316941428571

00:24:23.522 --> 00:24:25.630 collaboration with Gregg Von's

NOTE Confidence: 0.950316941428571

00:24:25.721 --> 00:24:28.153 lab at UNC discovered MS177A.

NOTE Confidence: 0.950316941428571

00:24:28.153 --> 00:24:31.518 Novel CRBN recruiting is H2

NOTE Confidence: 0.950316941428571

00:24:31.520 --> 00:24:33.495 protect degrader which is highly

NOTE Confidence: 0.950316941428571

00:24:33.495 --> 00:24:36.280 selected for is H2 as shown here

NOTE Confidence: 0.92427904

00:24:38.920 --> 00:24:44.040 177 totally degraded is H2 in a

NOTE Confidence: 0.92427904

00:24:44.040 --> 00:24:48.960 time CRBN and UPS dependent manner.

NOTE Confidence: 0.92427904

00:24:48.960 --> 00:24:54.192 And 177 also totally degraded CMIC in a

NOTE Confidence: 0.92427904

00:24:54.192 --> 00:24:59.120 Crbn easy shoe and UPS dependent manner

NOTE Confidence: 0.92427904

00:24:59.120 --> 00:25:02.115 and phenotypically 177 totally inhibit

NOTE Confidence: 0.92427904

00:25:02.115 --> 00:25:05.640 the proliferation of MML range look,

NOTE Confidence: 0.92427904

00:25:05.640 --> 00:25:10.477 AML cell lines and primary patient cells.

NOTE Confidence: 0.92427904

00:25:10.480 --> 00:25:14.664 It was much more effective than easy shoe

NOTE Confidence: 0.92427904

00:25:14.664 --> 00:25:18.190 inhibitors in inhibiting the growth of.

NOTE Confidence: 0.92427904

00:25:18.190 --> 00:25:21.195 The proliferation and the tumor tumor

NOTE Confidence: 0.92427904

00:25:21.195 --> 00:25:26.310 genesis in MML ranged AML cells and

NOTE Confidence: 0.92427904

00:25:26.310 --> 00:25:30.041 177 also effectively induced apoptosis

NOTE Confidence: 0.92427904

00:25:30.041 --> 00:25:34.187 in an easy issue dependent manner.

NOTE Confidence: 0.92427904

00:25:34.190 --> 00:25:37.894 And importantly 177 significantly inhibit

NOTE Confidence: 0.92427904

00:25:37.894 --> 00:25:41.302 tumor growth in vivo and prolonged

NOTE Confidence: 0.92427904

00:25:41.302 --> 00:25:44.708 survival in multiple in vivo mass models.

NOTE Confidence: 0.92427904

00:25:44.710 --> 00:25:49.904 Including this MML ranged AML PDX model

NOTE Confidence: 0.92427904

00:25:49.910 --> 00:25:53.110 with PKPD relationship established

NOTE Confidence: 0.937678652272727

00:25:55.630 --> 00:25:58.240 so in collaboration using 177 Greg

NOTE Confidence: 0.937678652272727

00:25:58.240 --> 00:26:01.982 Watts lab and my lab also and covered

NOTE Confidence: 0.937678652272727

00:26:01.982 --> 00:26:04.372 a similar non canonical function

NOTE Confidence: 0.937678652272727

00:26:04.372 --> 00:26:07.665 of easy issue in multiple myeloma,

NOTE Confidence: 0.937678652272727

00:26:07.665 --> 00:26:10.790 an activation of uncle gene

NOTE Confidence: 0.937678652272727

00:26:10.790 --> 00:26:14.576 where binding of cimic and P300.

NOTE Confidence: 0.937678652272727

00:26:14.580 --> 00:26:18.060 Where Sue the hidden transactive

NOTE Confidence: 0.937678652272727

00:26:18.060 --> 00:26:23.219 activation domain of EH2 and we show

NOTE Confidence: 0.937678652272727

00:26:23.220 --> 00:26:26.010 MS177 can effectively target both

NOTE Confidence: 0.937678652272727

00:26:26.010 --> 00:26:29.411 canonical and a non canonical function

NOTE Confidence: 0.937678652272727

00:26:29.411 --> 00:26:33.523 of EH2 and inhibit the growth of multiple

NOTE Confidence: 0.937678652272727

00:26:33.523 --> 00:26:36.256 myeloma cells in vitro and vivo.

NOTE Confidence: 0.937678652272727

00:26:36.260 --> 00:26:41.450 So lastly using MS177.

NOTE Confidence: 0.937678652272727

00:26:41.450 --> 00:26:43.330 Ling Tai's lab at University

NOTE Confidence: 0.937678652272727

00:26:43.330 --> 00:26:45.210 of North Carolina Chapel Hill,

NOTE Confidence: 0.937678652272727

00:26:45.210 --> 00:26:48.414 Greg Watts lab at UNC and my lab also

NOTE Confidence: 0.937678652272727

00:26:48.414 --> 00:26:51.333 and discovered a novel non canonical

NOTE Confidence: 0.937678652272727

00:26:51.333 --> 00:26:54.860 function of easy shoe in prostate cancer.

NOTE Confidence: 0.937678652272727

00:26:54.860 --> 00:27:00.322 So easy shoe finds both AR and AR splice

NOTE Confidence: 0.937678652272727

00:27:00.322 --> 00:27:03.774 wearing AR-7 ARV 7A constituently

NOTE Confidence: 0.937678652272727

00:27:03.774 --> 00:27:07.746 active AR variants enriched in advanced

NOTE Confidence: 0.937678652272727

00:27:07.746 --> 00:27:10.294 castration resistant prostate cancer.

NOTE Confidence: 0.937678652272727

00:27:10.294 --> 00:27:14.390 Where the transactivation domain

NOTE Confidence: 0.937678652272727

00:27:14.390 --> 00:27:17.805 promoting Uncle Genesis and Crpc

NOTE Confidence: 0.937678652272727

00:27:17.805 --> 00:27:23.470 growth in mutual and in evil and we

NOTE Confidence: 0.937678652272727

00:27:23.470 --> 00:27:27.337 show MS177 can effectively target

NOTE Confidence: 0.937678652272727

00:27:27.337 --> 00:27:30.272 both canonical and non canonical

NOTE Confidence: 0.937678652272727

00:27:30.272 --> 00:27:34.270 oncogenic functions of E day 2IN Crpc.

NOTE Confidence: 0.931474127272727

00:27:38.610 --> 00:27:42.222 So the key, the key takeaways from

NOTE Confidence: 0.931474127272727

00:27:42.222 --> 00:27:44.922 these studies are first pharmacological

NOTE Confidence: 0.931474127272727

00:27:44.922 --> 00:27:47.986 degradation of the issue but not

NOTE Confidence: 0.931474127272727

00:27:47.986 --> 00:27:49.698 pharmacological inhibition of the

NOTE Confidence: 0.931474127272727

00:27:49.698 --> 00:27:52.650 issue could be a effective short

NOTE Confidence: 0.931474127272727

00:27:52.650 --> 00:27:55.170 periodic strategy for treating TNBC,

NOTE Confidence: 0.931474127272727

00:27:55.170 --> 00:27:58.470 MML range of leukemia, multiple

NOTE Confidence: 0.931474127272727

00:27:58.470 --> 00:28:01.770 myeloma and advanced prostate cancer.

NOTE Confidence: 0.931474127272727

00:28:01.770 --> 00:28:04.290 In addition to the another take

NOTE Confidence: 0.931474127272727

00:28:04.290 --> 00:28:07.369 away from this from this studies is.

NOTE Confidence: 0.931474127272727

00:28:07.370 --> 00:28:09.686 In addition to the protect technology,

NOTE Confidence: 0.931474127272727

00:28:09.690 --> 00:28:12.270 the hydrophobic tag based approach

NOTE Confidence: 0.931474127272727

00:28:12.270 --> 00:28:14.850 which have been understudied and

NOTE Confidence: 0.931474127272727

00:28:14.936 --> 00:28:18.230 under appreciated by the field and can

NOTE Confidence: 0.931474127272727

00:28:18.230 --> 00:28:21.170 lead to degraders that are already

NOTE Confidence: 0.931474127272727

00:28:21.170 --> 00:28:24.288 by available and advocacious in EVO.

NOTE Confidence: 0.931474127272727

00:28:24.290 --> 00:28:27.314 So well this degraders and this

NOTE Confidence: 0.931474127272727

00:28:27.314 --> 00:28:29.330 technologies are very promising.

NOTE Confidence: 0.942718871428571

00:28:31.650 --> 00:28:33.696 The conventional protect

NOTE Confidence: 0.942718871428571

00:28:33.696 --> 00:28:36.424 approach cannot be utilized.

NOTE Confidence: 0.942718871428571

00:28:36.430 --> 00:28:39.268 To target and drug work proteins,

NOTE Confidence: 0.942718871428571

00:28:39.270 --> 00:28:41.790 which lack a small molecule binders

NOTE Confidence: 0.942718871428571

00:28:41.790 --> 00:28:44.751 as a small molecule binder of the

NOTE Confidence: 0.942718871428571

00:28:44.751 --> 00:28:47.730 target protein is needed for the

NOTE Confidence: 0.942718871428571

00:28:47.730 --> 00:28:50.430 traditional protect approach to work.

NOTE Confidence: 0.942718871428571

00:28:50.430 --> 00:28:54.595 So to target and drug work proteins

NOTE Confidence: 0.942718871428571

00:28:54.595 --> 00:28:56.830 including transcription factors TFs,

NOTE Confidence: 0.942718871428571

00:28:56.830 --> 00:29:00.310 we developed two novel approaches,

NOTE Confidence: 0.942718871428571

00:29:00.310 --> 00:29:02.113 First bridge protect,

NOTE Confidence: 0.942718871428571

00:29:02.113 --> 00:29:06.320 second TF protect and TF Dub tag.

NOTE Confidence: 0.942718871428571

00:29:06.320 --> 00:29:07.592 So now I'm going to talk

NOTE Confidence: 0.942718871428571

00:29:07.592 --> 00:29:08.440 about these two approaches.

NOTE Confidence: 0.907133255555556

00:29:10.560 --> 00:29:12.980 So we hypothesized and drug

NOTE Confidence: 0.907133255555556

00:29:12.980 --> 00:29:14.916 war proteins which lack

NOTE Confidence: 0.94830432

00:29:17.120 --> 00:29:21.132 lacks a small worker binders could be

NOTE Confidence: 0.94830432

00:29:21.132 --> 00:29:24.666 targeted by breached protect if this

NOTE Confidence: 0.94830432

00:29:24.666 --> 00:29:28.022 and drug war protein interacts with

NOTE Confidence: 0.94830432

00:29:28.022 --> 00:29:31.277 another protein termed bridge protein,

NOTE Confidence: 0.94830432

00:29:31.280 --> 00:29:35.088 which have has a small molecule binder.

NOTE Confidence: 0.94830432

00:29:35.090 --> 00:29:38.126 So by exploiting this bridge protein

NOTE Confidence: 0.94830432

00:29:38.130 --> 00:29:41.046 we're linking a small molecule binder

NOTE Confidence: 0.94830432

00:29:41.046 --> 00:29:44.853 of this bridge protein to a ES3 ligas

NOTE Confidence: 0.94830432

00:29:44.853 --> 00:29:47.523 ligand with appropriate link link linker

NOTE Confidence: 0.94830432

00:29:47.530 --> 00:29:52.450 bridge protein and induces close proximity

NOTE Confidence: 0.94830432

00:29:52.450 --> 00:29:55.672 between the ubiquitin machinery and to

NOTE Confidence: 0.94830432

00:29:55.672 --> 00:29:58.932 this and drug protein bridge protein

NOTE Confidence: 0.94830432

00:29:58.932 --> 00:30:02.868 complex and could lead to a selective.

NOTE Confidence: 0.94830432

00:30:02.868 --> 00:30:04.246 Of polyclination,

NOTE Confidence: 0.94830432

00:30:04.246 --> 00:30:07.691 of preferential polyblination and degradation

NOTE Confidence: 0.94830432

00:30:07.691 --> 00:30:13.536 of this and drug protein over bridge protein.

NOTE Confidence: 0.94830432

00:30:13.540 --> 00:30:17.988 OK, so we selected cycling D1 as the

NOTE Confidence: 0.94830432

00:30:17.988 --> 00:30:22.131 first target for this bridge protect

NOTE Confidence: 0.94830432

00:30:22.131 --> 00:30:25.260 approach for the following reasons.

NOTE Confidence: 0.94830432

00:30:25.260 --> 00:30:29.332 So the first second D1 is the

NOTE Confidence: 0.94830432

00:30:29.332 --> 00:30:32.920 talk cancer drug target ranked by.

NOTE Confidence: 0.94830432

00:30:32.920 --> 00:30:33.878 Damat however,

NOTE Confidence: 0.94830432

00:30:33.878 --> 00:30:37.231 it is end druggable as it's lack

NOTE Confidence: 0.94830432

00:30:37.231 --> 00:30:39.960 a small molecule binder.

NOTE Confidence: 0.94830432

00:30:39.960 --> 00:30:40.461 Second,

NOTE Confidence: 0.94830432

00:30:40.461 --> 00:30:43.968 it's well known second D one former

NOTE Confidence: 0.94830432

00:30:43.968 --> 00:30:46.532 protein complex with CD46 and

NOTE Confidence: 0.94830432

00:30:46.532 --> 00:30:49.344 highly potent and selective CD46

NOTE Confidence: 0.94830432

00:30:49.344 --> 00:30:51.520 inhibitors have been developed.

NOTE Confidence: 0.94830432

00:30:51.520 --> 00:30:56.712 So by testing all of our CD46 cortex,

NOTE Confidence: 0.94830432

00:30:56.712 --> 00:31:01.011 we identified MS-28 as the first.

NOTE Confidence: 0.94830432

00:31:01.011 --> 00:31:04.593 Which protect of cycling D1 which

NOTE Confidence: 0.94830432

00:31:04.593 --> 00:31:08.956 contain this Hubble site clip as

NOTE Confidence: 0.94830432

00:31:08.956 --> 00:31:13.110 a CDK 46 binder linked to a Wechao

NOTE Confidence: 0.94830432

00:31:13.110 --> 00:31:15.335 ligan where a short linker.

NOTE Confidence: 0.94830432

00:31:15.340 --> 00:31:19.008 So this work was spearheaded by Yang

NOTE Confidence: 0.94830432

00:31:19.008 --> 00:31:21.898 Xun assistant professor in my lab and

NOTE Confidence: 0.94830432

00:31:21.898 --> 00:31:25.840 we are June and Leah Leah Rin and both.

NOTE Confidence: 0.94830432

00:31:25.840 --> 00:31:28.477 Both of them are PhD student in the lab.

NOTE Confidence: 0.94830432

00:31:28.480 --> 00:31:30.874 So Yan did most of the country

NOTE Confidence: 0.94830432

00:31:30.874 --> 00:31:34.115 work and you and Leah did all the

NOTE Confidence: 0.94830432

00:31:34.115 --> 00:31:36.039 biological studies for for this work.

NOTE Confidence: 0.949059075

00:31:39.880 --> 00:31:43.750 So MS-28 for for gradually degrade

NOTE Confidence: 0.949059075

00:31:43.750 --> 00:31:47.520 cycling D1 over CDK four and CD

NOTE Confidence: 0.949059075

00:31:47.520 --> 00:31:52.040 CD6 and did not change MRA level

NOTE Confidence: 0.949059075

00:31:52.040 --> 00:31:57.348 of cycling D1, CDK 4 and CD6.

NOTE Confidence: 0.949059075

00:31:57.350 --> 00:32:00.180 The cycling D1 degradation induced

NOTE Confidence: 0.949059075

00:32:00.180 --> 00:32:04.230 by MS-28IS dependent on VHL,

NOTE Confidence: 0.949059075

00:32:04.230 --> 00:32:09.310 CDK 6 and UPS and MS-28

NOTE Confidence: 0.949059075

00:32:09.310 --> 00:32:12.510 can induce cycling D1,

NOTE Confidence: 0.949059075

00:32:12.510 --> 00:32:18.346 CDK 6MS28 and VHL quanary complex formation

NOTE Confidence: 0.849647856666667

00:32:21.310 --> 00:32:23.956 and our cycling D1 the greater MS-28.

NOTE Confidence: 0.849647856666667

00:32:23.956 --> 00:32:28.220 Is a superior to the the parent CDK

NOTE Confidence: 0.849647856666667

00:32:28.220 --> 00:32:31.810 46 inhibitor PABO cyclip and known

NOTE Confidence: 0.849647856666667

00:32:31.810 --> 00:32:37.106 CDK 46 degrader BSJ which degree CDK

NOTE Confidence: 0.849647856666667

00:32:37.106 --> 00:32:40.850 46 but not cyclin B1 in suppressing

NOTE Confidence: 0.849647856666667

00:32:40.850 --> 00:32:43.625 the proliferation in multiple non

NOTE Confidence: 0.849647856666667

00:32:43.625 --> 00:32:46.939 small cell lung cancer cell lines.

NOTE Confidence: 0.849647856666667

00:32:46.940 --> 00:32:52.057 We also applied this rich cortex strategy.

NOTE Confidence: 0.849647856666667

00:32:52.060 --> 00:32:54.715 To target PRC One components

NOTE Confidence: 0.849647856666667

00:32:54.715 --> 00:32:58.320 of PMI One and Room 1B, well,

NOTE Confidence: 0.849647856666667

00:32:58.320 --> 00:33:02.820 the EED is the core component of PRC 2.

NOTE Confidence: 0.849647856666667

00:33:02.820 --> 00:33:06.614 EED also interacts with PRC One components,

NOTE Confidence: 0.849647856666667

00:33:06.620 --> 00:33:08.820 PMI one and Room 1B.

NOTE Confidence: 0.849647856666667

00:33:08.820 --> 00:33:14.172 So we aimed to develop a EED binding

NOTE Confidence: 0.849647856666667

00:33:14.172 --> 00:33:17.292 protect that can preferentially degrade

NOTE Confidence: 0.849647856666667

00:33:17.292 --> 00:33:21.693 PMI One and Room 1B over EED indeed.

NOTE Confidence: 0.849647856666667

00:33:21.693 --> 00:33:27.100 We discovered MS147 and the

NOTE Confidence: 0.849647856666667

00:33:27.100 --> 00:33:30.200 first P RC1 bridge protect,

NOTE Confidence: 0.849647856666667

00:33:30.200 --> 00:33:33.956 which is the way child recruiting

NOTE Confidence: 0.849647856666667

00:33:33.960 --> 00:33:37.120 and EE D binding protect.

NOTE Confidence: 0.849647856666667

00:33:37.120 --> 00:33:40.120 So this work was spearheaded by Kwansu Park,

NOTE Confidence: 0.849647856666667

00:33:40.120 --> 00:33:41.600 an instructor in the lab,

NOTE Confidence: 0.849647856666667

00:33:41.600 --> 00:33:42.996 and Lee Hui Chin,

NOTE Confidence: 0.849647856666667

00:33:42.996 --> 00:33:46.127 a former post out in the lab and MD

NOTE Confidence: 0.849647856666667

00:33:46.127 --> 00:33:47.840 Cab Bear APHD student in the lab.

NOTE Confidence: 0.849647856666667

00:33:47.840 --> 00:33:49.972 He just actually successfully

NOTE Confidence: 0.849647856666667

00:33:49.972 --> 00:33:51.395 defended his PhD.

NOTE Confidence: 0.849647856666667

00:33:51.395 --> 00:33:53.525 And Kwansu and MD did the

NOTE Confidence: 0.849647856666667

00:33:53.525 --> 00:33:55.346 biological studies and Lee Hua

NOTE Confidence: 0.849647856666667

00:33:55.346 --> 00:33:57.066 did chemistry for this work.

NOTE Confidence: 0.9201268

00:33:59.750 --> 00:34:03.306 So MS147 preferentially degraded

NOTE Confidence: 0.9201268

00:34:03.306 --> 00:34:07.458 PRC one components BMI one and

NOTE Confidence: 0.9201268

00:34:07.458 --> 00:34:11.710 room 1B and selectively reduced

NOTE Confidence: 0.9201268

00:34:11.710 --> 00:34:14.650 H2A Lysing 119 monoclination which

NOTE Confidence: 0.9201268

00:34:14.650 --> 00:34:19.243 is catalyzed by PRC 1 / P RED.

NOTE Confidence: 0.9201268

00:34:19.243 --> 00:34:23.660 And the other PRC 2 components is H2

NOTE Confidence: 0.9201268

00:34:23.660 --> 00:34:28.050 and SUZ 12 and H3K27 trimethylation

NOTE Confidence: 0.9201268

00:34:28.050 --> 00:34:30.660 which is catalyzed by PRC Two

NOTE Confidence: 0.943128857142857

00:34:32.740 --> 00:34:35.584 and the PRC one degradation induced

NOTE Confidence: 0.943128857142857

00:34:35.584 --> 00:34:39.420 by MS147 is dependent on Ed,

NOTE Confidence: 0.943128857142857

00:34:39.420 --> 00:34:45.299 VHL and UPS and our PRC

NOTE Confidence: 0.943128857142857

00:34:45.299 --> 00:34:48.243 One bridge protect MS147.

NOTE Confidence: 0.943128857142857

00:34:48.243 --> 00:34:52.672 Is a superior to the parent Ed Ed two

NOTE Confidence: 0.943128857142857

00:34:52.672 --> 00:34:56.625 to six and the known PRC 2 degrader

NOTE Confidence: 0.943128857142857

00:34:56.625 --> 00:34:59.450 Protech 2 developed by Astrozeneca

NOTE Confidence: 0.943128857142857

00:34:59.450 --> 00:35:02.420 in suppressing the proliferation

NOTE Confidence: 0.943128857142857

00:35:02.420 --> 00:35:04.445 in multiple cancer cell lines.

NOTE Confidence: 0.930190308

00:35:07.130 --> 00:35:10.570 So now I'm going to briefly talk about our

NOTE Confidence: 0.930190308

00:35:10.570 --> 00:35:15.367 TF Protech and the TF dub tech approach.

NOTE Confidence: 0.930190308

00:35:15.370 --> 00:35:18.700 So as you know many.

NOTE Confidence: 0.930190308

00:35:18.700 --> 00:35:23.226 Transcription factors are and druggable

NOTE Confidence: 0.930190308

00:35:23.226 --> 00:35:26.187 due to the lack of suitable small

NOTE Confidence: 0.930190308

00:35:26.187 --> 00:35:29.008 molecule binding pockets and therefore

NOTE Confidence: 0.930190308

00:35:29.008 --> 00:35:32.572 this Tf's cannot be targeted by

NOTE Confidence: 0.930190308

00:35:32.572 --> 00:35:35.620 the traditional pro tech approach.

NOTE Confidence: 0.930190308

00:35:35.620 --> 00:35:39.990 So to target and druggable oncogenic

NOTE Confidence: 0.930190308

00:35:39.990 --> 00:35:43.650 Tf's Weiwei's lab at Howard Medical

NOTE Confidence: 0.930190308

00:35:43.650 --> 00:35:48.279 School and my lab developed TF pro tech.

NOTE Confidence: 0.930190308

00:35:48.280 --> 00:35:52.036 By conjugating a DNA oligar nucleotide

NOTE Confidence: 0.930190308

00:35:52.040 --> 00:35:55.785 which is specific to the TF of

NOTE Confidence: 0.930190308

00:35:55.785 --> 00:35:58.280 interest to a ESV ligas ligand,

NOTE Confidence: 0.930190308

00:35:58.280 --> 00:36:00.200 in this case VHL ligand,

NOTE Confidence: 0.930190308

00:36:00.200 --> 00:36:02.460 where a click action,

NOTE Confidence: 0.930190308

00:36:02.460 --> 00:36:06.494 so the resulting DNA oligar nucleotide and

NOTE Confidence: 0.930190308

00:36:06.494 --> 00:36:09.293 and VHL ligand conjugates simultaneously

NOTE Confidence: 0.930190308

00:36:09.293 --> 00:36:14.197 binds the TF of interest and the VHL

NOTE Confidence: 0.930190308

00:36:14.197 --> 00:36:17.436 ESV ligas this induced proximity.

NOTE Confidence: 0.930190308

00:36:17.436 --> 00:36:20.044 Leads to selective ubiquitation

NOTE Confidence: 0.930190308

00:36:20.044 --> 00:36:23.815 of the TF of interest and its

NOTE Confidence: 0.930190308

00:36:23.815 --> 00:36:25.787 subsequent degradation at Prozone.

NOTE Confidence: 0.930190308

00:36:25.790 --> 00:36:29.198 So we have we developed a 2 proof

NOTE Confidence: 0.930190308

00:36:29.198 --> 00:36:32.699 concept TF protects which effectively

NOTE Confidence: 0.930190308

00:36:32.699 --> 00:36:36.430 degraded NF Kappa B&E to F respectively.

NOTE Confidence: 0.917806314166667

00:36:38.870 --> 00:36:42.150 And we are not the only group developed

NOTE Confidence: 0.917806314166667

00:36:42.150 --> 00:36:45.888 the TF protect technology and in fact.

NOTE Confidence: 0.917806314166667

00:36:45.888 --> 00:36:47.722 Three papers, including ours,

NOTE Confidence: 0.917806314166667

00:36:47.722 --> 00:36:52.080 were published around the same time in 2021,

NOTE Confidence: 0.917806314166667

00:36:52.080 --> 00:36:56.140 and so this Craig Ku's Trav

NOTE Confidence: 0.917806314166667

00:36:56.140 --> 00:36:58.940 Tech paper describing A keynote

NOTE Confidence: 0.917806314166667

00:36:58.940 --> 00:37:00.928 A chemo genetic approach,

NOTE Confidence: 0.917806314166667

00:37:00.928 --> 00:37:03.500 was published first, and then this

NOTE Confidence: 0.845030619090909

00:37:05.700 --> 00:37:08.647 this paper on a legal protag by

NOTE Confidence: 0.845030619090909

00:37:08.647 --> 00:37:12.508 Hao JF One's lab and was published

NOTE Confidence: 0.845030619090909

00:37:12.508 --> 00:37:16.592 in advance Advanced Science.

NOTE Confidence: 0.845030619090909

00:37:16.592 --> 00:37:19.200 In shortly after our papers

NOTE Confidence: 0.845030619090909

00:37:19.200 --> 00:37:20.500 was published in Jax,

NOTE Confidence: 0.943128857142857

00:37:22.540 --> 00:37:25.774 So similar to the TF protag approach,

NOTE Confidence: 0.943128857142857

00:37:25.780 --> 00:37:29.784 Weiwei's lab and my lab also developed

NOTE Confidence: 0.943128857142857

00:37:29.784 --> 00:37:34.140 TF dub tech as a general platform

NOTE Confidence: 0.943128857142857

00:37:34.140 --> 00:37:37.384 for stabilizing and drugable tumors

NOTE Confidence: 0.943128857142857

00:37:37.384 --> 00:37:40.404 suppressive Tf's by hijacking a

NOTE Confidence: 0.943128857142857

00:37:40.404 --> 00:37:44.060 deal pickiness a dub so briefly.

NOTE Confidence: 0.943128857142857

00:37:44.060 --> 00:37:47.160 We conjugated ADNL organ nucleotide,

NOTE Confidence: 0.943128857142857

00:37:47.160 --> 00:37:49.960 which is specific to the target TF,

NOTE Confidence: 0.943128857142857

00:37:49.960 --> 00:37:53.480 to a small molecule ligand of a deopinase,

NOTE Confidence: 0.943128857142857

00:37:53.480 --> 00:37:58.795 a DUB, in this case OTU B1 ligand which was

NOTE Confidence: 0.943128857142857

00:37:58.795 --> 00:38:01.360 previously developed by Danny Morris lab.

NOTE Confidence: 0.943128857142857

00:38:01.360 --> 00:38:03.796 We are a click a click reaction,

NOTE Confidence: 0.943128857142857

00:38:03.800 --> 00:38:07.892 so this resulting DNA organ

NOTE Confidence: 0.943128857142857

00:38:07.892 --> 00:38:11.422 nucleotide OTU B1 ligand conjugate

NOTE Confidence: 0.943128857142857

00:38:11.422 --> 00:38:13.436 simultaneously binds that.

NOTE Confidence: 0.943128857142857

00:38:13.436 --> 00:38:17.608 Target TF and the OTV one dub.

NOTE Confidence: 0.943128857142857

00:38:17.610 --> 00:38:21.175 This induced proximity lead to

NOTE Confidence: 0.943128857142857

00:38:21.175 --> 00:38:25.533 selective deuption of the target TF

NOTE Confidence: 0.943128857142857

00:38:25.533 --> 00:38:28.581 and its stabilization and we have

NOTE Confidence: 0.943128857142857

00:38:28.581 --> 00:38:30.603 we developed the three proof concept

NOTE Confidence: 0.943128857142857

00:38:30.603 --> 00:38:33.434 TF dub packs which effectively

NOTE Confidence: 0.943128857142857

00:38:33.434 --> 00:38:37.970 stabilized tumor suppressors FOX

NOTE Confidence: 0.943128857142857

00:38:37.970 --> 00:38:40.890 O3AP53 and IRF 3 respective.

NOTE Confidence: 0.941801815384615

00:38:42.900 --> 00:38:46.281 So lastly, I'm just going to very

NOTE Confidence: 0.941801815384615

00:38:46.281 --> 00:38:49.099 briefly mention our Keep One work.

NOTE Confidence: 0.941801815384615

00:38:49.100 --> 00:38:51.680 As many of you know out

NOTE Confidence: 0.941801815384615

00:38:51.680 --> 00:38:54.180 of 600 plus E3 legacies,

NOTE Confidence: 0.941801815384615

00:38:54.180 --> 00:38:56.880 only very limited of them have

NOTE Confidence: 0.941801815384615

00:38:56.880 --> 00:38:59.219 been harnessed for targeted protein

NOTE Confidence: 0.941801815384615

00:38:59.219 --> 00:39:02.425 degradation with the CRBN and we gel

NOTE Confidence: 0.941801815384615

00:39:02.425 --> 00:39:04.740 being utilized most extensively.

NOTE Confidence: 0.941801815384615

00:39:04.740 --> 00:39:07.732 So we demonstrated the Call 3 E 3

NOTE Confidence: 0.941801815384615

00:39:07.732 --> 00:39:11.233 like us Keep 1, can be harnessed.

NOTE Confidence: 0.941801815384615

00:39:11.233 --> 00:39:15.410 For protective element by using

NOTE Confidence: 0.941801815384615

00:39:15.410 --> 00:39:18.295 potent selective and non covalent

NOTE Confidence: 0.941801815384615

00:39:18.295 --> 00:39:21.190 ligand of keep one which was

NOTE Confidence: 0.941801815384615

00:39:21.190 --> 00:39:23.365 previously developed by Glaxosmus 1.

NOTE Confidence: 0.941801815384615

00:39:23.370 --> 00:39:24.210 So we developed

NOTE Confidence: 0.950317

00:39:26.690 --> 00:39:29.922 MS-83 approved concept Keep one

NOTE Confidence: 0.950317

00:39:29.922 --> 00:39:31.904 recruiting PRD three, PRD 4,

NOTE Confidence: 0.950317

00:39:31.904 --> 00:39:35.173 Protech which degraded PRD four and PRD

NOTE Confidence: 0.950317

00:39:35.173 --> 00:39:38.698 three more durably than the well known.

NOTE Confidence: 0.950317

00:39:38.700 --> 00:39:42.410 BRD this well known CRB and recruiting

NOTE Confidence: 0.950317

00:39:42.410 --> 00:39:48.004 BRD 234 portag DBAT One MS-83 also have a

NOTE Confidence: 0.950317

00:39:48.004 --> 00:39:50.620 superior selectivity profile to dbat 1.

NOTE Confidence: 0.950317

00:39:50.620 --> 00:39:53.612 Interestingly, 83 selectively degraded

NOTE Confidence: 0.950317

00:39:53.612 --> 00:39:58.657 BRD 4 short isoform also over BRD

NOTE Confidence: 0.950317

00:39:58.657 --> 00:40:02.276 4 long isoform in MBA MB 231 cells.

NOTE Confidence: 0.950317

00:40:02.276 --> 00:40:05.489 So we hope this work expands.

NOTE Confidence: 0.950317

00:40:05.489 --> 00:40:08.404 The limited toolbox for targeted

NOTE Confidence: 0.950317

00:40:08.404 --> 00:40:09.570 protein degradation.

NOTE Confidence: 0.943128857142857

00:40:12.010 --> 00:40:15.209 So in addition to the bridged Protag,

NOTE Confidence: 0.943128857142857

00:40:15.210 --> 00:40:18.690 TF Protag and TF Dubtech technologies

NOTE Confidence: 0.943128857142857

00:40:18.690 --> 00:40:22.530 and the key point work I just mentioned,

NOTE Confidence: 0.943128857142857

00:40:22.530 --> 00:40:25.380 we in collaboration with Weiwei's lab

NOTE Confidence: 0.943128857142857

00:40:25.380 --> 00:40:29.050 also developed fully caged Protag and

NOTE Confidence: 0.943128857142857

00:40:29.050 --> 00:40:31.810 Optoprotag for selectively targeting cancer

NOTE Confidence: 0.943128857142857

00:40:31.810 --> 00:40:35.300 cells over normal cells and TeleTech.

NOTE Confidence: 0.943128857142857

00:40:35.300 --> 00:40:38.825 For selective devolution of telemeric

NOTE Confidence: 0.943128857142857

00:40:38.825 --> 00:40:42.764 binding of telemeric repeat binding factors,

NOTE Confidence: 0.943128857142857

00:40:42.764 --> 00:40:45.522 in collaboration with May Hathaway's lab at

NOTE Confidence: 0.943128857142857

00:40:45.522 --> 00:40:48.166 University of North Carolina at Chapel Hill,

NOTE Confidence: 0.943128857142857

00:40:48.170 --> 00:40:53.322 we also developed a chemo genetic based hydro

NOTE Confidence: 0.943128857142857

00:40:53.322 --> 00:40:56.129 bifunctional deaccillators and accillators.

NOTE Confidence: 0.943128857142857

00:40:56.130 --> 00:40:57.648 And in the interest of time,

NOTE Confidence: 0.943128857142857

00:40:57.650 --> 00:41:01.290 I will not talk about this work today.

NOTE Confidence: 0.943128857142857

00:41:01.290 --> 00:41:02.550 So with that.

NOTE Confidence: 0.943128857142857

00:41:02.550 --> 00:41:04.650 I thank all our collaborators

NOTE Confidence: 0.943128857142857

00:41:04.650 --> 00:41:06.680 for their contributions,

NOTE Confidence: 0.943128857142857

00:41:06.680 --> 00:41:11.117 in particularly Greg Wong and his lab at UNC,

NOTE Confidence: 0.943128857142857

00:41:11.120 --> 00:41:14.765 a new AGUA slab at Mount Sinai and Alan

NOTE Confidence: 0.943128857142857

00:41:14.765 --> 00:41:19.224 Tarka's lab at Arkansas for the WDR 5

NOTE Confidence: 0.943128857142857

00:41:19.224 --> 00:41:22.832 Protect work and Ramon Parson's lab,

NOTE Confidence: 0.943128857142857

00:41:22.832 --> 00:41:25.525 Samir Parak Lab and Anas Gusiani's

NOTE Confidence: 0.943128857142857

00:41:25.525 --> 00:41:28.565 lab at Mount Sinai for the easy

NOTE Confidence: 0.943128857142857

00:41:28.565 --> 00:41:30.306 H2 DEGRADER MS1943 work.

NOTE Confidence: 0.943128857142857

00:41:30.306 --> 00:41:33.477 And Greg Wang's lab and Ling Tai's

NOTE Confidence: 0.943128857142857

00:41:33.477 --> 00:41:36.690 lab at UNC for the easy to protect

NOTE Confidence: 0.943128857142857

00:41:36.690 --> 00:41:41.386 MS177 work and you assume for at

NOTE Confidence: 0.943128857142857

00:41:41.386 --> 00:41:43.738 college and for for his help on

NOTE Confidence: 0.943128857142857

00:41:43.738 --> 00:41:46.330 the 2nd D1 bridge protect work.

NOTE Confidence: 0.943128857142857

00:41:46.330 --> 00:41:49.396 And of course when he and his

NOTE Confidence: 0.943128857142857

00:41:49.396 --> 00:41:52.169 lab members for the TI Protag,

NOTE Confidence: 0.943128857142857

00:41:52.170 --> 00:41:53.850 TF DUB Tag,

NOTE Confidence: 0.943128857142857

00:41:53.850 --> 00:41:57.210 TeleTech 40K H Protag and Optoprotag

NOTE Confidence: 0.943128857142857

00:41:57.210 --> 00:41:58.300 work and.

NOTE Confidence: 0.943128857142857

00:41:58.300 --> 00:42:02.136 Then Shan Chen and his lab for

NOTE Confidence: 0.943128857142857

00:42:02.136 --> 00:42:04.966 conducting pretty much all our

NOTE Confidence: 0.943128857142857

00:42:04.970 --> 00:42:08.810 mass back based proteomic studies.

NOTE Confidence: 0.943128857142857

00:42:08.810 --> 00:42:12.218 So I also thank my current and former

NOTE Confidence: 0.943128857142857

00:42:12.218 --> 00:42:15.249 lab members for their contributions.

NOTE Confidence: 0.943128857142857

00:42:15.250 --> 00:42:17.326 So mention some of their names

NOTE Confidence: 0.943128857142857

00:42:17.326 --> 00:42:19.750 during the talk and thank funding

NOTE Confidence: 0.943128857142857

00:42:19.750 --> 00:42:22.050 agencies for the financial support.

NOTE Confidence: 0.943128857142857

00:42:22.050 --> 00:42:23.226 Last but not least,

NOTE Confidence: 0.943128857142857

00:42:23.226 --> 00:42:25.969 thank you very much for your kind attention.

NOTE Confidence: 0.943128857142857

00:42:25.970 --> 00:42:27.450 Happy to answer the questions you may have.

NOTE Confidence: 0.93824092

00:42:34.450 --> 00:42:37.010 I'm for a good question. Actually

NOTE Confidence: 0.9402536

00:42:40.650 --> 00:42:41.610 I'm curious to

NOTE Confidence: 0.9553487

00:42:45.210 --> 00:42:46.650 be mentioned

NOTE Confidence: 0.9352219

00:42:50.650 --> 00:42:50.930 with the

NOTE Confidence: 0.2866596

00:42:57.570 --> 00:42:58.170 pro that.

NOTE Confidence: 0.944566485714286

00:43:07.940 --> 00:43:10.978 Right. And Don that's a great question.

NOTE Confidence: 0.944566485714286

00:43:10.980 --> 00:43:16.260 The the, the new substrate issues

NOTE Confidence: 0.944566485714286

00:43:16.260 --> 00:43:20.298 if if you like all opportunity,

NOTE Confidence: 0.944566485714286

00:43:20.300 --> 00:43:23.751 it's mainly through the CRBN ligands

NOTE Confidence: 0.944566485714286

00:43:23.751 --> 00:43:26.908 of the the CRBN history like this

NOTE Confidence: 0.944566485714286

00:43:26.908 --> 00:43:30.010 and to date the no new substrates

NOTE Confidence: 0.944566485714286

00:43:30.010 --> 00:43:32.260 have been identified for VHL.

NOTE Confidence: 0.944566485714286

00:43:32.260 --> 00:43:34.910 And so, so therefore we

NOTE Confidence: 0.944566485714286

00:43:34.910 --> 00:43:36.500 shall recruiting protects.

NOTE Confidence: 0.944566485714286

00:43:36.500 --> 00:43:39.348 So far we have not seen the new

NOTE Confidence: 0.944566485714286

00:43:39.348 --> 00:43:42.316 substrate issue and having said

NOTE Confidence: 0.944566485714286

00:43:42.316 --> 00:43:45.395 that the I should know that more

NOTE Confidence: 0.944566485714286

00:43:45.395 --> 00:43:47.462 than 20 protects have been advanced

NOTE Confidence: 0.944566485714286

00:43:47.462 --> 00:43:50.504 to clinical trials all but one

NOTE Confidence: 0.944566485714286

00:43:50.504 --> 00:43:53.209 are CRBN recruiting compost. OK.

NOTE Confidence: 0.944566485714286

00:43:53.209 --> 00:43:55.303 So therefore in those cases the

NOTE Confidence: 0.944566485714286

00:43:55.303 --> 00:43:57.581 new substrates of the CRBN really

NOTE Confidence: 0.944566485714286

00:43:57.581 --> 00:43:59.521 need to be carefully monitored

NOTE Confidence: 0.944566485714286

00:43:59.521 --> 00:44:01.382 and actually to to this day.

NOTE Confidence: 0.944566485714286

00:44:01.382 --> 00:44:03.440 And new new substrates of the CRBN

NOTE Confidence: 0.944566485714286

00:44:03.508 --> 00:44:05.462 are still being discovered, OK.

NOTE Confidence: 0.944566485714286

00:44:05.462 --> 00:44:07.296 So that the field really need to

NOTE Confidence: 0.944566485714286

00:44:07.296 --> 00:44:08.855 watch that carefully but like

NOTE Confidence: 0.944566485714286

00:44:08.855 --> 00:44:10.640 you said on the other hand we

NOTE Confidence: 0.944566485714286

00:44:10.640 --> 00:44:12.595 could have turned this around and

NOTE Confidence: 0.944566485714286

00:44:12.595 --> 00:44:14.725 use this as opportunity and two

NOTE Confidence: 0.944566485714286

00:44:14.725 --> 00:44:16.277 actually generated potentially more

NOTE Confidence: 0.944566485714286

00:44:16.277 --> 00:44:17.997 effective anti cancer therapeutics,

NOTE Confidence: 0.915551049310344

00:44:25.000 --> 00:44:27.359 all right. So that part of we

NOTE Confidence: 0.915551049310344

00:44:27.359 --> 00:44:29.987 child part of that I I don't but

NOTE Confidence: 0.915551049310344

00:44:29.987 --> 00:44:32.313 for the CRBN part of it really

NOTE Confidence: 0.915551049310344

00:44:32.313 --> 00:44:34.812 is the CRBN ligand and and the.

NOTE Confidence: 0.915551049310344

00:44:34.820 --> 00:44:37.172 It kind of pretty promiscuous and doesn't

NOTE Confidence: 0.915551049310344

00:44:37.172 --> 00:44:39.380 matter actually what linker you put it in.

NOTE Confidence: 0.915551049310344

00:44:39.380 --> 00:44:41.140 It still binds to crbn,

NOTE Confidence: 0.915551049310344

00:44:41.140 --> 00:44:43.807 but the because the linker will change

NOTE Confidence: 0.915551049310344

00:44:43.807 --> 00:44:46.876 a little bit that lead to actually

NOTE Confidence: 0.915551049310344

00:44:46.876 --> 00:44:48.848 different new substrate got degraded.

NOTE Confidence: 0.915551049310344

00:44:48.848 --> 00:44:51.668 So we do Actually we have pretty

NOTE Confidence: 0.915551049310344

00:44:51.668 --> 00:44:54.058 good understanding how to change

NOTE Confidence: 0.915551049310344

00:44:54.058 --> 00:44:56.244 linkers to eliminate the.

NOTE Confidence: 0.915551049310344

00:44:56.244 --> 00:45:00.696 Let's see the IKCF one and three degradation.

NOTE Confidence: 0.915551049310344

00:45:00.696 --> 00:45:04.028 Oh how to eliminate GSPT 1 degradation.

NOTE Confidence: 0.915551049310344

00:45:04.030 --> 00:45:07.096 And but if you want to incorporate

NOTE Confidence: 0.915551049310344

00:45:07.096 --> 00:45:10.509 some of the new substrate into in

NOTE Confidence: 0.915551049310344

00:45:10.510 --> 00:45:12.898 addition to the devolution of your

NOTE Confidence: 0.915551049310344

00:45:12.898 --> 00:45:15.166 target protein in that case and

NOTE Confidence: 0.915551049310344

00:45:15.166 --> 00:45:17.310 more linker exploration is needed.

NOTE Confidence: 0.42692143

00:45:57.180 --> 00:45:57.340 Akshay.

NOTE Confidence: 0.616956

00:46:21.820 --> 00:46:23.300 Thank you.

NOTE Confidence: 0.898283401666667

00:46:32.220 --> 00:46:34.140 Right. That's a great question also.

NOTE Confidence: 0.898283401666667

00:46:34.140 --> 00:46:36.453 So let me kind of it's a loaded question.

NOTE Confidence: 0.898283401666667

00:46:36.460 --> 00:46:39.126 Let me try to answer 1 by 1. OK, right.

NOTE Confidence: 0.898283401666667

00:46:39.126 --> 00:46:41.614 So first about MS-40, OK, right.

NOTE Confidence: 0.898283401666667

00:46:41.614 --> 00:46:43.973 Then we're going to talk about the

NOTE Confidence: 0.898283401666667

00:46:43.980 --> 00:46:47.142 selectivity of the resistance, OK, right.

NOTE Confidence: 0.898283401666667

00:46:47.142 --> 00:46:52.476 The the MS-40 uses selective WDR 5

NOTE Confidence: 0.898283401666667

00:46:52.476 --> 00:46:56.580 binder as a moiety, as a binder of WD-5.

NOTE Confidence: 0.898283401666667

00:46:56.580 --> 00:47:00.780 So the parent inhibitor does not inhibit.

NOTE Confidence: 0.898283401666667

00:47:00.780 --> 00:47:03.090 Lead to degradation of the CRBN

NOTE Confidence: 0.898283401666667

00:47:03.090 --> 00:47:05.339 new substrate IKZF 1:00 and 3:00.

NOTE Confidence: 0.898283401666667

00:47:05.340 --> 00:47:08.100 So this the degradation of IKZF

NOTE Confidence: 0.898283401666667

00:47:08.100 --> 00:47:11.537 1/3 only happened to WDR 5 degrader

NOTE Confidence: 0.898283401666667

00:47:11.537 --> 00:47:15.366 not WDR 5 inhibitor. OK all right.

NOTE Confidence: 0.898283401666667

00:47:15.366 --> 00:47:18.489 So that that because the the compound it

NOTE Confidence: 0.898283401666667

00:47:18.489 --> 00:47:21.425 does not bind to the the the inhibitor

NOTE Confidence: 0.898283401666667

00:47:21.425 --> 00:47:23.420 portion the does not bind to CRBN.

NOTE Confidence: 0.898283401666667

00:47:23.420 --> 00:47:24.050 OK, right.

NOTE Confidence: 0.898283401666667

00:47:24.050 --> 00:47:26.570 So that that that that part is that

NOTE Confidence: 0.898283401666667

00:47:26.639 --> 00:47:28.900 that is so you know you're right.

NOTE Confidence: 0.898283401666667

00:47:28.900 --> 00:47:30.355 I mean the.

NOTE Confidence: 0.898283401666667

00:47:30.355 --> 00:47:33.956 And and in this case the degraders

NOTE Confidence: 0.898283401666667

00:47:33.956 --> 00:47:37.484 could be actually so so-called less

NOTE Confidence: 0.898283401666667

00:47:37.484 --> 00:47:40.540 selective than the inhibitor because the

NOTE Confidence: 0.898283401666667

00:47:40.540 --> 00:47:43.360 the degrader degrades the new substrate

NOTE Confidence: 0.898283401666667

00:47:43.433 --> 00:47:46.504 of CRBN which inhibitor does not, OK right.

NOTE Confidence: 0.898283401666667

00:47:46.504 --> 00:47:49.580 But on the other hand the I

NOTE Confidence: 0.898283401666667

00:47:49.580 --> 00:47:51.020 just want to point it out,

NOTE Confidence: 0.898283401666667

00:47:51.020 --> 00:47:53.810 the degraders sometimes actually could

NOTE Confidence: 0.898283401666667

00:47:53.810 --> 00:47:57.540 be much more selective than inhibitor.

NOTE Confidence: 0.898283401666667

00:47:57.540 --> 00:47:59.976 Let's see the in the cases.

NOTE Confidence: 0.898283401666667

00:47:59.980 --> 00:48:02.200 We have a multiple isoforms

NOTE Confidence: 0.898283401666667

00:48:02.200 --> 00:48:03.976 of a multiple subtypes,

NOTE Confidence: 0.898283401666667

00:48:03.980 --> 00:48:06.176 for example cilicate four and six.

NOTE Confidence: 0.898283401666667

00:48:06.180 --> 00:48:09.100 OK As you know the that D

NOTE Confidence: 0.898283401666667

00:48:09.100 --> 00:48:10.300 approved drugs polycyclip,

NOTE Confidence: 0.898283401666667

00:48:10.300 --> 00:48:12.060 ribocyclip and a bamocyclip.

NOTE Confidence: 0.898283401666667

00:48:12.060 --> 00:48:14.700 They all have a similar potency

NOTE Confidence: 0.898283401666667

00:48:14.773 --> 00:48:16.458 for cilicate 4 and six.

NOTE Confidence: 0.898283401666667

00:48:16.460 --> 00:48:19.668 OK but but using the same the ligand

NOTE Confidence: 0.898283401666667

00:48:19.668 --> 00:48:22.973 which bind to cilicate 4/6 with same

NOTE Confidence: 0.898283401666667

00:48:22.973 --> 00:48:25.260 affinity but the cilicate 46 degraders,

NOTE Confidence: 0.898283401666667

00:48:25.260 --> 00:48:27.690 the degraders can actually achieve

NOTE Confidence: 0.898283401666667

00:48:27.690 --> 00:48:30.120 selective degradation of cilicate 4.

NOTE Confidence: 0.898283401666667

00:48:30.120 --> 00:48:32.800 Over 6 and vice versa.

NOTE Confidence: 0.898283401666667

00:48:32.800 --> 00:48:35.554 Mainly it's because not so much of A binding,

NOTE Confidence: 0.898283401666667

00:48:35.560 --> 00:48:38.600 but the binding is the it's one event.

NOTE Confidence: 0.898283401666667

00:48:38.600 --> 00:48:40.412 But the second event is a

NOTE Confidence: 0.898283401666667

00:48:40.412 --> 00:48:41.318 ternary complex formation.

NOTE Confidence: 0.898283401666667

00:48:41.320 --> 00:48:43.714 OK, so then the so the degrader,

NOTE Confidence: 0.898283401666667

00:48:43.720 --> 00:48:45.350 this ternary complex formation and

NOTE Confidence: 0.898283401666667

00:48:45.350 --> 00:48:47.520 whether or not the license residues,

NOTE Confidence: 0.898283401666667

00:48:47.520 --> 00:48:49.310 appropriate license residues on the

NOTE Confidence: 0.898283401666667

00:48:49.310 --> 00:48:52.260 target 14 in this case city four and

NOTE Confidence: 0.898283401666667

00:48:52.260 --> 00:48:54.075 six are available for eucalation,

NOTE Confidence: 0.898283401666667

00:48:54.080 --> 00:48:56.380 give you basically another dimension

NOTE Confidence: 0.898283401666667

00:48:56.380 --> 00:48:57.760 to achieve selectivity.

NOTE Confidence: 0.898283401666667

00:48:57.760 --> 00:49:01.440 So people have achieved selectivity that way.

NOTE Confidence: 0.898283401666667

00:49:01.440 --> 00:49:04.240 Even you have a ligand bind to

NOTE Confidence: 0.898283401666667

00:49:04.240 --> 00:49:06.400 the isoforms of the subtypes of

NOTE Confidence: 0.898283401666667

00:49:06.400 --> 00:49:07.840 proteins with same affinity,

NOTE Confidence: 0.898283401666667

00:49:07.840 --> 00:49:10.408 you can achieve selective degradation of

NOTE Confidence: 0.898283401666667

00:49:10.408 --> 00:49:13.159 1 particular isoform over other isoforms.

NOTE Confidence: 0.898283401666667

00:49:13.160 --> 00:49:14.376 OK, right.

NOTE Confidence: 0.898283401666667

00:49:14.376 --> 00:49:18.632 So then in terms of drug resistance,

NOTE Confidence: 0.898283401666667

00:49:18.640 --> 00:49:19.970 the.

NOTE Confidence: 0.898283401666667

00:49:19.970 --> 00:49:22.160 The as you know the kines

NOTE Confidence: 0.898283401666667

00:49:22.160 --> 00:49:24.654 inhabitation OF646 inhabit the

NOTE Confidence: 0.898283401666667

00:49:24.654 --> 00:49:27.996 drug resistance have been observed

NOTE Confidence: 0.898283401666667

00:49:27.996 --> 00:49:30.526 in clinical in clinical setting.

NOTE Confidence: 0.898283401666667

00:49:30.530 --> 00:49:35.082 And the I mean whether or not the

NOTE Confidence: 0.898283401666667

00:49:35.082 --> 00:49:37.036 drug distance going to happen to the

NOTE Confidence: 0.898283401666667

00:49:37.036 --> 00:49:39.506 protests is remain to be seen and in a

NOTE Confidence: 0.898283401666667

00:49:39.506 --> 00:49:41.682 clinical setting so far have not been seen.

NOTE Confidence: 0.898283401666667

00:49:41.690 --> 00:49:44.630 And part part of the reason for

NOTE Confidence: 0.898283401666667

00:49:44.630 --> 00:49:47.514 that is the the binding of the

NOTE Confidence: 0.898283401666667

00:49:47.514 --> 00:49:49.544 protect to the target protein.

NOTE Confidence: 0.898283401666667

00:49:49.550 --> 00:49:51.185 And the that binary requirement

NOTE Confidence: 0.898283401666667

00:49:51.185 --> 00:49:53.491 of the high affinity is not it's

NOTE Confidence: 0.898283401666667

00:49:53.491 --> 00:49:55.612 not very stringent as long as the

NOTE Confidence: 0.898283401666667

00:49:55.612 --> 00:49:57.708 compound binds somewhat even with you,

NOTE Confidence: 0.898283401666667

00:49:57.710 --> 00:50:01.310 you have a lose lost the binary affinity

NOTE Confidence: 0.850175642

00:50:01.310 --> 00:50:02.302 tenfold, twentyfold,

NOTE Confidence: 0.850175642

00:50:02.302 --> 00:50:04.286 thirtyfold you still could

NOTE Confidence: 0.850175642

00:50:04.286 --> 00:50:06.270 lead to selective declaration.

NOTE Confidence: 0.850175642

00:50:06.270 --> 00:50:09.510 OK, right. And having said that,

NOTE Confidence: 0.850175642

00:50:09.510 --> 00:50:11.925 people have done in the

NOTE Confidence: 0.850175642

00:50:11.925 --> 00:50:13.374 laboratory setting observed.

NOTE Confidence: 0.850175642

00:50:13.380 --> 00:50:16.004 The resistance to degraders,

NOTE Confidence: 0.850175642

00:50:16.004 --> 00:50:17.960 OK and kind of initial

NOTE Confidence: 0.850175642

00:50:17.960 --> 00:50:19.260 report kind of interesting.

NOTE Confidence: 0.850175642

00:50:19.260 --> 00:50:21.530 The resistance happened actually not

NOTE Confidence: 0.850175642

00:50:21.530 --> 00:50:25.100 as it's not a point mutation in the

NOTE Confidence: 0.850175642

00:50:25.100 --> 00:50:26.780 binding pocket of your target protein,

NOTE Confidence: 0.850175642

00:50:26.780 --> 00:50:28.830 but actually rather is the

NOTE Confidence: 0.850175642

00:50:28.830 --> 00:50:31.440 done regulation of the E3

NOTE Confidence: 0.850175642

00:50:31.440 --> 00:50:33.894 like this complex component.

NOTE Confidence: 0.850175642

00:50:33.894 --> 00:50:37.116 OK, so people have observed done

NOTE Confidence: 0.850175642

00:50:37.116 --> 00:50:40.016 regulation of call 2 and call 4 for

NOTE Confidence: 0.850175642

00:50:40.020 --> 00:50:42.580 HL&CRB and including compounds respected.

NOTE Confidence: 0.9402536

00:51:04.110 --> 00:51:04.812 That's great question.

NOTE Confidence: 0.9402536

00:51:04.812 --> 00:51:06.909 I would love to test that we have not.

NOTE Confidence: 0.9402536

00:51:06.910 --> 00:51:08.382 We tested in the cell lines in the

NOTE Confidence: 0.9402536

00:51:08.382 --> 00:51:10.628 graph bottle, but not a PDX model and.

NOTE Confidence: 0.802513427777778

00:51:14.420 --> 00:51:16.526 Yeah, we tested as a single

NOTE Confidence: 0.802513427777778

00:51:16.526 --> 00:51:18.480 agent in the cell lines model,

NOTE Confidence: 0.802513427777778

00:51:18.480 --> 00:51:20.580 but not as not in the PDX.

NOTE Confidence: 0.802513427777778

00:51:20.580 --> 00:51:23.184 And also the probably would be in

NOTE Confidence: 0.802513427777778

00:51:23.184 --> 00:51:25.979 addition to PDX probably test in the.

NOTE Confidence: 0.941691228571429

00:51:28.810 --> 00:51:31.246 Not, not in the e-mail compromised mice.

NOTE Confidence: 0.941691228571429

00:51:31.250 --> 00:51:33.530 Let's see just you know regular mouse models,

NOTE Confidence: 0.941691228571429

00:51:33.530 --> 00:51:36.260 syngenate mouse models probably could also

NOTE Confidence: 0.941691228571429

00:51:36.260 --> 00:51:38.650 see some potential additional benefit.

NOTE Confidence: 0.941691228571429

00:51:38.650 --> 00:51:41.380 As you know is issue also actually

NOTE Confidence: 0.941691228571429

00:51:41.380 --> 00:51:43.453 involved e-mail response and there's

NOTE Confidence: 0.941691228571429

00:51:43.453 --> 00:51:45.455 number of reports actually either

NOTE Confidence: 0.941691228571429

00:51:45.455 --> 00:51:47.405 inhibition of user two or declaration

NOTE Confidence: 0.941691228571429

00:51:47.405 --> 00:51:50.066 of user two could lead to actually

NOTE Confidence: 0.941691228571429

00:51:50.066 --> 00:51:51.284 increased e-mail response.

NOTE Confidence: 0.941691228571429

00:51:51.290 --> 00:51:52.170 We have not done that.

NOTE Confidence: 0.94025356

00:52:22.880 --> 00:52:24.864 Yeah. And these are this.

NOTE Confidence: 0.94025356

00:52:24.864 --> 00:52:26.844 These are great questions and.

NOTE Confidence: 0.94025356

00:52:26.850 --> 00:52:30.464 We have not seen the the the over

NOTE Confidence: 0.94025356

00:52:30.464 --> 00:52:33.692 the amplification of the target and

NOTE Confidence: 0.94025356

00:52:33.692 --> 00:52:36.108 and the acid resistance mechanism

NOTE Confidence: 0.94025356

00:52:36.108 --> 00:52:39.967 so far and but it could well happen

NOTE Confidence: 0.94025356

00:52:39.967 --> 00:52:42.568 and and so as the bridge protect

NOTE Confidence: 0.94025356

00:52:42.568 --> 00:52:44.884 approach the ideal situation I mean

NOTE Confidence: 0.94025356

00:52:44.884 --> 00:52:47.662 we we here I showed you 2 proof

NOTE Confidence: 0.94025356

00:52:47.662 --> 00:52:49.730 concept studies and they are they

NOTE Confidence: 0.94025356

00:52:49.730 --> 00:52:51.830 look promising but they're not perfect

NOTE Confidence: 0.94025356

00:52:51.899 --> 00:52:54.305 right so the the the city of the

NOTE Confidence: 0.94025356

00:52:54.305 --> 00:52:56.590 cycling D1 degrade are still degrade.

NOTE Confidence: 0.94025356

00:52:56.590 --> 00:53:00.310 CDK 46 somewhat but it's a less definitely

NOTE Confidence: 0.94025356

00:53:00.310 --> 00:53:03.670 less than a second D1 and the the the

NOTE Confidence: 0.936659528571429

00:53:06.110 --> 00:53:08.294 MS147 the PRC one degrader it also

NOTE Confidence: 0.936659528571429

00:53:08.294 --> 00:53:10.149 degrade a little bit of the Ed.

NOTE Confidence: 0.936659528571429

00:53:10.150 --> 00:53:12.094 Ideally we would like to actually

NOTE Confidence: 0.936659528571429

00:53:12.094 --> 00:53:14.073 the bridge protect do not degrade

NOTE Confidence: 0.936659528571429

00:53:14.073 --> 00:53:15.945 the bridge protein OK if we

NOTE Confidence: 0.936659528571429

00:53:15.945 --> 00:53:17.750 don't degrade the bridge protein.

NOTE Confidence: 0.936659528571429

00:53:17.750 --> 00:53:22.202 So that may be actually potentially could

NOTE Confidence: 0.936659528571429

00:53:22.202 --> 00:53:25.368 actually for cells develop resistant to that.

NOTE Confidence: 0.936659528571429

00:53:25.370 --> 00:53:27.566 Maybe actually it's the last kind of a a,

NOTE Confidence: 0.936659528571429

00:53:27.570 --> 00:53:28.773 a opportunity there.

NOTE Confidence: 0.936659528571429

00:53:28.773 --> 00:53:31.580 I so we've been thinking about what

NOTE Confidence: 0.936659528571429

00:53:31.654 --> 00:53:33.462 would be a ideal bridge protein.

NOTE Confidence: 0.936659528571429

00:53:33.462 --> 00:53:36.619 So the a bridge protein ideally would be have

NOTE Confidence: 0.936659528571429

00:53:36.619 --> 00:53:39.290 like a kind of some kind of lessened desert.

NOTE Confidence: 0.936659528571429

00:53:39.290 --> 00:53:41.314 So basically you have a small molecule but

NOTE Confidence: 0.936659528571429

00:53:41.314 --> 00:53:43.211 this this protein have lessened desert

NOTE Confidence: 0.936659528571429

00:53:43.211 --> 00:53:45.110 actually does not get ubuccinated and

NOTE Confidence: 0.936659528571429

00:53:45.110 --> 00:53:46.650 and so therefore do not get degraded.

NOTE Confidence: 0.936659528571429

00:53:46.650 --> 00:53:49.513 So that would be we're we're actually

NOTE Confidence: 0.936659528571429

00:53:49.513 --> 00:53:51.758 working on that try to try to

NOTE Confidence: 0.936659528571429

00:53:51.758 --> 00:53:53.810 discover like a a a improved compost.

NOTE Confidence: 0.93421556

00:53:56.930 --> 00:53:59.769 Let me brief out that some type of

NOTE Confidence: 0.93421556

00:53:59.769 --> 00:54:02.090 patient to them in the pool, Silent

NOTE Confidence: 0.8120707

00:54:05.850 --> 00:54:06.010 room

NOTE Confidence: 0.87124155

00:54:08.090 --> 00:54:09.090 after the time.

NOTE Confidence: 0.9603804

00:54:11.170 --> 00:54:12.848 What's your generous study?

NOTE Confidence: 0.8998047

00:54:15.250 --> 00:54:18.320 Find, What's the letters?

NOTE Confidence: 0.8998047

00:54:18.320 --> 00:54:19.610 Whatever the study.

NOTE Confidence: 0.941930833333333

00:54:20.460 --> 00:54:22.260 Yeah, and it's a great question.

NOTE Confidence: 0.941930833333333

00:54:22.260 --> 00:54:25.596 I got to ask the the,

NOTE Confidence: 0.941930833333333

00:54:25.596 --> 00:54:29.576 the this is the really is actually it

NOTE Confidence: 0.941930833333333

00:54:29.576 --> 00:54:32.843 depends on the target and depend on the

NOTE Confidence: 0.941930833333333

00:54:32.843 --> 00:54:36.158 target We Chin and I have been working

NOTE Confidence: 0.941930833333333

00:54:36.158 --> 00:54:37.938 on his favorite target for a long time,

NOTE Confidence: 0.941930833333333

00:54:37.940 --> 00:54:42.580 a long time. And on the other hand the,

NOTE Confidence: 0.941930833333333

00:54:42.580 --> 00:54:47.140 I mean for the WD R5 and the AKT

NOTE Confidence: 0.941930833333333

00:54:47.140 --> 00:54:49.556 or CD46 Protax, I didn't.

NOTE Confidence: 0.941930833333333

00:54:49.556 --> 00:54:50.980 The AKT and four,

NOTE Confidence: 0.941930833333333

00:54:50.980 --> 00:54:53.584 six protects I didn't talk about today in

NOTE Confidence: 0.941930833333333

00:54:53.584 --> 00:54:56.496 those cases in the first round of compounds,

NOTE Confidence: 0.941930833333333

00:54:56.500 --> 00:54:59.940 let's see first a a few dozen compounds,

NOTE Confidence: 0.941930833333333

00:54:59.940 --> 00:55:02.190 we already have a good hits, OK, right.

NOTE Confidence: 0.941930833333333

00:55:02.190 --> 00:55:03.900 Then as you continue to optimize,

NOTE Confidence: 0.941930833333333

00:55:03.900 --> 00:55:05.461 I mean the head rate actually is

NOTE Confidence: 0.941930833333333

00:55:05.461 --> 00:55:07.035 very high in those target you,

NOTE Confidence: 0.941930833333333

00:55:07.035 --> 00:55:09.075 you and the the when I see the

NOTE Confidence: 0.941930833333333

00:55:09.075 --> 00:55:11.351 initial run getting hits is not a

NOTE Confidence: 0.941930833333333

00:55:11.351 --> 00:55:13.140 single hit multiple compounds active,

NOTE Confidence: 0.941930833333333

00:55:13.140 --> 00:55:15.233 you see the trend of the SER

NOTE Confidence: 0.941930833333333

00:55:15.233 --> 00:55:16.650 point to you which.

NOTE Confidence: 0.941930833333333

00:55:16.650 --> 00:55:18.005 Linker links is likely favor

NOTE Confidence: 0.941930833333333

00:55:18.005 --> 00:55:19.430 those kind of things, right.

NOTE Confidence: 0.941930833333333

00:55:19.430 --> 00:55:22.430 But on the other hand we have like a

NOTE Confidence: 0.941930833333333

00:55:22.430 --> 00:55:24.726 some of other targets we have a case

NOTE Confidence: 0.941930833333333

00:55:24.726 --> 00:55:26.872 that's a lot worse than the the ones

NOTE Confidence: 0.941930833333333

00:55:26.872 --> 00:55:28.490 you're we've been working on many,

NOTE Confidence: 0.941930833333333

00:55:28.490 --> 00:55:29.146 many years.

NOTE Confidence: 0.941930833333333

00:55:29.146 --> 00:55:31.442 We're just having no heads what's that?

NOTE Confidence: 0.941930833333333

00:55:31.450 --> 00:55:32.602 OK, right.

NOTE Confidence: 0.941930833333333

00:55:32.602 --> 00:55:35.461 But you know we actually trying

NOTE Confidence: 0.941930833333333

00:55:35.461 --> 00:55:38.100 to now turn this around to use

NOTE Confidence: 0.941930833333333

00:55:38.185 --> 00:55:39.978 those as the bridge protein,

NOTE Confidence: 0.941930833333333

00:55:39.978 --> 00:55:42.590 OK because they don't get degraded, right.

NOTE Confidence: 0.941930833333333

00:55:42.590 --> 00:55:46.090 So if they can detect with our.

NOTE Confidence: 0.941930833333333

00:55:46.090 --> 00:55:48.130 Favored and drug protein, right.

NOTE Confidence: 0.941930833333333

00:55:48.130 --> 00:55:51.210 So therefore we we already have a rich

NOTE Confidence: 0.941930833333333

00:55:51.210 --> 00:55:54.220 protein which does not get degraded, right.

NOTE Confidence: 0.941930833333333

00:55:54.220 --> 00:55:56.810 So so it wears quite a bit.

NOTE Confidence: 0.941930833333333

00:55:56.810 --> 00:56:02.230 And then we we typically use a crystal

NOTE Confidence: 0.941930833333333

00:56:02.230 --> 00:56:05.310 structure of the binary complex to

NOTE Confidence: 0.941930833333333

00:56:05.310 --> 00:56:08.172 identify solving exposed region and we we,

NOTE Confidence: 0.941930833333333

00:56:08.172 --> 00:56:09.859 I mean we try to do modeling

NOTE Confidence: 0.941930833333333

00:56:09.859 --> 00:56:12.209 and so far the modeling of the

NOTE Confidence: 0.941930833333333

00:56:12.209 --> 00:56:14.105 ternary complex formation is quite

NOTE Confidence: 0.941930833333333

00:56:14.105 --> 00:56:16.130 difficult and so to this stage.

NOTE Confidence: 0.941930833333333

00:56:16.130 --> 00:56:17.090 The example I showed you,

NOTE Confidence: 0.941930833333333

00:56:17.090 --> 00:56:20.570 the WDF 5, we have two high

NOTE Confidence: 0.941930833333333

00:56:20.570 --> 00:56:21.890 revolution crystal structures,

NOTE Confidence: 0.941930833333333

00:56:21.890 --> 00:56:22.330 right?

NOTE Confidence: 0.941930833333333

00:56:22.330 --> 00:56:24.472 So the first one really helped

NOTE Confidence: 0.941930833333333

00:56:24.472 --> 00:56:25.900 us tremendously to generating

NOTE Confidence: 0.941930833333333

00:56:25.963 --> 00:56:27.687 much more effective protects.

NOTE Confidence: 0.941930833333333

00:56:27.690 --> 00:56:28.990 Then we confirmed that

NOTE Confidence: 0.941930833333333

00:56:28.990 --> 00:56:30.290 using the second structure.

NOTE Confidence: 0.945285226666667

00:56:46.710 --> 00:56:48.150 Right. Yeah, it's a great question.

NOTE Confidence: 0.945285226666667

00:56:48.150 --> 00:56:52.122 Also just a general speaking,

NOTE Confidence: 0.945285226666667

00:56:52.122 --> 00:56:54.470 there are kind of two approaches, right.

NOTE Confidence: 0.945285226666667

00:56:54.470 --> 00:56:56.711 So the one approach we we do so this

NOTE Confidence: 0.945285226666667

00:56:56.711 --> 00:56:59.066 is in collaboration with Eva's lab,

NOTE Confidence: 0.945285226666667

00:56:59.070 --> 00:57:01.990 we call this controllable protects.

NOTE Confidence: 0.945285226666667

00:57:01.990 --> 00:57:06.120 So basically we make the protect but

NOTE Confidence: 0.945285226666667

00:57:06.120 --> 00:57:09.587 capped caged with a with a cage group.

NOTE Confidence: 0.945285226666667

00:57:09.590 --> 00:57:11.585 So the protect itself is not active,

NOTE Confidence: 0.945285226666667

00:57:11.590 --> 00:57:14.428 OK, right. So only when we.

NOTE Confidence: 0.945285226666667

00:57:14.430 --> 00:57:17.070 End cage that that by that

NOTE Confidence: 0.945285226666667

00:57:17.070 --> 00:57:21.330 can be by UV light or by some

NOTE Confidence: 0.945285226666667

00:57:21.330 --> 00:57:23.366 hopefully by hypoxic condition.

NOTE Confidence: 0.945285226666667

00:57:23.366 --> 00:57:24.222 OK. Right.

NOTE Confidence: 0.945285226666667

00:57:24.222 --> 00:57:26.790 So therefore our radiation OK right.

NOTE Confidence: 0.945285226666667

00:57:26.790 --> 00:57:30.076 So then the cage group is released

NOTE Confidence: 0.945285226666667

00:57:30.076 --> 00:57:32.638 or cleaved so now we have active

NOTE Confidence: 0.945285226666667

00:57:32.638 --> 00:57:34.548 protect and that can lead to

NOTE Confidence: 0.9343832325

00:57:36.950 --> 00:57:38.896 you know so, so then we can

NOTE Confidence: 0.9343832325

00:57:38.896 --> 00:57:40.527 basically turn on and off right

NOTE Confidence: 0.9343832325

00:57:40.527 --> 00:57:42.309 another way we've been doing it.

NOTE Confidence: 0.9343832325

00:57:42.310 --> 00:57:43.806 So part of the.

NOTE Confidence: 0.9343832325

00:57:43.806 --> 00:57:45.676 Controllable protag is we published

NOTE Confidence: 0.9343832325

00:57:45.676 --> 00:57:48.331 a couple of papers together with

NOTE Confidence: 0.9343832325

00:57:48.331 --> 00:57:51.628 many labs so-called Foley caged protag.

NOTE Confidence: 0.9343832325

00:57:51.628 --> 00:57:54.440 So basically again the protag

NOTE Confidence: 0.9343832325

00:57:54.440 --> 00:57:56.940 were caged with a Foley.

NOTE Confidence: 0.9343832325

00:57:56.940 --> 00:58:00.150 Foley Foley receptor are receptors

NOTE Confidence: 0.9343832325

00:58:00.150 --> 00:58:03.990 are overexpressed in cancer cells over

NOTE Confidence: 0.9343832325

00:58:03.990 --> 00:58:06.940 normal cells and binding of the Foley

NOTE Confidence: 0.9343832325

00:58:06.940 --> 00:58:09.850 group to the Foley receptor leads to

NOTE Confidence: 0.9343832325

00:58:09.850 --> 00:58:12.425 endocytosis of the entire molecule.

NOTE Confidence: 0.9343832325

00:58:12.430 --> 00:58:15.342 Then the that Foley that Foley cage

NOTE Confidence: 0.9343832325

00:58:15.342 --> 00:58:18.670 group is cleaved in the in the zone

NOTE Confidence: 0.9343832325

00:58:18.670 --> 00:58:20.910 release the active protect lead to

NOTE Confidence: 0.9343832325

00:58:20.910 --> 00:58:23.988 a degradation of a target protein.

NOTE Confidence: 0.9343832325

00:58:23.990 --> 00:58:26.590 OK so in cancer cells over normal cell.

NOTE Confidence: 0.9343832325

00:58:26.590 --> 00:58:28.780 So this kind of a controllable

NOTE Confidence: 0.9343832325

00:58:28.780 --> 00:58:29.510 protect approach.

NOTE Confidence: 0.9343832325

00:58:29.510 --> 00:58:32.326 Another way we've been a lot of

NOTE Confidence: 0.9343832325

00:58:32.326 --> 00:58:34.062 us are trying to do basically is

NOTE Confidence: 0.9343832325

00:58:34.062 --> 00:58:35.878 to find the targets of working

NOTE Confidence: 0.9343832325

00:58:35.878 --> 00:58:37.808 on the targets that are really.

NOTE Confidence: 0.9343832325

00:58:37.808 --> 00:58:40.316 Driving tumors or Tumogenesis are like

NOTE Confidence: 0.9343832325

00:58:40.316 --> 00:58:43.710 I mean the the critical for that but

NOTE Confidence: 0.9343832325

00:58:43.710 --> 00:58:46.830 it's non essential in normal cells

NOTE Confidence: 0.9343832325

00:58:46.830 --> 00:58:49.470 and and so one example is cycling D1.

NOTE Confidence: 0.9343832325

00:58:49.470 --> 00:58:51.640 Cycling D1 is non essential gene OK

NOTE Confidence: 0.9343832325

00:58:51.640 --> 00:58:53.997 normal cells do not care right So then

NOTE Confidence: 0.9343832325

00:58:53.997 --> 00:58:55.744 you you you really you completely

NOTE Confidence: 0.9343832325

00:58:55.744 --> 00:58:57.956 knock out of the 2nd D1 basically

NOTE Confidence: 0.9343832325

00:58:57.956 --> 00:59:00.525 have no feedback and so that that

NOTE Confidence: 0.9343832325

00:59:00.525 --> 00:59:03.761 and but cycling D1 is important in

NOTE Confidence: 0.9343832325

00:59:03.761 --> 00:59:06.706 Tumogenesis so therefore in this case.

NOTE Confidence: 0.9343832325

00:59:06.706 --> 00:59:08.938 We believe cycling D1 degrader would

NOTE Confidence: 0.9343832325

00:59:08.938 --> 00:59:11.067 have very good circuit window.

NOTE Confidence: 0.93421556

00:59:14.510 --> 00:59:15.670 We have not done that.

NOTE Confidence: 0.93421556

00:59:15.670 --> 00:59:17.070 People have done that, yes,

NOTE Confidence: 0.60941184

00:59:37.770 --> 00:59:37.890 yeah.

NOTE Confidence: 0.94629164

00:59:49.310 --> 00:59:51.310 Yeah those are great points.

NOTE Confidence: 0.94629164

00:59:51.310 --> 00:59:54.966 The just the the second point 1st and

NOTE Confidence: 0.94629164

00:59:54.966 --> 00:59:57.410 and actually protest can be actually the

NOTE Confidence: 0.94629164

00:59:57.410 --> 01:00:00.108 youth can the PGP substrates, OK, right.

NOTE Confidence: 0.94629164

01:00:00.108 --> 01:00:02.022 So some of them actually got

NOTE Confidence: 0.94629164

01:00:02.022 --> 01:00:03.919 Eflex after quite dramatically.

NOTE Confidence: 0.94629164

01:00:03.920 --> 01:00:05.915 And so then it really depends on,

NOTE Confidence: 0.94629164

01:00:05.920 --> 01:00:09.691 so the try to avoid the PGP substrate is

NOTE Confidence: 0.94629164

01:00:09.691 --> 01:00:12.193 important because otherwise you know the

NOTE Confidence: 0.94629164

01:00:12.200 --> 01:00:13.977 the molecules are already very big, right.

NOTE Confidence: 0.94629164

01:00:13.977 --> 01:00:15.279 Very difficult to get in cell.

NOTE Confidence: 0.94629164

01:00:15.280 --> 01:00:16.869 But if you even the small amount

NOTE Confidence: 0.94629164

01:00:16.869 --> 01:00:18.953 get in the cell got, if got, got,

NOTE Confidence: 0.94629164

01:00:18.953 --> 01:00:20.990 got if likes out then you really

NOTE Confidence: 0.94629164

01:00:21.062 --> 01:00:22.491 don't have a don't have active

NOTE Confidence: 0.94629164

01:00:22.491 --> 01:00:24.102 compost in the inside the cell, right.

NOTE Confidence: 0.94629164

01:00:24.102 --> 01:00:25.914 So that's that's kind of important.

NOTE Confidence: 0.94629164

01:00:25.920 --> 01:00:26.400 OK, right.

NOTE Confidence: 0.953061541818182

01:00:29.840 --> 01:00:31.211 It's great point.

NOTE Confidence: 0.953061541818182

01:00:31.211 --> 01:00:33.496 We actually currently working on

NOTE Confidence: 0.953061541818182

01:00:33.496 --> 01:00:35.614 this especially for a brain tumors,

NOTE Confidence: 0.953061541818182

01:00:35.614 --> 01:00:37.462 the protag's so big right make

NOTE Confidence: 0.953061541818182

01:00:37.462 --> 01:00:39.519 it already by available already

NOTE Confidence: 0.953061541818182

01:00:39.519 --> 01:00:41.624 difficult make it already by

NOTE Confidence: 0.953061541818182

01:00:41.624 --> 01:00:43.369 available and brain penetrant,

NOTE Confidence: 0.953061541818182

01:00:43.370 --> 01:00:44.990 it's almost impossible.

NOTE Confidence: 0.953061541818182

01:00:44.990 --> 01:00:47.690 OK, so therefore really using

NOTE Confidence: 0.953061541818182

01:00:47.690 --> 01:00:49.188 nanoparticle technologies to

NOTE Confidence: 0.953061541818182

01:00:49.188 --> 01:00:50.782 deliver protax to the brain,

NOTE Confidence: 0.953061541818182

01:00:50.782 --> 01:00:52.754 I think, I think that's kind

NOTE Confidence: 0.953061541818182

01:00:52.754 --> 01:00:54.250 of One Direction to go.

NOTE Confidence: 0.933544666666667

01:01:07.790 --> 01:01:08.999 Thanks a lot.