WEBVTT

NOTE duration:"00:52:10"

NOTE recognizability:0.835

NOTE language:en-us

NOTE Confidence: 0.877895235

00:00:00.000 --> 00:00:01.896 On behalf of my Co leader,

NOTE Confidence: 0.877895235

00:00:01.900 --> 00:00:03.348 Barbara Burtness and I,

NOTE Confidence: 0.877895235

00:00:03.348 --> 00:00:05.520 I'm pleased to introduce Bill Jorgensen,

NOTE Confidence: 0.877895235

00:00:05.520 --> 00:00:07.974 one of our developmental therapeutic program

NOTE Confidence: 0.877895235

00:00:07.974 --> 00:00:11.149 members and also my long term collaborator.

NOTE Confidence: 0.877895235

00:00:11.150 --> 00:00:13.850 Bill is a graduate of Princeton and Harvard,

NOTE Confidence: 0.877895235

00:00:13.850 --> 00:00:16.666 spent 15 years on the faculty at Purdue,

NOTE Confidence: 0.877895235

00:00:16.670 --> 00:00:19.148 and in 1990 he moved to Yale,

NOTE Confidence: 0.877895235

00:00:19.150 --> 00:00:21.150 where he's currently Sterling

NOTE Confidence: 0.877895235

00:00:21.150 --> 00:00:23.650 Professor in the Chemistry department.

NOTE Confidence: 0.877895235

00:00:23.650 --> 00:00:25.178 Bill is internationally recognized

NOTE Confidence: 0.877895235

00:00:25.178 --> 00:00:27.979 as one of the world leaders in

NOTE Confidence: 0.877895235

00:00:27.979 --> 00:00:30.189 computational chemistry and drug design.

NOTE Confidence: 0.877895235

00:00:30.190 --> 00:00:32.300 His research has been recognized

NOTE Confidence: 0.877895235

00:00:32.300 --> 00:00:33.566 by many honors,

NOTE Confidence: 0.877895235

00:00:33.570 --> 00:00:36.468 and among among those include the American

NOTE Confidence: 0.877895235

00:00:36.468 --> 00:00:38.689 Chemical Society Cope Scholar Award,

NOTE Confidence: 0.877895235

00:00:38.690 --> 00:00:41.540 the ACS Award for computers.

NOTE Confidence: 0.877895235

00:00:41.540 --> 00:00:44.060 Chemical and pharmaceutical research,

NOTE Confidence: 0.877895235

00:00:44.060 --> 00:00:46.580 the ACS Hildebrand Award,

NOTE Confidence: 0.877895235

00:00:46.580 --> 00:00:50.759 the ISTQB P award in computational biology,

NOTE Confidence: 0.877895235

00:00:50.760 --> 00:00:53.560 the Sato International Award from

NOTE Confidence: 0.877895235

00:00:53.560 --> 00:00:56.360 the Pharmaceutical Society of Japan.

NOTE Confidence: 0.877895235

00:00:56.360 --> 00:00:58.155 He's been elected to membership

NOTE Confidence: 0.877895235

00:00:58.155 --> 00:00:59.591 in the International Academy

NOTE Confidence: 0.877895235

00:00:59.591 --> 00:01:01.500 of Quantum Molecular Science,

NOTE Confidence: 0.877895235

00:01:01.500 --> 00:01:03.918 American Academy of Arts and Sciences,

NOTE Confidence: 0.877895235

00:01:03.920 --> 00:01:07.119 and the US National Academy of Sciences.

NOTE Confidence: 0.877895235

00:01:07.120 --> 00:01:08.832 Another recent honor in

NOTE Confidence: 0.877895235

00:01:08.832 --> 00:01:11.400 2020 includes one of the 16.

NOTE Confidence: 0.877895235

00:01:11.400 --> 00:01:15.138 Researchers selected for a Nobel Laureate

NOTE Confidence: 0.877895235

00:01:15.138 --> 00:01:17.630 Citation for individuals considered

NOTE Confidence: 0.877895235

00:01:17.720 --> 00:01:20.025 doing Nobel Nobel Class Research

NOTE Confidence: 0.877895235

00:01:20.025 --> 00:01:23.309 that has been cited over 2000 times.

NOTE Confidence: 0.877895235

00:01:23.310 --> 00:01:26.208 Today he's going to tell you a little bit

NOTE Confidence: 0.877895235

00:01:26.208 --> 00:01:28.869 about some of his work on SARS COVID 2.

NOTE Confidence: 0.877895235

00:01:28.870 --> 00:01:30.502 So without further ado,

NOTE Confidence: 0.877895235

00:01:30.502 --> 00:01:30.910 Bill,

NOTE Confidence: 0.877895235

00:01:30.910 --> 00:01:31.738 take it away.

NOTE Confidence: 0.885065780769231

00:01:33.030 --> 00:01:35.046 Yeah. Well, thank you very much

NOTE Confidence: 0.885065780769231

00:01:35.046 --> 00:01:37.078 Karen and the pleasure to be here

NOTE Confidence: 0.885065780769231

00:01:37.080 --> 00:01:38.856 the other side of the campus.

NOTE Confidence: 0.885065780769231

00:01:38.860 --> 00:01:41.713 So the our work I'll tell you about today

NOTE Confidence: 0.885065780769231

00:01:41.713 --> 00:01:44.512 is totally a collaboration between my

NOTE Confidence: 0.885065780769231

00:01:44.512 --> 00:01:47.271 research group and chemistry and Karen's

NOTE Confidence: 0.885065780769231

00:01:47.271 --> 00:01:49.999 group over here in the the Med school.

NOTE Confidence: 0.885065780769231

00:01:50.000 --> 00:01:53.168 So I'll talk a little bit in general about

NOTE Confidence: 0.885065780769231

00:01:53.168 --> 00:01:55.709 computer aided drug discovery and then

NOTE Confidence: 0.885065780769231

00:01:55.709 --> 00:01:58.557 specifically about our work and finding

NOTE Confidence: 0.885065780769231

00:01:58.557 --> 00:02:02.979 very potent protease inhibitors for SARS.

NOTE Confidence: 0.885065780769231

00:02:02.980 --> 00:02:07.792 Move two. So a key element of drug design

NOTE Confidence: 0.885065780769231

00:02:07.792 --> 00:02:12.239 is the fact of trying to make inhibitors

NOTE Confidence: 0.885065780769231

00:02:12.240 --> 00:02:15.198 that bind to an enzyme typically.

NOTE Confidence: 0.885065780769231

00:02:15.200 --> 00:02:18.908 So and we'll be talking about again a small

NOTE Confidence: 0.885065780769231

00:02:18.908 --> 00:02:21.935 molecule binding to SARS Cove 2 protease.

NOTE Confidence: 0.885065780769231

00:02:21.940 --> 00:02:24.284 And so this is governed by an equilibrium

NOTE Confidence: 0.885065780769231

00:02:24.284 --> 00:02:26.478 where you have the protein and water,

NOTE Confidence: 0.885065780769231

00:02:26.480 --> 00:02:28.492 the inhibitor and water,

NOTE Confidence: 0.885065780769231

00:02:28.492 --> 00:02:31.007 there's a free energy of

NOTE Confidence: 0.885065780769231

00:02:31.007 --> 00:02:33.457 binding and then the complex.

NOTE Confidence: 0.885065780769231

00:02:33.460 --> 00:02:36.268 So the free energy of binding the G because

NOTE Confidence: 0.885065780769231

00:02:36.268 --> 00:02:38.758 we're working in the constant pressure,

NOTE Confidence: 0.885065780769231

00:02:38.760 --> 00:02:42.138 constant temperature world is for Gibbs.

NOTE Confidence: 0.885065780769231

00:02:42.140 --> 00:02:45.792 So it's a Gibbs free energy and I put the

NOTE Confidence: 0.885065780769231

00:02:45.792 --> 00:02:50.034 stamp of our former colleague Jay Willard.

NOTE Confidence: 0.885065780769231

00:02:50.040 --> 00:02:52.650 Gibbs here is the father of.

NOTE Confidence: 0.885065780769231

00:02:52.650 --> 00:02:53.198 Thermodynamics.

NOTE Confidence: 0.885065780769231

00:02:53.198 --> 00:02:57.582 So the free energy binding just to introduce

NOTE Confidence: 0.885065780769231

00:02:57.582 --> 00:03:01.046 the concept of a nanomolar inhibitor.

NOTE Confidence: 0.885065780769231

00:03:01.050 --> 00:03:03.794 So the free energy of binding is given

NOTE Confidence: 0.885065780769231

00:03:03.794 --> 00:03:06.308 by minus RTL and the dissociation

NOTE Confidence: 0.885065780769231

00:03:06.308 --> 00:03:08.936 constant if you have a dissociation

NOTE Confidence: 0.885065780769231

00:03:09.011 --> 00:03:11.859 constant of 10 to the minus nine molar.

NOTE Confidence: 0.885065780769231

00:03:11.860 --> 00:03:15.538 That would correspond to A1 nanomolar.

NOTE Confidence: 0.885065780769231

00:03:15.540 --> 00:03:22.140 Inhibitor or an inhibitor that has that KD,

NOTE Confidence: 0.885065780769231

00:03:22.140 --> 00:03:24.093 one that has a KD of 10 to the

NOTE Confidence: 0.885065780769231

00:03:24.093 --> 00:03:26.125 minus six would be a micromolar

NOTE Confidence: 0.885065780769231

00:03:26.125 --> 00:03:28.019 inhibitor and our binder.

NOTE Confidence: 0.885065780769231

00:03:28.019 --> 00:03:31.610 And the reason I bring this up

NOTE Confidence: 0.885065780769231

00:03:31.730 --> 00:03:35.696 is that most drugs turn out to be

NOTE Confidence: 0.885065780769231

00:03:35.696 --> 00:03:39.306 typically one to let's say 20 or

NOTE Confidence: 0.885065780769231

00:03:39.306 --> 00:03:41.856 so nanomolar in a binding assay.

NOTE Confidence: 0.885065780769231

00:03:41.856 --> 00:03:44.837 And this all ultimately has to do with

NOTE Confidence: 0.885065780769231

00:03:44.837 --> 00:03:47.081 the farm human pharmacology and just

NOTE Confidence: 0.885065780769231

00:03:47.081 --> 00:03:50.058 how big a pill one is willing to take.

NOTE Confidence: 0.885065780769231

00:03:50.060 --> 00:03:52.690 So this obsession with nanomolar

NOTE Confidence: 0.885065780769231

00:03:52.690 --> 00:03:55.714 inhibitors just to, you know,

NOTE Confidence: 0.885065780769231

00:03:55.714 --> 00:03:57.880 reflects this fact,

NOTE Confidence: 0.885065780769231

00:03:57.880 --> 00:03:58.327 so.

NOTE Confidence: 0.885065780769231

00:03:58.327 --> 00:04:01.456 Ultimately here we're going to have to

NOTE Confidence: 0.885065780769231

00:04:01.456 --> 00:04:03.936 do simulations on computer simulations

NOTE Confidence: 0.885065780769231

00:04:03.936 --> 00:04:07.450 of proteins binding to ligands in water.

NOTE Confidence: 0.885065780769231

00:04:07.450 --> 00:04:09.088 And so how did this arise?

NOTE Confidence: 0.885065780769231

00:04:09.090 --> 00:04:11.729 When did it with such things happen?

NOTE Confidence: 0.885065780769231

00:04:11.730 --> 00:04:13.406 And the answer is,

NOTE Confidence: 0.885065780769231

00:04:13.406 --> 00:04:15.501 there really wasn't any significant

NOTE Confidence: 0.885065780769231

00:04:15.501 --> 00:04:18.297 work on doing computer simulations of

NOTE Confidence: 0.885065780769231

00:04:18.297 --> 00:04:21.052 molecular fluids before the late 1970s.

NOTE Confidence: 0.885065780769231

00:04:21.052 --> 00:04:25.030 And then of course it grew slowly after that.

NOTE Confidence: 0.885065780769231

00:04:25.030 --> 00:04:27.145 The problem is you have a lot of particles,

NOTE Confidence: 0.885065780769231

00:04:27.150 --> 00:04:29.182 you're using classical force.

NOTE Confidence: 0.885065780769231

00:04:29.182 --> 00:04:31.214 Those describe the interactions,

NOTE Confidence: 0.885065780769231

00:04:31.220 --> 00:04:33.754 but there's still a lot of particles

NOTE Confidence: 0.885065780769231

00:04:33.754 --> 00:04:35.140 and you have to.

NOTE Confidence: 0.885065780769231

00:04:35.140 --> 00:04:37.750 Observe the system over a significant

NOTE Confidence: 0.885065780769231

00:04:37.750 --> 00:04:38.620 time period.

NOTE Confidence: 0.885065780769231

00:04:38.620 --> 00:04:40.798 So if you're doing molecular dynamics,

NOTE Confidence: 0.885065780769231

00:04:40.800 --> 00:04:43.872 we might want to run the molecular dynamics

NOTE Confidence: 0.885065780769231

00:04:43.872 --> 00:04:46.532 for picosecond hundreds of picoseconds,

NOTE Confidence: 0.885065780769231

00:04:46.532 --> 00:04:49.940 nanoseconds and this just we didn't

NOTE Confidence: 0.885065780769231

00:04:50.020 --> 00:04:53.135 have the computer resources to do that.

NOTE Confidence: 0.885065780769231

00:04:53.140 --> 00:04:55.708 And then making it more complicated

NOTE Confidence: 0.885065780769231

00:04:55.708 --> 00:04:58.782 by putting a protein into it and

NOTE Confidence: 0.885065780769231

00:04:58.782 --> 00:05:00.922 describing the energetics of the

NOTE Confidence: 0.885065780769231

00:05:00.922 --> 00:05:02.619 protein and the water.

NOTE Confidence: 0.885065780769231

00:05:02.620 --> 00:05:06.040 That really didn't happen until mid.

NOTE Confidence: 0.885065780769231

00:05:06.040 --> 00:05:08.140 1980s and my colleague here,

NOTE Confidence: 0.885065780769231

00:05:08.140 --> 00:05:10.385 Julian Torrado Rivas and I

NOTE Confidence: 0.885065780769231

00:05:10.385 --> 00:05:12.630 published one of the first

NOTE Confidence: 0.828101986785715

00:05:12.721 --> 00:05:15.673 calculations for a protein in water

NOTE Confidence: 0.828101986785715

00:05:15.673 --> 00:05:18.659 where we did molecular dynamics for

NOTE Confidence: 0.828101986785715

00:05:18.659 --> 00:05:21.951 100 picoseconds and that was in 1988.

NOTE Confidence: 0.828101986785715

00:05:21.951 --> 00:05:24.897 So doing the type of calculations

NOTE Confidence: 0.828101986785715

00:05:24.897 --> 00:05:27.720 we're talking about today is

NOTE Confidence: 0.828101986785715

00:05:27.720 --> 00:05:29.616 relatively recent phenomenon.

NOTE Confidence: 0.828101986785715

00:05:29.620 --> 00:05:31.750 This is a picture we'll talk

NOTE Confidence: 0.828101986785715

00:05:31.750 --> 00:05:33.170 about HIV reverse transcriptase

NOTE Confidence: 0.828101986785715

00:05:33.238 --> 00:05:34.780 and just to get the sense,

NOTE Confidence: 0.828101986785715

00:05:34.780 --> 00:05:36.220 I usually give this to less.

NOTE Confidence: 0.828101986785715

00:05:36.220 --> 00:05:37.114 Sophisticated audiences

NOTE Confidence: 0.828101986785715

00:05:37.114 --> 00:05:39.349 to point out the yellow,

NOTE Confidence: 0.828101986785715

00:05:39.350 --> 00:05:41.326 little yellow pieces inhibitor

NOTE Confidence: 0.828101986785715

00:05:41.326 --> 00:05:44.290 and that's enough to shut down

NOTE Confidence: 0.828101986785715

00:05:44.290 --> 00:05:46.845 this enzyme and this is an example

NOTE Confidence: 0.828101986785715

00:05:46.845 --> 00:05:49.493 of one of the compounds that

NOTE Confidence: 0.828101986785715

00:05:49.493 --> 00:05:51.938 developed through Karens and in

NOTE Confidence: 0.828101986785715

00:05:51.938 --> 00:05:55.121 our work that is a inhibitor of

NOTE Confidence: 0.828101986785715

00:05:55.121 --> 00:05:57.236 HIV RT that little molecule.

NOTE Confidence: 0.828101986785715

00:05:57.240 --> 00:06:00.236 So here's the way we do it.

NOTE Confidence: 0.828101986785715

00:06:00.240 --> 00:06:02.406 We normally start with an X-ray

NOTE Confidence: 0.828101986785715

00:06:02.406 --> 00:06:04.727 structure and the first phase of

NOTE Confidence: 0.828101986785715

00:06:04.727 --> 00:06:06.732 this we're looking for micromolar

NOTE Confidence: 0.828101986785715

00:06:06.732 --> 00:06:08.977 hit compounds that then we have to

NOTE Confidence: 0.828101986785715

00:06:08.977 --> 00:06:11.811 do a lot of hard work on to bring

NOTE Confidence: 0.828101986785715

00:06:11.811 --> 00:06:14.553 them to the low nanomolar level.

NOTE Confidence: 0.828101986785715

00:06:14.560 --> 00:06:16.828 So we normally start with an X-ray

NOTE Confidence: 0.828101986785715

00:06:16.828 --> 00:06:18.741 structure and this can be from

NOTE Confidence: 0.828101986785715

00:06:18.741 --> 00:06:20.499 you know somebody else's work and

NOTE Confidence: 0.828101986785715

00:06:20.499 --> 00:06:22.537 we remove the ligand that might

NOTE Confidence: 0.828101986785715

00:06:22.537 --> 00:06:24.606 be in that X-ray structure and

NOTE Confidence: 0.828101986785715

00:06:24.606 --> 00:06:27.308 then we try to design our new

NOTE Confidence: 0.828101986785715

00:06:27.308 --> 00:06:30.024 our own inhibitors and that this.

NOTE Confidence: 0.828101986785715

00:06:30.024 --> 00:06:32.940 Started out we do a virtual

NOTE Confidence: 0.828101986785715

00:06:33.033 --> 00:06:35.509 screening which is docking.

NOTE Confidence: 0.828101986785715

00:06:35.510 --> 00:06:36.902 And I'll tell you a little

NOTE Confidence: 0.828101986785715

00:06:36.902 --> 00:06:37.830 bit more about that,

NOTE Confidence: 0.828101986785715

00:06:37.830 --> 00:06:40.090 where we literally fly molecules

NOTE Confidence: 0.828101986785715

00:06:40.090 --> 00:06:42.350 into the protein structure and

NOTE Confidence: 0.828101986785715

00:06:42.427 --> 00:06:44.509 see which ones look the best.

NOTE Confidence: 0.828101986785715

00:06:44.510 --> 00:06:47.206 Or are we do denovo design where we

NOTE Confidence: 0.828101986785715

00:06:47.206 --> 00:06:50.147 use a growing program that I wrote

NOTE Confidence: 0.828101986785715

00:06:50.147 --> 00:06:53.197 a while back that starts with the

NOTE Confidence: 0.828101986785715

00:06:53.197 --> 00:06:55.948 little seed core of a molecule of,

NOTE Confidence: 0.828101986785715

00:06:55.950 --> 00:06:59.126 say benzene you place in the binding site.

NOTE Confidence: 0.828101986785715

00:06:59.130 --> 00:07:01.965 And then the program will build libraries

NOTE Confidence: 0.828101986785715

00:07:01.965 --> 00:07:04.220 of compounds starting from that core,

NOTE Confidence: 0.828101986785715

00:07:04.220 --> 00:07:06.208 growing them out in the binding site.

NOTE Confidence: 0.828101986785715

00:07:06.210 --> 00:07:08.110 And then you have to.

NOTE Confidence: 0.828101986785715

00:07:08.110 --> 00:07:09.494 A score of them,

NOTE Confidence: 0.828101986785715

00:07:09.494 --> 00:07:11.570 evaluate them in the same manner

NOTE Confidence: 0.828101986785715

00:07:11.642 --> 00:07:14.032 that this invariably gives us

NOTE Confidence: 0.828101986785715

00:07:14.032 --> 00:07:15.944 these micromolar hit compounds.

NOTE Confidence: 0.828101986785715

00:07:15.950 --> 00:07:18.218 But we've never been fortunate enough

NOTE Confidence: 0.828101986785715

00:07:18.218 --> 00:07:21.257 to do this initial part of the work

NOTE Confidence: 0.828101986785715

00:07:21.257 --> 00:07:23.441 and end up with nanomolar inhibitors.

NOTE Confidence: 0.828101986785715

00:07:23.450 --> 00:07:25.550 We're close, you know,

NOTE Confidence: 0.828101986785715

00:07:25.550 --> 00:07:27.125 single digit micromolar.

NOTE Confidence: 0.828101986785715

00:07:27.130 --> 00:07:30.330 So then the hard part is the lead

NOTE Confidence: 0.828101986785715

00:07:30.330 --> 00:07:32.360 optimization because we're going to

NOTE Confidence: 0.828101986785715

00:07:32.360 --> 00:07:35.055 have to refine the micromolar hits by

NOTE Confidence: 0.828101986785715

00:07:35.133 --> 00:07:37.797 making small changes that we decide.

NOTE Confidence: 0.828101986785715

00:07:37.800 --> 00:07:38.751 What to do?

NOTE Confidence: 0.828101986785715

00:07:38.751 --> 00:07:40.653 By a lot of structure building

NOTE Confidence: 0.828101986785715

00:07:40.653 --> 00:07:42.499 and energy minimizations.

NOTE Confidence: 0.828101986785715

00:07:42.500 --> 00:07:45.251 So this bond program of mining can

NOTE Confidence: 0.828101986785715

00:07:45.251 --> 00:07:47.699 rapidly build protein ligand complexes.

NOTE Confidence: 0.828101986785715

00:07:47.700 --> 00:07:49.740 We can energy minimize them.

NOTE Confidence: 0.828101986785715

00:07:49.740 --> 00:07:51.960 That's just a fast calculation

NOTE Confidence: 0.828101986785715

00:07:51.960 --> 00:07:54.180 compared to adding the water

NOTE Confidence: 0.828101986785715

00:07:54.264 --> 00:07:56.300 doing the molecular anamax.

NOTE Confidence: 0.828101986785715

00:07:56.300 --> 00:07:58.380 And so we do a lot of the structure building,

NOTE Confidence: 0.828101986785715

00:07:58.380 --> 00:08:01.935 energy minimization and then for

NOTE Confidence: 0.828101986785715

00:08:01.935 --> 00:08:06.506 select cases we will do, excuse me,

NOTE Confidence: 0.828101986785715

00:08:06.506 --> 00:08:08.538 the free energy calculations

NOTE Confidence: 0.828101986785715

00:08:08.538 --> 00:08:11.849 that are sort of our hallmark.

NOTE Confidence: 0.828101986785715

00:08:11.850 --> 00:08:13.730 We call them FEP,

NOTE Confidence: 0.828101986785715

00:08:13.730 --> 00:08:15.610 free energy perturbation calculations.

NOTE Confidence: 0.828101986785715

00:08:15.610 --> 00:08:17.230 Virtually all pharmaceutical

NOTE Confidence: 0.828101986785715

00:08:17.230 --> 00:08:18.850 companies today are,

NOTE Confidence: 0.828101986785715

00:08:18.850 --> 00:08:19.694 you know,

NOTE Confidence: 0.828101986785715

00:08:19.694 --> 00:08:20.960 jumped on this.

NOTE Confidence: 0.828101986785715

00:08:20.960 --> 00:08:23.544 Everybody's doing FP calculations

NOTE Confidence: 0.828101986785715

00:08:23.544 --> 00:08:26.128 for a drug design.

NOTE Confidence: 0.828101986785715

00:08:26.130 --> 00:08:29.019 So then you have to make a decision on

NOTE Confidence: 0.828101986785715

00:08:29.019 --> 00:08:32.109 what molecules to synthesize their assay.

NOTE Confidence: 0.828101986785715

00:08:32.110 --> 00:08:35.368 So you need somebody like Karen to help out

NOTE Confidence: 0.828101986785715

00:08:35.368 --> 00:08:38.729 in the assaying and the crystallography,

NOTE Confidence: 0.828101986785715

00:08:38.730 --> 00:08:41.439 the crystallography isn't.

NOTE Confidence: 0.828101986785715

00:08:41.440 --> 00:08:41.811 Critical,

NOTE Confidence: 0.828101986785715

00:08:41.811 --> 00:08:45.150 but it sure is helpful if you know very

NOTE Confidence: 0.88412208

00:08:45.226 --> 00:08:47.042 much helps reinforce what

NOTE Confidence: 0.88412208

00:08:47.042 --> 00:08:48.858 the modeling is doing.

NOTE Confidence: 0.88412208

00:08:48.860 --> 00:08:50.840 And also sometimes you'll see that

NOTE Confidence: 0.88412208

00:08:50.840 --> 00:08:53.252 the there the there's a change in

NOTE Confidence: 0.88412208

00:08:53.252 --> 00:08:55.304 the protein structure from what you

NOTE Confidence: 0.88412208

00:08:55.304 --> 00:08:57.127 originally started with that you

NOTE Confidence: 0.88412208

00:08:57.127 --> 00:08:58.897 will see in the crystallography.

NOTE Confidence: 0.88412208

00:08:58.900 --> 00:09:00.188 You don't necessarily see

NOTE Confidence: 0.88412208

00:09:00.188 --> 00:09:01.476 it in the computation.

NOTE Confidence: 0.88412208

00:09:01.480 --> 00:09:05.968 So the crystallography is really helpful.

NOTE Confidence: 0.88412208

00:09:05.970 --> 00:09:07.690 When the HIV area,

NOTE Confidence: 0.88412208

00:09:07.690 --> 00:09:10.936 Karen and I got along for quite a few

NOTE Confidence: 0.88412208

00:09:10.936 --> 00:09:13.050 years without a crystal structures,

NOTE Confidence: 0.88412208

00:09:13.050 --> 00:09:14.655 but then once we certainly

NOTE Confidence: 0.88412208

00:09:14.655 --> 00:09:16.260 current lab start getting them,

NOTE Confidence: 0.88412208

00:09:16.260 --> 00:09:20.108 it certainly made life a lot more confident.

NOTE Confidence: 0.88412208

00:09:20.110 --> 00:09:22.936 So you repeat the cycle until

NOTE Confidence: 0.88412208

00:09:22.936 --> 00:09:25.790 you get the potency you want.

NOTE Confidence: 0.88412208

00:09:25.790 --> 00:09:29.078 All the while we are mindful of properties,

NOTE Confidence: 0.88412208

00:09:29.080 --> 00:09:33.013 so we want the compounds to be drug like.

NOTE Confidence: 0.88412208

00:09:33.020 --> 00:09:35.684 And that requires a having things

NOTE Confidence: 0.88412208

00:09:35.684 --> 00:09:37.016 like reasonable solubility,

NOTE Confidence: 0.88412208

00:09:37.020 --> 00:09:38.766 reasonable cell permeability,

NOTE Confidence: 0.88412208

00:09:38.766 --> 00:09:41.094 no reactive functional groups.

NOTE Confidence: 0.88412208

00:09:41.100 --> 00:09:43.781 So we have software that checks that

NOTE Confidence: 0.88412208

00:09:43.781 --> 00:09:47.207 and then we also do some measurements

NOTE Confidence: 0.88412208

00:09:47.207 --> 00:09:49.952 of solubility and cell permeability,

NOTE Confidence: 0.88412208

00:09:49.960 --> 00:09:50.382 OK.

NOTE Confidence: 0.88412208

00:09:50.382 --> 00:09:53.336 So the FP calculations are done for

NOTE Confidence: 0.88412208

00:09:53.336 --> 00:09:57.157 where you do molecular dynamics or Monte

NOTE Confidence: 0.88412208

00:09:57.157 --> 00:10:00.042 Carlo simulations for protein ligand

NOTE Confidence: 0.88412208

00:10:00.137 --> 00:10:03.497 and a typically a ball of several 1000.

NOTE Confidence: 0.88412208

00:10:03.500 --> 00:10:04.698 Water molecules.

NOTE Confidence: 0.88412208

00:10:04.698 --> 00:10:08.292 And you do a calculation where

NOTE Confidence: 0.88412208

00:10:08.292 --> 00:10:11.178 you're comparing the green ligand,

NOTE Confidence: 0.88412208

00:10:11.180 --> 00:10:13.120 green inhibitor with the blue.

NOTE Confidence: 0.88412208

00:10:13.120 --> 00:10:14.560 So you do calculation.

NOTE Confidence: 0.88412208

00:10:14.560 --> 00:10:17.190 We have protein green legging to give

NOTE Confidence: 0.88412208

00:10:17.190 --> 00:10:19.997 complex protein blue ligand to give complex.

NOTE Confidence: 0.88412208

00:10:20.000 --> 00:10:21.316 And what we do on the computer,

NOTE Confidence: 0.88412208

00:10:21.320 --> 00:10:24.542 it turns out to be easier is to mutate

NOTE Confidence: 0.88412208

00:10:24.542 --> 00:10:27.487 the green leg into the blue unbound

NOTE Confidence: 0.88412208

00:10:27.487 --> 00:10:30.439 in water and then bound protein.

NOTE Confidence: 0.88412208

00:10:30.440 --> 00:10:32.540 And the difference in the two

NOTE Confidence: 0.88412208

00:10:32.540 --> 00:10:34.745 vertical numbers there then gives us

NOTE Confidence: 0.88412208

00:10:34.745 --> 00:10:36.590 the difference in predicted free.

NOTE Confidence: 0.88412208

00:10:36.590 --> 00:10:38.920 Energy binding.

NOTE Confidence: 0.88412208

00:10:38.920 --> 00:10:42.112 And so this type of calculation wasn't

NOTE Confidence: 0.88412208

00:10:42.112 --> 00:10:45.900 done at all before 1985 or just the

NOTE Confidence: 0.88412208

00:10:45.900 --> 00:10:50.219 simple green to blue in water FP calculation.

NOTE Confidence: 0.88412208

00:10:50.220 --> 00:10:53.450 That was something that I.

NOTE Confidence: 0.88412208

00:10:53.450 --> 00:10:55.935 It will take credit for doing the

NOTE Confidence: 0.88412208

00:10:55.935 --> 00:10:58.118 first calculation of that type again.

NOTE Confidence: 0.88412208

00:10:58.120 --> 00:10:59.184 Then there's no software.

NOTE Confidence: 0.88412208

00:10:59.184 --> 00:11:01.320 You had to write all the software,

NOTE Confidence: 0.88412208

00:11:01.320 --> 00:11:02.976 you know the force fields we

NOTE Confidence: 0.88412208

00:11:02.976 --> 00:11:04.080 had to develop etcetera.

NOTE Confidence: 0.88412208

00:11:04.080 --> 00:11:07.904 So it was very different world in 1985, OK.

NOTE Confidence: 0.88412208

00:11:07.904 --> 00:11:11.240 So here are just a little bit on HIV.

NOTE Confidence: 0.88412208

00:11:11.240 --> 00:11:14.216 HIV is still a big problem.

NOTE Confidence: 0.88412208

00:11:14.220 --> 00:11:16.008 Some of the statistics

NOTE Confidence: 0.88412208

00:11:16.008 --> 00:11:18.158 are shown there for 2021.

NOTE Confidence: 0.88412208

00:11:18.158 --> 00:11:18.516 They're,

NOTE Confidence: 0.88412208

00:11:18.516 --> 00:11:19.232 you know,

NOTE Confidence: 0.88412208

00:11:19.232 --> 00:11:22.043 close to 40 million people in the world

NOTE Confidence: 0.88412208

00:11:22.043 --> 00:11:25.814 that are infected with HIV and about 1

NOTE Confidence: 0.88412208

00:11:25.814 --> 00:11:30.280 to 2,000,000 each year are becoming infected.

NOTE Confidence: 0.88412208

00:11:30.280 --> 00:11:34.076 And they're on the order of 650,000 deaths.

NOTE Confidence: 0.88412208

00:11:34.076 --> 00:11:38.260 So that's down quite a bit from what it was.

NOTE Confidence: 0.88412208

00:11:38.260 --> 00:11:39.160 But still,

NOTE Confidence: 0.88412208

00:11:39.160 --> 00:11:40.060 you know,

NOTE Confidence: 0.88412208

00:11:40.060 --> 00:11:42.760 from a very serious problem and

NOTE Confidence: 0.88412208

00:11:42.853 --> 00:11:44.497 a Long story short.

NOTE Confidence: 0.88412208

00:11:44.500 --> 00:11:48.021 We have worked on with Karen on

NOTE Confidence: 0.88412208

00:11:48.021 --> 00:11:50.240 the reverse transcriptase and the

NOTE Confidence: 0.88412208

00:11:50.240 --> 00:11:54.227 so this is a an RNA virus and it

NOTE Confidence: 0.88412208

00:11:54.227 --> 00:11:58.104 has a reverse transcriptase which

NOTE Confidence: 0.88412208

00:11:58.104 --> 00:12:00.948 converts the RNA to DNA which

NOTE Confidence: 0.88412208

00:12:00.948 --> 00:12:03.331 is incorporated into the host

NOTE Confidence: 0.88412208

00:12:03.331 --> 00:12:05.935 cells a genome by HIV integrase.

NOTE Confidence: 0.88412208

00:12:05.940 --> 00:12:08.100 So HIV reverse transcriptase has

NOTE Confidence: 0.88412208

00:12:08.100 --> 00:12:10.695 been the principal target for anti

NOTE Confidence: 0.88412208

00:12:10.695 --> 00:12:13.194 HIV drugs and there are two classes,

NOTE Confidence: 0.88412208

00:12:13.200 --> 00:12:14.282 the nucleosides.

NOTE Confidence: 0.88412208

00:12:14.282 --> 00:12:16.987 And the non nuclear science,

NOTE Confidence: 0.88412208

00:12:16.990 --> 00:12:18.690 Karen has worked on both.

NOTE Confidence: 0.88412208

00:12:18.690 --> 00:12:20.688 So in our collaboration with Karen

NOTE Confidence: 0.88412208

00:12:20.688 --> 00:12:23.169 we've only worked on non nuclear sites,

NOTE Confidence: 0.5872419725

00:12:23.170 --> 00:12:25.662 the NRT I and there are allosteric

NOTE Confidence: 0.5872419725

00:12:25.662 --> 00:12:29.045 inhibitors. They bind in this little

NOTE Confidence: 0.5872419725

00:12:29.045 --> 00:12:32.098 pocket that is about 10 angstroms or

NOTE Confidence: 0.5872419725

00:12:32.098 --> 00:12:34.750 so from the polymerase active site.

NOTE Confidence: 0.5872419725

00:12:34.750 --> 00:12:38.575 It's one of the few examples of of allosteric

NOTE Confidence: 0.5872419725

00:12:38.575 --> 00:12:41.407 inhibitor that's that have become drugs.

NOTE Confidence: 0.5872419725

00:12:41.410 --> 00:12:44.212 It's very, very, very very I'm, I'm, I'm.

NOTE Confidence: 0.5872419725

00:12:44.212 --> 00:12:46.620 Have to think of it to find others.

NOTE Confidence: 0.5872419725

00:12:46.620 --> 00:12:49.020 This is the principal example.

NOTE Confidence: 0.5872419725

00:12:49.020 --> 00:12:50.562 The crystal structure.

NOTE Confidence: 0.5872419725

00:12:50.562 --> 00:12:52.618 Again a Yale connection.

NOTE Confidence: 0.5872419725

00:12:52.620 --> 00:12:55.050 The original crystal structure of HIV

NOTE Confidence: 0.5872419725

00:12:55.050 --> 00:12:58.308 RT was done in the sites lab 1992.

NOTE Confidence: 0.5872419725

00:12:58.308 --> 00:13:01.884 This is a very big. You know,

NOTE Confidence: 0.5872419725

00:13:01.884 --> 00:13:04.803 discovery at the time because the HIV

NOTE Confidence: 0.5872419725

00:13:04.803 --> 00:13:08.157 crisis was so severe and it's a big protein,

NOTE Confidence: 0.5872419725

00:13:08.160 --> 00:13:09.996 thousand of residues.

NOTE Confidence: 0.5872419725

00:13:09.996 --> 00:13:12.444 So Long story short,

NOTE Confidence: 0.5872419725

00:13:12.450 --> 00:13:14.600 we've tried to make better

NOTE Confidence: 0.5872419725

00:13:14.600 --> 00:13:15.890 non nucleoside inhibitors.

NOTE Confidence: 0.5872419725

00:13:15.890 --> 00:13:18.550 The original ones have limitations.

NOTE Confidence: 0.5872419725

00:13:18.550 --> 00:13:20.698 They're susceptible to mutations

NOTE Confidence: 0.5872419725

00:13:20.698 --> 00:13:22.309 that arise quickly.

NOTE Confidence: 0.5872419725

00:13:22.310 --> 00:13:26.270 They also had some undesirable pharmacology.

NOTE Confidence: 0.5872419725

00:13:26.270 --> 00:13:28.604 So the way we proceed on

NOTE Confidence: 0.5872419725

00:13:28.604 --> 00:13:31.139 HIV is the same with the.

NOTE Confidence: 0.5872419725

00:13:31.140 --> 00:13:37.372 COVID and the trick in lead optimization is

NOTE Confidence: 0.5872419725

00:13:37.372 --> 00:13:42.257 making systematic changes small changes in.

NOTE Confidence: 0.5872419725

00:13:42.260 --> 00:13:43.799 Substituents on rings,

NOTE Confidence: 0.5872419725

00:13:43.799 --> 00:13:46.364 the rings themselves and groups

NOTE Confidence: 0.5872419725

00:13:46.364 --> 00:13:48.680 that link rings together,

NOTE Confidence: 0.5872419725

00:13:48.680 --> 00:13:52.235 and if you know the right changes to make,

NOTE Confidence: 0.5872419725

00:13:52.240 --> 00:13:54.400 they can have profound effects.

NOTE Confidence: 0.5872419725

00:13:54.400 --> 00:13:57.935 So this is an early HIV compound

NOTE Confidence: 0.5872419725

00:13:57.935 --> 00:14:01.834 of of ours that we came about from

NOTE Confidence: 0.5872419725

00:14:01.834 --> 00:14:05.180 a de Novo design and Karen's lab.

NOTE Confidence: 0.5872419725

00:14:05.180 --> 00:14:08.868 The assay they're running is an infected T

NOTE Confidence: 0.5872419725

00:14:08.868 --> 00:14:12.489 cell assay and this compound had an EC50.

NOTE Confidence: 0.5872419725

00:14:12.490 --> 00:14:14.550 For inhibiting the reproduction

NOTE Confidence: 0.5872419725

00:14:14.550 --> 00:14:18.961 of of of the HIV in the infected

NOTE Confidence: 0.5872419725

00:14:18.961 --> 00:14:21.385 cells of 10 micromolar,

NOTE Confidence: 0.5872419725

00:14:21.390 --> 00:14:22.668 so 10,000 nanomolar.

NOTE Confidence: 0.5872419725

00:14:22.668 --> 00:14:25.224 So that's a reasonable starting place,

NOTE Confidence: 0.5872419725

00:14:25.230 --> 00:14:28.422 a small molecule, but we've got to

NOTE Confidence: 0.5872419725

00:14:28.422 --> 00:14:31.370 increase the potency by a thousandfold.

NOTE Confidence: 0.5872419725

00:14:31.370 --> 00:14:33.656 So I I point out here that if you

NOTE Confidence: 0.5872419725

00:14:33.656 --> 00:14:35.758 happen to know to put a cyano group

NOTE Confidence: 0.5872419725

00:14:35.758 --> 00:14:37.990 in the four position of this ring,

NOTE Confidence: 0.5872419725

00:14:37.990 --> 00:14:40.186 you get a very big boost,

NOTE Confidence: 0.5872419725

00:14:40.190 --> 00:14:44.390 50 fold boost to 200 nanomolar.

NOTE Confidence: 0.5872419725

00:14:44.390 --> 00:14:44.850 OK.

NOTE Confidence: 0.5872419725

00:14:44.850 --> 00:14:47.610 Then if you happen to change

NOTE Confidence: 0.5872419725

00:14:47.610 --> 00:14:50.280 the thiazole into a pyrimidine,

NOTE Confidence: 0.5872419725

00:14:50.280 --> 00:14:53.070 you get another tenfold boost and

NOTE Confidence: 0.5872419725

00:14:53.070 --> 00:14:55.935 you're at 17 nanul. So quite amazing.

NOTE Confidence: 0.5872419725

00:14:55.935 --> 00:14:58.698 And then if you happen to know to

NOTE Confidence: 0.5872419725

00:14:58.698 --> 00:15:01.092 put a methoxy group and the the

NOTE Confidence: 0.5872419725

00:15:01.092 --> 00:15:03.050 three position of the pyrimidine

NOTE Confidence: 0.5872419725

00:15:03.050 --> 00:15:04.646 ring here 2 nanomolar.

NOTE Confidence: 0.5872419725

00:15:04.650 --> 00:15:06.474 So you have more potency than

NOTE Confidence: 0.5872419725

00:15:06.474 --> 00:15:08.110 you need for a drug.

NOTE Confidence: 0.5872419725

00:15:08.110 --> 00:15:10.254 So this is all fine and this is

NOTE Confidence: 0.5872419725

00:15:10.254 --> 00:15:12.718 what we use the FEP calculations to

NOTE Confidence: 0.5872419725

00:15:12.718 --> 00:15:15.000 help us with because these changes

NOTE Confidence: 0.5872419725

00:15:15.000 --> 00:15:17.464 are in a sea of possible changes.

NOTE Confidence: 0.5872419725

00:15:17.470 --> 00:15:19.780 So we do however scans where we

NOTE Confidence: 0.5872419725

00:15:19.780 --> 00:15:22.428 have we have a compound like this,

NOTE Confidence: 0.5872419725

00:15:22.430 --> 00:15:26.358 we'll scan in chlorine atoms at each open.

NOTE Confidence: 0.5872419725

00:15:26.360 --> 00:15:29.056 To see if we can add a little

NOTE Confidence: 0.5872419725

00:15:29.056 --> 00:15:31.919 beef to it and that might have,

NOTE Confidence: 0.5872419725

00:15:31.920 --> 00:15:34.755 if we did that it would show that this

NOTE Confidence: 0.5872419725

00:15:34.760 --> 00:15:37.418 four position is good for chlorine,

NOTE Confidence: 0.5872419725

00:15:37.420 --> 00:15:38.818 well if it's good for chlorine

NOTE Confidence: 0.5872419725

00:15:38.818 --> 00:15:40.701 and may also be good or even

NOTE Confidence: 0.5872419725

00:15:40.701 --> 00:15:42.196 better for cyano because they're

NOTE Confidence: 0.5872419725

00:15:42.196 --> 00:15:43.810 both somewhat electronic drawing.

NOTE Confidence: 0.5872419725

00:15:43.810 --> 00:15:46.138 So then we would try siana.

NOTE Confidence: 0.5872419725

00:15:46.140 --> 00:15:48.198 But we do these initial scans,

NOTE Confidence: 0.5872419725

00:15:48.200 --> 00:15:50.684 we also do heterocycle scans of

NOTE Confidence: 0.5872419725

00:15:50.684 --> 00:15:53.227 five and six membered rings because

NOTE Confidence: 0.5872419725

00:15:53.227 --> 00:15:55.312 they are obviously affect hydrogen

NOTE Confidence: 0.5872419725

00:15:55.312 --> 00:15:56.980 bonding patterns and hopefully

NOTE Confidence: 0.5872419725

00:15:57.046 --> 00:15:58.864 that would have picked up that

NOTE Confidence: 0.5872419725

00:15:58.864 --> 00:16:00.076 the pyrimidine was the

NOTE Confidence: 0.853624669130435

00:16:00.138 --> 00:16:02.735 way to go. And then finally we do

NOTE Confidence: 0.853624669130435

00:16:02.735 --> 00:16:04.760 another substituent scan on the

NOTE Confidence: 0.853624669130435

00:16:04.838 --> 00:16:07.538 pyrimidine of methyls and chlorines,

NOTE Confidence: 0.853624669130435

00:16:07.540 --> 00:16:10.158 we would see that substitution and the

NOTE Confidence: 0.853624669130435

00:16:10.158 --> 00:16:12.552 three position is a good thing and

NOTE Confidence: 0.853624669130435

00:16:12.552 --> 00:16:15.230 before long we would come to the methoxy.

NOTE Confidence: 0.853624669130435

00:16:15.230 --> 00:16:16.658 So that's the way it's done.

NOTE Confidence: 0.853624669130435

00:16:16.660 --> 00:16:19.257 And that's attuned animal or very potent

NOTE Confidence: 0.853624669130435

00:16:19.257 --> 00:16:21.656 compound we did in collaboration with

NOTE Confidence: 0.853624669130435

00:16:21.656 --> 00:16:24.080 Eddie Arnold got a crystal structure

NOTE Confidence: 0.853624669130435

00:16:24.080 --> 00:16:26.744 of that there's quite a quite a bit

NOTE Confidence: 0.853624669130435

00:16:26.744 --> 00:16:28.988 later and that was the only crystal

NOTE Confidence: 0.853624669130435

00:16:28.988 --> 00:16:31.448 structure we had until Karen's group

NOTE Confidence: 0.853624669130435

00:16:31.448 --> 00:16:34.318 started getting some around 2012.

NOTE Confidence: 0.853624669130435

00:16:34.320 --> 00:16:37.312 OK, so here is just some of the

NOTE Confidence: 0.853624669130435

00:16:37.312 --> 00:16:38.700 work with Karen.

NOTE Confidence: 0.853624669130435

00:16:38.700 --> 00:16:43.440 These are all publications on different.

NOTE Confidence: 0.853624669130435

00:16:43.440 --> 00:16:47.016 And an RTI's and you might say well

NOTE Confidence: 0.853624669130435

00:16:47.016 --> 00:16:49.765 Gee and from 2006 you have these two

NOTE Confidence: 0.853624669130435

00:16:49.765 --> 00:16:51.380 national or compound aren't you done,

NOTE Confidence: 0.853624669130435

00:16:51.380 --> 00:16:53.908 why are you why are you keeping doing

NOTE Confidence: 0.853624669130435

00:16:53.908 --> 00:16:56.325 this and the answer is that that

NOTE Confidence: 0.853624669130435

00:16:56.325 --> 00:16:58.870 number is against the wild type virus.

NOTE Confidence: 0.853624669130435

00:16:58.870 --> 00:17:01.313 But the virus as you know have

NOTE Confidence: 0.853624669130435

00:17:01.313 --> 00:17:03.610 mutates just like COVID is mutating

NOTE Confidence: 0.853624669130435

00:17:03.610 --> 00:17:06.354 and there's a whole panel of mutants

NOTE Confidence: 0.853624669130435

00:17:06.434 --> 00:17:09.338 with the HIV and you need to have

NOTE Confidence: 0.853624669130435

00:17:09.338 --> 00:17:12.018 efficacy against all of the common

NOTE Confidence: 0.853624669130435

00:17:12.018 --> 00:17:13.966 mutants with one compound.

NOTE Confidence: 0.853624669130435

00:17:13.970 --> 00:17:15.242 So it's tough.

NOTE Confidence: 0.853624669130435

00:17:15.242 --> 00:17:17.786 So that initial compound like initial.

NOTE Confidence: 0.825470216666667

00:17:19.840 --> 00:17:21.692 Compounds in this class,

NOTE Confidence: 0.825470216666667

00:17:21.692 --> 00:17:22.997 such as nevirapine,

NOTE Confidence: 0.825470216666667

00:17:22.997 --> 00:17:25.259 was the first approved drug in

NOTE Confidence: 0.825470216666667

00:17:25.259 --> 00:17:26.966 this class, like nevirapine.

NOTE Confidence: 0.825470216666667

00:17:26.966 --> 00:17:29.331 It was good against wild

NOTE Confidence: 0.825470216666667

00:17:29.331 --> 00:17:32.069 type but not not much else.

NOTE Confidence: 0.825470216666667

00:17:32.070 --> 00:17:33.985 So these other compounds that

NOTE Confidence: 0.825470216666667

00:17:33.985 --> 00:17:36.270 I'll just skip to this one,

NOTE Confidence: 0.825470216666667

00:17:36.270 --> 00:17:37.700 one of our better compounds,

NOTE Confidence: 0.825470216666667

00:17:37.700 --> 00:17:39.376 we've increased the potency,

NOTE Confidence: 0.825470216666667

00:17:39.376 --> 00:17:41.890 but we very much increased the

NOTE Confidence: 0.825470216666667

00:17:41.890 --> 00:17:43.678 performance again mutant panels,

NOTE Confidence: 0.825470216666667

00:17:43.678 --> 00:17:45.466 so very difficult mutant

NOTE Confidence: 0.825470216666667

00:17:45.466 --> 00:17:50.050 is a double mutant K10 3N.

NOTE Confidence: 0.825470216666667

00:17:50.050 --> 00:17:52.314 Y181C and this compound

NOTE Confidence: 0.825470216666667

00:17:52.314 --> 00:17:55.518 here is A10 animal or EC50,

NOTE Confidence: 0.825470216666667

00:17:55.518 --> 00:17:58.094 which is you know good and great

NOTE Confidence: 0.825470216666667

00:17:58.094 --> 00:18:00.179 against that whereas the original

NOTE Confidence: 0.825470216666667

00:18:00.179 --> 00:18:02.304 compounds here would have had

NOTE Confidence: 0.825470216666667

00:18:02.304 --> 00:18:04.630 no efficacy against that mutant.

NOTE Confidence: 0.825470216666667

00:18:04.630 --> 00:18:06.530 And we've gone on,

NOTE Confidence: 0.825470216666667

00:18:06.530 --> 00:18:08.483 we even see something that looks like

NOTE Confidence: 0.825470216666667

00:18:08.483 --> 00:18:09.948 a covalent inhibitor which it is.

NOTE Confidence: 0.825470216666667

00:18:09.950 --> 00:18:13.270 We with cooperation with Karen,

NOTE Confidence: 0.825470216666667

00:18:13.270 --> 00:18:19.126 we have covalent inhibitors for HIV RT Wild.

NOTE Confidence: 0.825470216666667

00:18:19.130 --> 00:18:23.120 Type and also the Y181C mutant.

NOTE Confidence: 0.825470216666667

00:18:23.120 --> 00:18:26.328 But I will go on now to what

NOTE Confidence: 0.825470216666667

00:18:26.328 --> 00:18:28.509 we did with COVID.

NOTE Confidence: 0.825470216666667

00:18:28.510 --> 00:18:33.286 So fortunately, because of our work on HIV.

NOTE Confidence: 0.825470216666667

00:18:33.290 --> 00:18:36.428 We're pretty well positioned just to

NOTE Confidence: 0.825470216666667

00:18:36.430 --> 00:18:39.286 try to do something when COVID rolled

NOTE Confidence: 0.825470216666667

00:18:39.286 --> 00:18:42.030 around at the beginning of 2020.

NOTE Confidence: 0.825470216666667

00:18:42.030 --> 00:18:47.043 So this is the IT again an RNA genome.

NOTE Confidence: 0.825470216666667

00:18:47.050 --> 00:18:49.647 And it some of the proteins that

NOTE Confidence: 0.825470216666667

00:18:49.647 --> 00:18:52.030 it encodes are indicated here,

NOTE Confidence: 0.825470216666667

00:18:52.030 --> 00:18:55.590 and not as many as with the HIV,

NOTE Confidence: 0.825470216666667

00:18:55.590 --> 00:18:58.830 but you do have.

NOTE Confidence: 0.825470216666667

00:18:58.830 --> 00:19:00.834 The The There's a proteases here

NOTE Confidence: 0.825470216666667

00:19:00.834 --> 00:19:03.393 that are sort of papain like protease

NOTE Confidence: 0.825470216666667

00:19:03.393 --> 00:19:06.067 and then the main protease and what

NOTE Confidence: 0.825470216666667

00:19:06.142 --> 00:19:08.669 we've worked on is the main protease.

NOTE Confidence: 0.825470216666667

00:19:08.670 --> 00:19:09.224 There's also,

NOTE Confidence: 0.825470216666667

00:19:09.224 --> 00:19:10.609 you've probably heard of the

NOTE Confidence: 0.825470216666667

00:19:10.609 --> 00:19:12.000 RNA dependent RNA polymerase.

NOTE Confidence: 0.825470216666667

00:19:12.000 --> 00:19:15.622 This is just to reproduce the RNA genome.

NOTE Confidence: 0.825470216666667

00:19:15.622 --> 00:19:18.470 That's another possible target,

NOTE Confidence: 0.825470216666667

00:19:18.470 --> 00:19:19.840 and some of the structural

NOTE Confidence: 0.825470216666667

00:19:19.840 --> 00:19:20.936 proteins are over here.

NOTE Confidence: 0.825470216666667

00:19:20.940 --> 00:19:23.520 There's the spike and the famous

NOTE Confidence: 0.825470216666667

00:19:23.520 --> 00:19:26.138 spike that is mutating and causing

NOTE Confidence: 0.825470216666667

00:19:26.138 --> 00:19:28.994 a lot of problems for the vaccines.

NOTE Confidence: 0.90919661

00:19:31.130 --> 00:19:35.561 So the cycle, the life cycle involves

NOTE Confidence: 0.90919661

00:19:35.561 --> 00:19:40.659 the COVID virus binding to the ACE 2

NOTE Confidence: 0.90919661

00:19:40.659 --> 00:19:45.040 receptors on the cells endocytosis.

NOTE Confidence: 0.90919661

00:19:45.040 --> 00:19:49.351 The RNA genome is unprocessed by a host of

NOTE Confidence: 0.90919661

00:19:49.351 --> 00:19:53.158 ribosomes to give you these two polyproteins.

NOTE Confidence: 0.90919661

00:19:53.160 --> 00:19:56.980 You similar situation with HIV,

NOTE Confidence: 0.90919661

00:19:56.980 --> 00:19:58.339 generating polyproteins that

NOTE Confidence: 0.90919661

00:19:58.339 --> 00:20:01.516 have to be cleaved by HIV. Areas.

NOTE Confidence: 0.90919661

00:20:01.516 --> 00:20:05.164 So here's where if we can stop this

NOTE Confidence: 0.90919661

00:20:05.164 --> 00:20:08.386 proteolysis step, the rest of the

NOTE Confidence: 0.90919661

00:20:08.386 --> 00:20:11.206 reproduction cycle stops and it's,

NOTE Confidence: 0.90919661

00:20:11.210 --> 00:20:13.765 I could say there aren't as many

NOTE Confidence: 0.90919661

00:20:13.765 --> 00:20:15.930 targets here as with the HIV.

NOTE Confidence: 0.90919661

00:20:15.930 --> 00:20:17.598 There's no integrase,

NOTE Confidence: 0.90919661

00:20:17.598 --> 00:20:19.266 no reverse transcriptase.

NOTE Confidence: 0.90919661

00:20:19.270 --> 00:20:22.310 And So what we picked in the beginning

NOTE Confidence: 0.90919661

00:20:22.310 --> 00:20:25.564 of 2020 that we would work on the

NOTE Confidence: 0.90919661

00:20:25.564 --> 00:20:26.999 protease almost because there's

NOTE Confidence: 0.90919661

00:20:26.999 --> 00:20:29.057 hardly anything else to work on

NOTE Confidence: 0.90919661

00:20:29.057 --> 00:20:31.239 and there was a crystal structure.

NOTE Confidence: 0.90919661

00:20:31.240 --> 00:20:36.364 Reported so the first thing we did.

NOTE Confidence: 0.90919661

00:20:36.370 --> 00:20:39.690 So this came about as as you recall,

NOTE Confidence: 0.90919661

00:20:39.690 --> 00:20:42.282 things got serious in late January

NOTE Confidence: 0.90919661

00:20:42.282 --> 00:20:45.340 2020 and then in March 2020 is

NOTE Confidence: 0.90919661

00:20:45.340 --> 00:20:49.540 one thing shut down. So we were.

NOTE Confidence: 0.90919661

00:20:49.540 --> 00:20:50.780 Sent out of the lab.

NOTE Confidence: 0.90919661

00:20:50.780 --> 00:20:52.887 You know, we could work from home.

NOTE Confidence: 0.90919661

00:20:52.890 --> 00:20:54.450 If you had special permission,

NOTE Confidence: 0.90919661

00:20:54.450 --> 00:20:55.830 you could work in the lab.

NOTE Confidence: 0.90919661

00:20:55.830 --> 00:20:57.930 But we didn't pursue that.

NOTE Confidence: 0.90919661

00:20:57.930 --> 00:20:59.778 But we decided for working at

NOTE Confidence: 0.90919661

00:20:59.778 --> 00:21:02.310 home that what we could do is we

NOTE Confidence: 0.90919661

00:21:02.310 --> 00:21:04.158 would do docking because we have

NOTE Confidence: 0.90919661

00:21:04.227 --> 00:21:05.670 the crystal structure,

NOTE Confidence: 0.90919661

00:21:05.670 --> 00:21:07.908 a crystal structure of the protease.

NOTE Confidence: 0.90919661

00:21:07.910 --> 00:21:09.510 So we would do docking.

NOTE Confidence: 0.90919661

00:21:09.510 --> 00:21:11.232 And the typical way docking works

NOTE Confidence: 0.90919661

00:21:11.232 --> 00:21:13.116 is you have the crystal structure

NOTE Confidence: 0.90919661

00:21:13.116 --> 00:21:15.454 and you have a library of compounds

NOTE Confidence: 0.90919661

00:21:15.454 --> 00:21:17.932 and these are typically commercially

NOTE Confidence: 0.90919661

00:21:17.932 --> 00:21:18.970 available compounds.

NOTE Confidence: 0.90919661

00:21:18.970 --> 00:21:19.788 There's a.

NOTE Confidence: 0.90919661

00:21:19.788 --> 00:21:21.833 Famous library called Zinc that

NOTE Confidence: 0.90919661

00:21:21.833 --> 00:21:24.803 has up to 100 million compounds

NOTE Confidence: 0.90919661

00:21:24.803 --> 00:21:27.708 and then the computers software

NOTE Confidence: 0.90919661

00:21:27.708 --> 00:21:30.519 combines them and it makes the

NOTE Confidence: 0.90919661

00:21:30.519 --> 00:21:33.416 complexes and then it has to score

NOTE Confidence: 0.90919661

00:21:33.416 --> 00:21:36.678 the complexes which is the weak spot.

NOTE Confidence: 0.90919661

00:21:36.680 --> 00:21:38.570 Often the scoring isn't very

NOTE Confidence: 0.90919661

00:21:38.570 --> 00:21:40.897 accurate but you can then test

NOTE Confidence: 0.90919661

00:21:40.897 --> 00:21:42.423 the high scoring molecules.

NOTE Confidence: 0.90919661

00:21:42.423 --> 00:21:46.230 Well that's a lot of compounds to deal with

NOTE Confidence: 0.90919661

00:21:46.309 --> 00:21:49.594 so I thought well we would do 1st instead.

NOTE Confidence: 0.90919661

00:21:49.600 --> 00:21:52.060 Is to dock known drugs,

NOTE Confidence: 0.90919661

00:21:52.060 --> 00:21:53.252 approved FDA approved drugs.

NOTE Confidence: 0.90919661

00:21:53.252 --> 00:21:55.873 So I happen to keep a library of

NOTE Confidence: 0.90919661

00:21:55.873 --> 00:21:58.547 these in the computer and there are

NOTE Confidence: 0.90919661

00:21:58.547 --> 00:22:00.427 three-dimensional structures of the drugs,

NOTE Confidence: 0.90919661

00:22:00.430 --> 00:22:02.866 which is this is all three-dimensional.

NOTE Confidence: 0.90919661

00:22:02.870 --> 00:22:07.049 And so I asked Muhammad and Julian.

NOTE Confidence: 0.90919661

00:22:07.050 --> 00:22:11.784 To dock the 2000 known drugs to see if

NOTE Confidence: 0.90919661

00:22:11.784 --> 00:22:16.363 we could see get some reasonable hits

NOTE Confidence: 0.90919661

00:22:16.363 --> 00:22:21.418 from that and So what happened was.

NOTE Confidence: 0.90919661

00:22:21.420 --> 00:22:24.796 The docking was done in a consensus fashion,

NOTE Confidence: 0.90919661

00:22:24.800 --> 00:22:26.700 meaning they used four different

NOTE Confidence: 0.90919661

00:22:26.700 --> 00:22:27.460 docking protocols,

NOTE Confidence: 0.90919661

00:22:27.460 --> 00:22:29.848 3 different programs and four ways

NOTE Confidence: 0.90919661

00:22:29.848 --> 00:22:32.333 of doing the docking because any

NOTE Confidence: 0.90919661

00:22:32.333 --> 00:22:34.775 one program we don't fully trust.

NOTE Confidence: 0.90919661

00:22:34.780 --> 00:22:38.420 So we're hoping that there will be a

NOTE Confidence: 0.90919661

00:22:38.420 --> 00:22:41.776 consensus where you score well in all four.

NOTE Confidence: 0.90919661

00:22:41.780 --> 00:22:46.064 Protocols. And so we got the list.

NOTE Confidence: 0.90919661

00:22:46.070 --> 00:22:52.499 Excuse me. I don't have code and I've tested.

NOTE Confidence: 0.90919661

00:22:52.500 --> 00:22:53.900 But.

NOTE Confidence: 0.90919661

00:22:53.900 --> 00:22:56.636 We we got the list of the top

NOTE Confidence: 0.90919661

00:22:56.636 --> 00:22:58.930 compounds and then, very importantly,

NOTE Confidence: 0.90919661

00:22:58.930 --> 00:23:01.755 we visualize the predicted poses,

NOTE Confidence: 0.90919661

00:23:01.760 --> 00:23:04.530 the complexes.

NOTE Confidence: 0.90919661

00:23:04.530 --> 00:23:07.210 And based on that visualization,

NOTE Confidence: 0.90919661

00:23:07.210 --> 00:23:10.269 we picked compounds that we think look

NOTE Confidence: 0.90919661

00:23:10.269 --> 00:23:13.080 good in the way they're positioned.

NOTE Confidence: 0.90919661

00:23:13.080 --> 00:23:16.230 And I also was very concerned about

NOTE Confidence: 0.90919661

00:23:16.230 --> 00:23:19.594 the idea that we would possibly be

NOTE Confidence: 0.90919661

00:23:19.594 --> 00:23:21.969 making analogs of these compounds

NOTE Confidence: 0.902261927142857

00:23:21.970 --> 00:23:25.072 because I didn't expect to have

NOTE Confidence: 0.902261927142857

00:23:25.072 --> 00:23:27.756 again come up with a 10 nanomolar

NOTE Confidence: 0.902261927142857

00:23:27.756 --> 00:23:30.148 compound we never have in the past.

NOTE Confidence: 0.902261927142857

00:23:30.150 --> 00:23:34.366 So we purchased 17 compounds and.

NOTE Confidence: 0.902261927142857

00:23:34.366 --> 00:23:37.196 Gave them to Karens lab,

NOTE Confidence: 0.902261927142857

00:23:37.200 --> 00:23:39.935 and Karen had meanwhile obtained

NOTE Confidence: 0.902261927142857

00:23:39.935 --> 00:23:41.892 the protein, expressed it,

NOTE Confidence: 0.902261927142857

00:23:41.892 --> 00:23:45.340 and she also had implemented the A fret

NOTE Confidence: 0.902261927142857

00:23:45.423 --> 00:23:48.267 assay that was from the literature.

NOTE Confidence: 0.902261927142857

00:23:48.270 --> 00:23:50.406 So she was ready to go.

NOTE Confidence: 0.902261927142857

00:23:50.410 --> 00:23:53.890 And the 17 compounds arrived.

NOTE Confidence: 0.902261927142857

00:23:53.890 --> 00:23:57.526 And to our surprise, in Karen's lab,

NOTE Confidence: 0.902261927142857

00:23:57.526 --> 00:24:01.626 14 of them showed some inhibition of the

NOTE Confidence: 0.902261927142857

00:24:01.626 --> 00:24:05.182 protease activity of Massar Scope 2 Proteus.

NOTE Confidence: 0.902261927142857

00:24:05.190 --> 00:24:06.210 So that was.

NOTE Confidence: 0.902261927142857

00:24:06.210 --> 00:24:06.550 Shocking.

NOTE Confidence: 0.902261927142857

00:24:06.550 --> 00:24:10.002 And so we were did very well on the

NOTE Confidence: 0.902261927142857

00:24:10.002 --> 00:24:12.222 compound selection and the most

NOTE Confidence: 0.902261927142857

00:24:12.222 --> 00:24:14.370 potent compounds are listed here.

NOTE Confidence: 0.902261927142857

00:24:14.370 --> 00:24:19.120 They were single digit micromolar.

NOTE Confidence: 0.902261927142857

00:24:19.120 --> 00:24:22.160 And but we had a bunch that were

NOTE Confidence: 0.902261927142857

00:24:22.160 --> 00:24:24.220 under about 50 micromolar.

NOTE Confidence: 0.902261927142857

00:24:24.220 --> 00:24:28.054 So that this we published and this is a

NOTE Confidence: 0.902261927142857

00:24:28.054 --> 00:24:31.289 picture of one of the dock structures.

NOTE Confidence: 0.902261927142857

00:24:31.290 --> 00:24:34.097 The binding site is you know is

NOTE Confidence: 0.902261927142857

00:24:34.097 --> 00:24:36.131 meant to accommodate a peptide

NOTE Confidence: 0.902261927142857

00:24:36.131 --> 00:24:38.770 that's going to get cleaved and we

NOTE Confidence: 0.902261927142857

00:24:38.770 --> 00:24:41.435 have site sub sites we call S1S1,

NOTE Confidence: 0.902261927142857

00:24:41.435 --> 00:24:44.901 Prime S2 and then this channel S3S4S5.

NOTE Confidence: 0.902261927142857

00:24:44.901 --> 00:24:47.918 So here's just a picture of a

NOTE Confidence: 0.902261927142857

00:24:47.918 --> 00:24:49.910 compound in that binding site.

NOTE Confidence: 0.902261927142857

00:24:49.910 --> 00:24:52.754 So we published that but of course

NOTE Confidence: 0.902261927142857

00:24:52.754 --> 00:24:55.280 we were looking very much now.

NOTE Confidence: 0.902261927142857

00:24:55.280 --> 00:24:57.404 And one of these compounds we're

NOTE Confidence: 0.902261927142857

00:24:57.404 --> 00:25:00.238 going to take and try to optimize it.

NOTE Confidence: 0.902261927142857

00:25:00.240 --> 00:25:02.180 And the compound we picked,

NOTE Confidence: 0.902261927142857

00:25:02.180 --> 00:25:04.068 we were we didn't say what it was

NOTE Confidence: 0.902261927142857

00:25:04.068 --> 00:25:06.099 going to be in this paper and it was

NOTE Confidence: 0.902261927142857

00:25:06.099 --> 00:25:07.977 not one of the most potent ones.

NOTE Confidence: 0.902261927142857

00:25:07.980 --> 00:25:11.388 In fact, it was this one param panel.

NOTE Confidence: 0.902261927142857

00:25:11.390 --> 00:25:14.650 Which is only 100 to 250 micromolar,

NOTE Confidence: 0.902261927142857

00:25:14.650 --> 00:25:17.679 so a relatively weak hit.

NOTE Confidence: 0.902261927142857

00:25:17.679 --> 00:25:23.940 But the fact was I liked the way it looked.

NOTE Confidence: 0.902261927142857

00:25:23.940 --> 00:25:28.188 And this was the dock structure.

NOTE Confidence: 0.902261927142857

00:25:28.190 --> 00:25:30.822 I'm orienting them all in the same

NOTE Confidence: 0.902261927142857

00:25:30.822 --> 00:25:34.354 way as 1S Primus 2 and I felt that

NOTE Confidence: 0.902261927142857

00:25:34.354 --> 00:25:36.384 the dock structure looked reasonable.

NOTE Confidence: 0.902261927142857

00:25:36.390 --> 00:25:38.870 Sometimes they they have features,

NOTE Confidence: 0.902261927142857

00:25:38.870 --> 00:25:41.068 they just say this doesn't feel right.

NOTE Confidence: 0.902261927142857

00:25:41.070 --> 00:25:42.514 But this looked reasonable.

NOTE Confidence: 0.902261927142857

00:25:42.514 --> 00:25:45.490 But I could also see that it had

NOTE Confidence: 0.902261927142857

00:25:45.490 --> 00:25:47.340 features that were not optimal.

NOTE Confidence: 0.902261927142857

00:25:47.340 --> 00:25:49.236 So looking at it over here,

NOTE Confidence: 0.902261927142857

00:25:49.240 --> 00:25:51.620 so the yellows are carbons,

NOTE Confidence: 0.902261927142857

00:25:51.620 --> 00:25:54.878 Reds are oxygens, Blues or nitrogens.

NOTE Confidence: 0.902261927142857

00:25:54.880 --> 00:25:57.448 I could see features that were not optimal.

NOTE Confidence: 0.902261927142857

00:25:57.450 --> 00:26:00.355 There's a histidine here and it could,

NOTE Confidence: 0.902261927142857

00:26:00.360 --> 00:26:02.504 it would be nice if it could form

NOTE Confidence: 0.902261927142857

00:26:02.504 --> 00:26:04.318 a hydrogen bond with this ring.

NOTE Confidence: 0.902261927142857

00:26:04.320 --> 00:26:06.464 So you probably want to put a nitrogen

NOTE Confidence: 0.902261927142857

00:26:06.464 --> 00:26:08.480 in here, this nitrogen of the purity,

NOTE Confidence: 0.902261927142857

00:26:08.480 --> 00:26:10.346 and that's not doing any good.

NOTE Confidence: 0.902261927142857

00:26:10.350 --> 00:26:12.639 So we can get rid of that.

NOTE Confidence: 0.902261927142857

00:26:12.640 --> 00:26:15.076 It's just spacing out into solvent.

NOTE Confidence: 0.902261927142857

00:26:15.080 --> 00:26:17.588 There's an NH over here that's.

NOTE Confidence: 0.902261927142857

00:26:17.590 --> 00:26:19.498 I would like to be in a hydrogen bond,

NOTE Confidence: 0.902261927142857

00:26:19.500 --> 00:26:20.853 but it isn't.

NOTE Confidence: 0.902261927142857

00:26:20.853 --> 00:26:21.304 Meanwhile,

NOTE Confidence: 0.902261927142857

00:26:21.304 --> 00:26:23.559 this carbonyl is just interacting

NOTE Confidence: 0.902261927142857

00:26:23.559 --> 00:26:24.660 with solvent,

NOTE Confidence: 0.902261927142857

00:26:24.660 --> 00:26:27.383 so maybe I could flip that from

NOTE Confidence: 0.902261927142857

00:26:27.383 --> 00:26:29.359 moving over left to there.

NOTE Confidence: 0.902261927142857

00:26:29.360 --> 00:26:31.817 Plus it looked like there was a

NOTE Confidence: 0.902261927142857

00:26:31.817 --> 00:26:34.772 little space in the meta position

NOTE Confidence: 0.902261927142857

00:26:34.772 --> 00:26:37.024 of that right ring.

NOTE Confidence: 0.902261927142857

00:26:37.030 --> 00:26:38.900 So.

NOTE Confidence: 0.902261927142857

00:26:38.900 --> 00:26:41.658 What happened next was we did some

NOTE Confidence: 0.902261927142857

00:26:41.658 --> 00:26:43.598 FEP calculations to test those

NOTE Confidence: 0.902261927142857

00:26:43.598 --> 00:26:45.992 ideas and this is what those are

NOTE Confidence: 0.902261927142857

00:26:45.992 --> 00:26:48.384 raw data looks like in an Excel

NOTE Confidence: 0.902261927142857

00:26:48.384 --> 00:26:51.308 sheet so that the the things I'm

NOTE Confidence: 0.902261927142857

00:26:51.308 --> 00:26:55.060 trying here are for the left ring.

NOTE Confidence: 0.869961365

00:26:55.060 --> 00:26:56.680 I'm going to try different rings.

NOTE Confidence: 0.869961365

00:26:56.680 --> 00:27:00.616 So ring scan where I did 234

NOTE Confidence: 0.869961365

00:27:00.616 --> 00:27:04.296 pyridinyl 4 pyrimidine 2 triazine,

NOTE Confidence: 0.869961365

00:27:04.300 --> 00:27:07.170 so a bunch of different rings there.

NOTE Confidence: 0.869961365

00:27:07.170 --> 00:27:10.242 They also did a calc and that those

NOTE Confidence: 0.869961365

00:27:10.242 --> 00:27:12.678 calculations said that the three pyridine

NOTE Confidence: 0.869961365

00:27:12.678 --> 00:27:15.510 the the negative number here is good.

NOTE Confidence: 0.869961365

00:27:15.510 --> 00:27:18.597 This is the change in free energy

NOTE Confidence: 0.869961365

00:27:18.597 --> 00:27:20.920 of binding relative to benzene.

NOTE Confidence: 0.869961365

00:27:20.920 --> 00:27:25.105 So this was saying go for the three pyrenee.

NOTE Confidence: 0.869961365

00:27:25.110 --> 00:27:27.902 Also I checked that ring flip of the

NOTE Confidence: 0.869961365

00:27:27.902 --> 00:27:30.027 carbonyl and that was very good,

NOTE Confidence: 0.869961365

00:27:30.030 --> 00:27:33.422 minus 4.7 and then over on the right

NOTE Confidence: 0.869961365

00:27:33.422 --> 00:27:36.270 side checking to see if we could

NOTE Confidence: 0.869961365

00:27:36.270 --> 00:27:39.030 put something in that meta position,

NOTE Confidence: 0.869961365

00:27:39.030 --> 00:27:41.984 indeed the meta position when we did

NOTE Confidence: 0.869961365

00:27:41.984 --> 00:27:44.718 a chlorine scan at each position,

NOTE Confidence: 0.869961365

00:27:44.720 --> 00:27:47.846 the meta here shed very good.

NOTE Confidence: 0.869961365

00:27:47.850 --> 00:27:50.066 Looks like we should put a chlorine there.

NOTE Confidence: 0.869961365

00:27:50.070 --> 00:27:52.985 So combining those three ideas

NOTE Confidence: 0.869961365

00:27:52.985 --> 00:27:55.317 led to then the.

NOTE Confidence: 0.869961365

00:27:55.320 --> 00:27:56.904 Three initial compounds

NOTE Confidence: 0.869961365

00:27:56.904 --> 00:27:58.488 that were synthesized.

NOTE Confidence: 0.869961365

00:27:58.490 --> 00:27:59.230 So here.

NOTE Confidence: 0.869961365

00:27:59.230 --> 00:28:01.450 Now I'm aligning everything so you

NOTE Confidence: 0.869961365

00:28:01.450 --> 00:28:04.450 can see the changes from parent panel,

NOTE Confidence: 0.869961365

00:28:04.450 --> 00:28:05.875 the three pyridyl.

NOTE Confidence: 0.869961365

00:28:05.875 --> 00:28:08.725 The carbonyl's been flipped and we've

NOTE Confidence: 0.869961365

00:28:08.725 --> 00:28:11.718 added the chlorine and we've left the

NOTE Confidence: 0.869961365

00:28:11.718 --> 00:28:14.419 the cyano phenyl from parent panel.

NOTE Confidence: 0.869961365

00:28:14.420 --> 00:28:18.868 I also from modeling with my bond program.

NOTE Confidence: 0.869961365

00:28:18.870 --> 00:28:19.392 Again, the,

NOTE Confidence: 0.869961365

00:28:19.392 --> 00:28:22.150 the slow part in all of this is synthesis.

NOTE Confidence: 0.869961365

00:28:22.150 --> 00:28:25.219 So we have plenty of time to do computer

NOTE Confidence: 0.869961365

00:28:25.219 --> 00:28:28.149 work while people are doing synthesis.

NOTE Confidence: 0.869961365

00:28:28.150 --> 00:28:31.594 So it's a natural thing to, you know,

NOTE Confidence: 0.869961365

00:28:31.594 --> 00:28:33.346 look very hard at these structures.

NOTE Confidence: 0.869961365

00:28:33.350 --> 00:28:35.915 And I had looked hard at this and I

NOTE Confidence: 0.869961365

00:28:35.915 --> 00:28:37.943 recognized maybe I could do something

NOTE Confidence: 0.869961365

00:28:37.943 --> 00:28:40.315 over with this ring because there's an

NOTE Confidence: 0.869961365

00:28:40.315 --> 00:28:42.527 edge that will show more clearly here

NOTE Confidence: 0.869961365

00:28:42.527 --> 00:28:46.554 of a loop that could use some hydrogen bonds.

NOTE Confidence: 0.869961365

00:28:46.560 --> 00:28:48.765 And I thought a uracil might work,

NOTE Confidence: 0.869961365

00:28:48.770 --> 00:28:49.730 so I'd modeled.

NOTE Confidence: 0.869961365

00:28:49.730 --> 00:28:51.330 Got with the program complex

NOTE Confidence: 0.869961365

00:28:51.330 --> 00:28:52.619 has looked very good.

NOTE Confidence: 0.869961365

00:28:52.620 --> 00:28:56.302 So we synthesized a uracil and also

NOTE Confidence: 0.869961365

00:28:56.302 --> 00:28:59.068 just this 35 dot clock compound.

NOTE Confidence: 0.869961365

00:28:59.068 --> 00:29:02.469 So this is a very happy day now.

NOTE Confidence: 0.869961365

00:29:02.470 --> 00:29:05.620 Because the potency of those original 3

NOTE Confidence: 0.869961365

00:29:05.620 --> 00:29:08.610 compounds was 10-6 and four micromolar.

NOTE Confidence: 0.869961365

00:29:08.610 --> 00:29:11.850 So here we've gotten a huge boost as

NOTE Confidence: 0.869961365

00:29:11.850 --> 00:29:14.448 expected from the FEP calculations.

NOTE Confidence: 0.869961365

00:29:14.450 --> 00:29:16.676 And this was the wonderful and I'll

NOTE Confidence: 0.869961365

00:29:16.676 --> 00:29:19.100 tell you the timing more in a bit,

NOTE Confidence: 0.869961365

00:29:19.100 --> 00:29:22.855 but this is now June of 2020.

NOTE Confidence: 0.869961365

00:29:22.855 --> 00:29:27.302 So we didn't get back into our lab until May.

NOTE Confidence: 0.869961365

00:29:27.302 --> 00:29:31.446 And now in June we have these,

NOTE Confidence: 0.869961365

00:29:31.450 --> 00:29:33.634 this 4 micromolar. Compound.

NOTE Confidence: 0.869961365

00:29:33.634 --> 00:29:34.726 We've only,

NOTE Confidence: 0.869961365

00:29:34.730 --> 00:29:37.978 and then it came a little later was

NOTE Confidence: 0.869961365

00:29:37.978 --> 00:29:40.250 actually October and Karen's group

NOTE Confidence: 0.869961365

00:29:40.250 --> 00:29:43.010 got a crystal structure for that

NOTE Confidence: 0.869961365

00:29:43.010 --> 00:29:45.709 dichloro compound and it's basically

NOTE Confidence: 0.869961365

00:29:45.709 --> 00:29:48.399 identical to what we've predicted.

NOTE Confidence: 0.869961365

00:29:48.400 --> 00:29:50.605 There's the carbonyl and hydrogen

NOTE Confidence: 0.869961365

00:29:50.605 --> 00:29:51.928 bond we wanted.

NOTE Confidence: 0.869961365

00:29:51.930 --> 00:29:53.760 There's a hydrogen bond between

NOTE Confidence: 0.869961365

00:29:53.760 --> 00:29:55.590 the pyridine and the histidine.

NOTE Confidence: 0.869961365

00:29:55.590 --> 00:29:58.110 We still have the nitrile hydrogen

NOTE Confidence: 0.869961365

00:29:58.110 --> 00:30:01.301 bonded in what he called the oxyanion

NOTE Confidence: 0.869961365

00:30:01.301 --> 00:30:04.633 sort of hole and the dichloro compound.

NOTE Confidence: 0.869961365

00:30:04.640 --> 00:30:07.110 Is again looking very good.

NOTE Confidence: 0.869961365

00:30:07.110 --> 00:30:07.555 Furthermore,

NOTE Confidence: 0.869961365

00:30:07.555 --> 00:30:10.670 we have this channel running N from

NOTE Confidence: 0.869961365

00:30:10.670 --> 00:30:13.792 the upper chlorine there and so we're

NOTE Confidence: 0.869961365

00:30:13.792 --> 00:30:16.438 ready to think about putting some

NOTE Confidence: 0.869961365

00:30:16.438 --> 00:30:18.940 of the something in that Channel.

NOTE Confidence: 0.869961365

00:30:18.940 --> 00:30:22.675 So the next thing was to try to grow

NOTE Confidence: 0.869961365

00:30:22.675 --> 00:30:24.922 substituents into that Channel and

NOTE Confidence: 0.869961365

00:30:24.922 --> 00:30:28.055 just for grins and I mean really not

NOTE Confidence: 0.869961365

00:30:28.055 --> 00:30:29.515 interested in methyl particularly,

NOTE Confidence: 0.784769928333333

00:30:29.520 --> 00:30:32.243 but just for grins, we did FP

NOTE Confidence: 0.784769928333333

00:30:32.243 --> 00:30:34.439 calculations for methyl ethyl propyl,

NOTE Confidence: 0.784769928333333

00:30:34.440 --> 00:30:36.756 O methyl ethyl propyl albuterol and

NOTE Confidence: 0.784769928333333

00:30:36.756 --> 00:30:39.555 then some ones with a hydroxyl that

NOTE Confidence: 0.784769928333333

00:30:39.555 --> 00:30:41.913 I figured probably wouldn't be very

NOTE Confidence: 0.784769928333333

00:30:41.913 --> 00:30:44.488 good problem with hydroxyl is it's

NOTE Confidence: 0.784769928333333

00:30:44.488 --> 00:30:46.840 very happy unbound said waters around

NOTE Confidence: 0.784769928333333

00:30:46.840 --> 00:30:49.000 and if you go bound it may be happy.

NOTE Confidence: 0.784769928333333

00:30:49.000 --> 00:30:51.544 Again, but you're not going to gain much.

NOTE Confidence: 0.784769928333333

00:30:51.550 --> 00:30:54.870 The way you gain is by having more

NOTE Confidence: 0.784769928333333

00:30:54.870 --> 00:30:57.632 hydrophobic pieces that are binding into

NOTE Confidence: 0.784769928333333

00:30:57.632 --> 00:31:00.404 hydrophobic part of the binding site.

NOTE Confidence: 0.784769928333333

00:31:00.410 --> 00:31:04.118 So this told us.

NOTE Confidence: 0.784769928333333

00:31:04.120 --> 00:31:06.360 Tried the O propyl compound

NOTE Confidence: 0.784769928333333

00:31:06.360 --> 00:31:08.152 so we synthesize on.

NOTE Confidence: 0.784769928333333

00:31:08.160 --> 00:31:10.180 There are two synthetic chemists

NOTE Confidence: 0.784769928333333

00:31:10.180 --> 00:31:14.016 are working on this so Lizzie and

NOTE Confidence: 0.784769928333333

00:31:14.016 --> 00:31:18.710 Chun way and so we they made.

NOTE Confidence: 0.784769928333333

00:31:18.710 --> 00:31:21.638 The proxy compound in both the

NOTE Confidence: 0.784769928333333

00:31:21.638 --> 00:31:25.120 cyano phenyl and the urea series,

NOTE Confidence: 0.784769928333333

00:31:25.120 --> 00:31:28.945 and this turned out great,

NOTE Confidence: 0.784769928333333

00:31:28.950 --> 00:31:33.356 140 nanomolar and 120 animal later on.

NOTE Confidence: 0.784769928333333

00:31:33.356 --> 00:31:34.968 This wasn't in sequence.

NOTE Confidence: 0.784769928333333

00:31:34.970 --> 00:31:37.586 We had made the trifluoromethyl analogs

NOTE Confidence: 0.784769928333333

00:31:37.586 --> 00:31:39.783 to that. They're more hydrophobic.

NOTE Confidence: 0.784769928333333

00:31:39.783 --> 00:31:42.258 They're probably going to be better

NOTE Confidence: 0.784769928333333

00:31:42.258 --> 00:31:44.382 binders as they were showing this

NOTE Confidence: 0.784769928333333

00:31:44.382 --> 00:31:46.597 one even down at 25 an animal,

NOTE Confidence: 0.784769928333333

00:31:46.600 --> 00:31:48.526 but generally I don't like CF.

NOTE Confidence: 0.784769928333333

00:31:48.530 --> 00:31:51.176 Big groups and drug like molecules

NOTE Confidence: 0.784769928333333

00:31:51.176 --> 00:31:53.495 because they really hurt the

NOTE Confidence: 0.784769928333333

00:31:53.495 --> 00:31:55.407 solubility of the compounds.

NOTE Confidence: 0.784769928333333

00:31:55.410 --> 00:31:58.659 So, but we're doing very well here 120.

NOTE Confidence: 0.784769928333333

00:31:58.659 --> 00:32:00.513 An animal or and I'll show

NOTE Confidence: 0.784769928333333

00:32:00.513 --> 00:32:02.050 you the timing on this,

NOTE Confidence: 0.784769928333333

00:32:02.050 --> 00:32:02.900 but this,

NOTE Confidence: 0.784769928333333

00:32:02.900 --> 00:32:06.500 this I think is in August now and

NOTE Confidence: 0.784769928333333

00:32:06.500 --> 00:32:09.650 Karen's group again got a crystal

NOTE Confidence: 0.784769928333333

00:32:09.650 --> 00:32:13.670 structure in October and it was exactly

NOTE Confidence: 0.784769928333333

00:32:13.670 --> 00:32:16.540 as expected including this bent.

NOTE Confidence: 0.784769928333333

00:32:16.540 --> 00:32:19.330 Hard at the at the end of the Propoxur group.

NOTE Confidence: 0.784769928333333

00:32:19.330 --> 00:32:21.800 And so it's a Ghosh. We call it a gauche.

NOTE Confidence: 0.784769928333333

00:32:21.800 --> 00:32:26.530 You've all taken organic chemistry, I'm sure.

NOTE Confidence: 0.784769928333333

00:32:26.530 --> 00:32:30.090 So that's the course you hated the most,

NOTE Confidence: 0.784769928333333

00:32:30.090 --> 00:32:31.778 but maybe, maybe not.

NOTE Confidence: 0.784769928333333

00:32:31.778 --> 00:32:33.466 But there it is.

NOTE Confidence: 0.784769928333333

00:32:33.470 --> 00:32:35.750 There's this gosche OCC and we

NOTE Confidence: 0.784769928333333

00:32:35.750 --> 00:32:38.019 had figured that was the case.

NOTE Confidence: 0.784769928333333

00:32:38.020 --> 00:32:40.981 The modeling told us that because at

NOTE Confidence: 0.784769928333333

00:32:40.981 --> 00:32:43.272 that terminal methyl fits right in

NOTE Confidence: 0.784769928333333

00:32:43.272 --> 00:32:47.930 the S4 site of the of that Channel.

NOTE Confidence: 0.784769928333333

00:32:47.930 --> 00:32:49.967 And so there's a lucine or problem,

NOTE Confidence: 0.784769928333333

00:32:49.970 --> 00:32:53.710 so hydrophobic site and so put

NOTE Confidence: 0.784769928333333

00:32:53.710 --> 00:32:55.580 it right in there also.

NOTE Confidence: 0.784769928333333

00:32:55.580 --> 00:32:57.300 Again, like I said,

NOTE Confidence: 0.784769928333333

00:32:57.300 --> 00:32:59.813 there's lots of time to do computing

NOTE Confidence: 0.784769928333333

00:32:59.813 --> 00:33:03.527 and so we considered benzel oxy groups.

NOTE Confidence: 0.784769928333333

00:33:03.527 --> 00:33:07.650 So you can imagine a benzene ring

NOTE Confidence: 0.784769928333333

00:33:07.772 --> 00:33:12.307 sitting here and potentially projecting.

NOTE Confidence: 0.784769928333333

00:33:12.310 --> 00:33:15.350 A substituent into that pocket.

NOTE Confidence: 0.784769928333333

00:33:15.350 --> 00:33:18.185 So sure enough we did modeling on

NOTE Confidence: 0.784769928333333

00:33:18.185 --> 00:33:21.135 these benzyl oxy analogs and did a

NOTE Confidence: 0.784769928333333

00:33:21.135 --> 00:33:24.103 chlorine scan on the fennel which said

NOTE Confidence: 0.784769928333333

00:33:24.103 --> 00:33:27.343 in a methyl scan and both methyl and

NOTE Confidence: 0.784769928333333

00:33:27.343 --> 00:33:30.216 chlorine were predicted to be very good.

NOTE Confidence: 0.784769928333333

00:33:30.220 --> 00:33:34.077 And so those compounds were made and

NOTE Confidence: 0.784769928333333

00:33:34.080 --> 00:33:37.280 the parent compounds 120 micromolar,

NOTE Confidence: 0.784769928333333

00:33:37.280 --> 00:33:40.500 but the ortho chloro compound

NOTE Confidence: 0.784769928333333

00:33:40.500 --> 00:33:44.308 18 an animal compound and this

NOTE Confidence: 0.784769928333333

00:33:44.308 --> 00:33:47.743 we had in October of of 2020.

NOTE Confidence: 0.784769928333333

00:33:47.743 --> 00:33:51.481 And Karen's group again got a

NOTE Confidence: 0.784769928333333

00:33:51.481 --> 00:33:55.367 crystal structure for the bend the

NOTE Confidence: 0.784769928333333

00:33:55.367 --> 00:33:58.537 parent Benz loxy components and

NOTE Confidence: 0.784769928333333

00:33:58.537 --> 00:34:01.669 is positioned as one expected.

NOTE Confidence: 0.784769928333333

00:34:01.670 --> 00:34:06.414 So this is just now a little video.

NOTE Confidence: 0.784769928333333

00:34:06.420 --> 00:34:10.380 To. Have those. Break this.

NOTE Confidence: 0.784769928333333

00:34:10.380 --> 00:34:12.319 This is a dimer, so they're two.

NOTE Confidence: 0.784769928333333

00:34:12.320 --> 00:34:15.835 This is Karen's crystal structure

NOTE Confidence: 0.784769928333333

00:34:15.835 --> 00:34:19.350 of the propoxur compound and

NOTE Confidence: 0.784769928333333

00:34:19.472 --> 00:34:21.967 just zeroing in on it.

NOTE Confidence: 0.784769928333333

00:34:21.970 --> 00:34:22.610 There.

NOTE Confidence: 0.9133051175

00:34:28.720 --> 00:34:30.348 OK, so you can.

NOTE Confidence: 0.76816073

00:34:34.270 --> 00:34:38.738 Run it again. So that little

NOTE Confidence: 0.76816073

00:34:38.738 --> 00:34:42.656 molecule is enough to shut down the

NOTE Confidence: 0.76816073

00:34:42.656 --> 00:34:45.900 enzymatic activity of that protein.

NOTE Confidence: 0.829809488333333

00:34:49.530 --> 00:34:54.240 OK, so this we published and.

NOTE Confidence: 0.829809488333333

00:34:54.240 --> 00:34:56.536 I was also saying a a second here,

NOTE Confidence: 0.829809488333333

00:34:56.540 --> 00:34:58.034 we're going to of course the

NOTE Confidence: 0.829809488333333

00:34:58.034 --> 00:34:59.687 well I've shown you so far

NOTE Confidence: 0.829809488333333

00:34:59.687 --> 00:35:00.895 is just protease inhibition.

NOTE Confidence: 0.829809488333333

00:35:00.900 --> 00:35:02.220 We've got to go into cells,

NOTE Confidence: 0.829809488333333

00:35:02.220 --> 00:35:05.020 infected cells and so that

NOTE Confidence: 0.829809488333333

00:35:05.020 --> 00:35:07.260 we published 28 compounds.

NOTE Confidence: 0.829809488333333

00:35:07.260 --> 00:35:08.815 Of course by the results

NOTE Confidence: 0.829809488333333

00:35:08.815 --> 00:35:10.370 I've talked about so far,

NOTE Confidence: 0.829809488333333

00:35:10.370 --> 00:35:12.554 we have lots of compounds here

NOTE Confidence: 0.829809488333333

00:35:12.554 --> 00:35:14.416 under the 50 nanomolar and

NOTE Confidence: 0.829809488333333

00:35:14.416 --> 00:35:16.420 you can see there are authors,

NOTE Confidence: 0.829809488333333

00:35:16.420 --> 00:35:18.484 lots of people involved and from

NOTE Confidence: 0.829809488333333

00:35:18.484 --> 00:35:20.190 the medical school, you know,

NOTE Confidence: 0.829809488333333

00:35:20.190 --> 00:35:22.200 fair and Isaacs and Brett Lindenbach,

NOTE Confidence: 0.829809488333333

00:35:22.200 --> 00:35:23.900 grouper and very important.

NOTE Confidence: 0.829809488333333

00:35:23.900 --> 00:35:26.450 Along with Karen in doing the

NOTE Confidence: 0.829809488333333

00:35:26.526 --> 00:35:28.626 cell assays that will describe in

NOTE Confidence: 0.829809488333333

00:35:28.626 --> 00:35:31.384 a Miller in a minute and Scott

NOTE Confidence: 0.829809488333333

00:35:31.384 --> 00:35:33.498 Miller in chemistry had donated

NOTE Confidence: 0.829809488333333

00:35:33.498 --> 00:35:35.538 his graduate student Lizzie Stone

NOTE Confidence: 0.829809488333333

00:35:35.538 --> 00:35:38.249 to help us with the synthesis,

NOTE Confidence: 0.829809488333333

00:35:38.250 --> 00:35:41.928 along with my postdoc Chunwei Zang.

NOTE Confidence: 0.829809488333333

00:35:41.930 --> 00:35:43.370 So that was good.

NOTE Confidence: 0.829809488333333

00:35:43.370 --> 00:35:45.530 We published that in ACS Central

NOTE Confidence: 0.829809488333333

00:35:45.602 --> 00:35:47.362 science in February 2022.

NOTE Confidence: 0.829809488333333

00:35:47.362 --> 00:35:49.714 A little later we also replaced

NOTE Confidence: 0.829809488333333

00:35:49.714 --> 00:35:52.329 the benzyl Oxy with heterocycles.

NOTE Confidence: 0.829809488333333

00:35:52.330 --> 00:35:54.190 This is a standard, I'd say,

NOTE Confidence: 0.829809488333333

00:35:54.190 --> 00:35:55.250 medicinal chemistry.

NOTE Confidence: 0.829809488333333

00:35:55.250 --> 00:35:58.690 This isn't, you know, genius stuff.

NOTE Confidence: 0.829809488333333

00:35:58.690 --> 00:36:01.933 Heterocycles often have some desirable

NOTE Confidence: 0.829809488333333

00:36:01.933 --> 00:36:04.948 properties over a substituted benzene.

NOTE Confidence: 0.829809488333333

00:36:04.950 --> 00:36:07.494 So we published some more compounds

NOTE Confidence: 0.829809488333333

00:36:07.494 --> 00:36:10.158 in the summer than of a 2021.

NOTE Confidence: 0.829809488333333

00:36:10.158 --> 00:36:11.294 We also.

NOTE Confidence: 0.829809488333333

00:36:11.294 --> 00:36:13.566 Tested cell permeability with

NOTE Confidence: 0.829809488333333

00:36:13.566 --> 00:36:17.782 a pampa assay in our lab and

NOTE Confidence: 0.829809488333333

00:36:17.782 --> 00:36:19.588 measured aqueous solubility.

NOTE Confidence: 0.829809488333333

00:36:19.590 --> 00:36:21.870 So now we have uracil's with

NOTE Confidence: 0.829809488333333

00:36:21.870 --> 00:36:24.169 the hydrogen or with a methyl.

NOTE Confidence: 0.829809488333333

00:36:24.170 --> 00:36:26.738 So the ones with the methyl are going

NOTE Confidence: 0.829809488333333

00:36:26.738 --> 00:36:28.794 to have better cell permeability.

NOTE Confidence: 0.829809488333333

00:36:28.794 --> 00:36:32.927 And so that is an issue because we want

NOTE Confidence: 0.829809488333333

00:36:32.927 --> 00:36:36.761 to show that we have efficacy and sell assay.

NOTE Confidence: 0.829809488333333

00:36:36.770 --> 00:36:38.550 So this is where the,

NOTE Confidence: 0.829809488333333

00:36:38.550 --> 00:36:40.475 again the folks here in the Med

NOTE Confidence: 0.829809488333333

00:36:40.475 --> 00:36:42.340 school are so important to us.

NOTE Confidence: 0.829809488333333

00:36:42.340 --> 00:36:45.430 The BSL three facility was used.

NOTE Confidence: 0.829809488333333

00:36:45.430 --> 00:36:48.800 There's krassimir getting suited up

NOTE Confidence: 0.829809488333333

00:36:48.800 --> 00:36:51.390 because COVID, of course, is airborne.

NOTE Confidence: 0.829809488333333

00:36:51.390 --> 00:36:53.975 He has to have a full breathing

NOTE Confidence: 0.829809488333333

00:36:53.975 --> 00:36:56.628 apparatus and the assays that were done.

NOTE Confidence: 0.829809488333333

00:36:56.630 --> 00:36:58.634 Karen certainly can describe these far

NOTE Confidence: 0.829809488333333

00:36:58.634 --> 00:37:01.380 better than I can, but there's one.

NOTE Confidence: 0.829809488333333

00:37:01.380 --> 00:37:05.270 It's a a plaque assay using infectious virus.

NOTE Confidence: 0.829809488333333

00:37:05.270 --> 00:37:08.645 And so you have the live these are Vero

NOTE Confidence: 0.829809488333333

00:37:08.650 --> 00:37:13.666 cells infected with large live SARS Cove two.

NOTE Confidence: 0.829809488333333

00:37:13.670 --> 00:37:15.836 And there's also then the replicon.

NOTE Confidence: 0.829809488333333

00:37:15.840 --> 00:37:18.000 Assay and the Republican

NOTE Confidence: 0.829809488333333

00:37:18.000 --> 00:37:20.160 isn't using infectious virus,

NOTE Confidence: 0.829809488333333

00:37:20.160 --> 00:37:22.416 but it's giving us a very

NOTE Confidence: 0.829809488333333

00:37:22.416 --> 00:37:23.544 virtually identical readout.

NOTE Confidence: 0.829809488333333

00:37:23.550 --> 00:37:27.878 So we're testing our compounds and we have

NOTE Confidence: 0.829809488333333

00:37:27.880 --> 00:37:31.996 as a as a reference compound remdesivir,

NOTE Confidence: 0.829809488333333

00:37:32.000 --> 00:37:36.500 which is A1 micromolar EC50

NOTE Confidence: 0.829809488333333

00:37:36.500 --> 00:37:40.280 and the assays that were done.

NOTE Confidence: 0.829809488333333

00:37:40.280 --> 00:37:42.338 And long short, we have many

NOTE Confidence: 0.829809488333333

00:37:42.338 --> 00:37:44.520 compounds that are one micromolar.

NOTE Confidence: 0.829809488333333

00:37:44.520 --> 00:37:46.240 We also have some compounds.

NOTE Confidence: 0.829809488333333

00:37:46.240 --> 00:37:49.318 This one's 38 nanomolar EC 50,

NOTE Confidence: 0.829809488333333

00:37:49.320 --> 00:37:51.628 that's inhibition of the

NOTE Confidence: 0.829809488333333

00:37:51.628 --> 00:37:53.936 of the protease activity,

NOTE Confidence: 0.829809488333333

00:37:53.940 --> 00:38:00.078 but it's not active in the replicant housing.

NOTE Confidence: 0.829809488333333

00:38:00.080 --> 00:38:01.420 And this simply because it

NOTE Confidence: 0.829809488333333

00:38:01.420 --> 00:38:02.760 doesn't get into the virus.

NOTE Confidence: 0.829809488333333

00:38:02.760 --> 00:38:04.740 Cell permeability is too low,

NOTE Confidence: 0.829809488333333

00:38:04.740 --> 00:38:07.638 so the cell permeability is critical.

NOTE Confidence: 0.829809488333333

00:38:07.640 --> 00:38:11.735 The quite remarkable compound is number 19.

NOTE Confidence: 0.829809488333333

00:38:11.740 --> 00:38:14.200 So this.

NOTE Confidence: 0.829809488333333

00:38:14.200 --> 00:38:17.302 Benzyl oxy compound that has a

NOTE Confidence: 0.829809488333333

00:38:17.302 --> 00:38:20.865 methylated uracil and in the assay it

NOTE Confidence: 0.829809488333333

00:38:20.865 --> 00:38:24.375 was 80 nanomolar in the infectious

NOTE Confidence: 0.829809488333333

00:38:24.375 --> 00:38:28.980 virus assay and 175 and the replicon assay.

NOTE Confidence: 0.829809488333333

00:38:28.980 --> 00:38:32.028 So this became our our lead

NOTE Confidence: 0.829809488333333

00:38:32.028 --> 00:38:35.180 compound for preclinical work.

NOTE Confidence: 0.829809488333333

00:38:35.180 --> 00:38:37.434 Now unfortunately in our world we can't,

NOTE Confidence: 0.778631126

00:38:37.440 --> 00:38:38.600 you know we're not Pfizer,

NOTE Confidence: 0.778631126

00:38:38.600 --> 00:38:41.168 so we can't take 10 compounds and put

NOTE Confidence: 0.778631126

00:38:41.168 --> 00:38:44.089 them all into preclinical studies but.

NOTE Confidence: 0.778631126

00:38:44.089 --> 00:38:48.321 We did work on 19 and a pharmaceutical

NOTE Confidence: 0.778631126

00:38:48.321 --> 00:38:51.648 company was very interested in 19.

NOTE Confidence: 0.778631126

00:38:51.650 --> 00:38:54.621 They took 19 and did their own sell

NOTE Confidence: 0.778631126

00:38:54.621 --> 00:38:57.218 assay and they came back and their

NOTE Confidence: 0.778631126

00:38:57.218 --> 00:39:00.166 cell was 15 animals they can confirmed

NOTE Confidence: 0.778631126

00:39:00.166 --> 00:39:03.070 everything that we we had reported.

NOTE Confidence: 0.778631126

00:39:03.070 --> 00:39:08.088 So that compound 19 is a very potent compound

NOTE Confidence: 0.778631126

00:39:08.088 --> 00:39:11.518 in infected cells and Karen's group has

NOTE Confidence: 0.778631126

00:39:11.518 --> 00:39:15.678 been working on the PK, it has very good.

NOTE Confidence: 0.778631126

00:39:15.678 --> 00:39:17.799 Basic PK bioavailability.

NOTE Confidence: 0.778631126

00:39:17.800 --> 00:39:21.496 And they have done with Pretty Kumar

NOTE Confidence: 0.778631126

00:39:21.496 --> 00:39:24.625 some initial mouse studies and this

NOTE Confidence: 0.778631126

00:39:24.625 --> 00:39:26.935 is with these humanized mouse mice,

NOTE Confidence: 0.778631126

00:39:26.940 --> 00:39:28.521 KTH 2 mice.

NOTE Confidence: 0.778631126

00:39:28.521 --> 00:39:31.156 And again Karen could describe

NOTE Confidence: 0.778631126

00:39:31.156 --> 00:39:33.778 the current status of this.

NOTE Confidence: 0.778631126

00:39:33.780 --> 00:39:37.014 But basically we were delighted a very

NOTE Confidence: 0.778631126

00:39:37.014 --> 00:39:41.088 low dose of the compounds that were using

NOTE Confidence: 0.778631126

00:39:41.088 --> 00:39:44.622 and if you don't untreated mouse after

NOTE Confidence: 0.778631126

00:39:44.622 --> 00:39:47.648 six days as this is now fluorescent.

NOTE Confidence: 0.778631126

00:39:47.648 --> 00:39:50.270 Imaging of where the virus is.

NOTE Confidence: 0.778631126

00:39:50.270 --> 00:39:53.406 So initially the virus goes into the lungs,

NOTE Confidence: 0.778631126

00:39:53.410 --> 00:39:56.858 but it makes its way into the brain.

NOTE Confidence: 0.778631126

00:39:56.860 --> 00:39:58.880 And at day six,

NOTE Confidence: 0.778631126

00:39:58.880 --> 00:40:01.450 the mouse is again horribly

NOTE Confidence: 0.778631126

00:40:01.450 --> 00:40:03.100 infected and dies.

NOTE Confidence: 0.778631126

00:40:03.100 --> 00:40:07.030 So we have tested we meaning Karen

NOTE Confidence: 0.778631126

00:40:07.030 --> 00:40:10.020 and pretty by both Ivy and oral.

NOTE Confidence: 0.881540801428571

00:40:12.100 --> 00:40:14.305 And the results have been very good.

NOTE Confidence: 0.881540801428571

00:40:14.310 --> 00:40:17.145 There's only one dose and you see

NOTE Confidence: 0.881540801428571

00:40:17.145 --> 00:40:19.462 protection for four days, you know,

NOTE Confidence: 0.881540801428571

00:40:19.462 --> 00:40:22.440 completely clean a mouse and even at 6 days.

NOTE Confidence: 0.881540801428571

00:40:22.440 --> 00:40:24.700 So with the oral, it's,

NOTE Confidence: 0.881540801428571

00:40:24.700 --> 00:40:26.340 you know, really very clean.

NOTE Confidence: 0.881540801428571

00:40:26.340 --> 00:40:28.500 So if this was being dosed every day,

NOTE Confidence: 0.881540801428571

00:40:28.500 --> 00:40:32.570 the feeling is infection that wouldn't go on.

NOTE Confidence: 0.881540801428571

00:40:32.570 --> 00:40:35.406 So we have very, you know,

NOTE Confidence: 0.881540801428571

00:40:35.406 --> 00:40:38.454 concur raging data with this compound.

NOTE Confidence: 0.881540801428571

00:40:38.460 --> 00:40:40.052 There has been some.

NOTE Confidence: 0.881540801428571

00:40:40.052 --> 00:40:42.042 You know again external interest

NOTE Confidence: 0.881540801428571

00:40:42.042 --> 00:40:43.730 in this compound, yeah,

NOTE Confidence: 0.881540801428571

00:40:43.730 --> 00:40:45.710 we think we if we had the resources we

NOTE Confidence: 0.881540801428571

00:40:45.760 --> 00:40:47.808 can come up with lots of other compounds,

NOTE Confidence: 0.881540801428571

00:40:47.810 --> 00:40:50.730 but we need support for this and are

NOTE Confidence: 0.881540801428571

00:40:50.730 --> 00:40:53.809 you know high level because these

NOTE Confidence: 0.881540801428571

00:40:53.809 --> 00:40:56.644 preclinical studies are are expensive.

NOTE Confidence: 0.881540801428571

00:40:56.650 --> 00:41:00.248 So just to compare what we've done.

NOTE Confidence: 0.881540801428571

00:41:00.250 --> 00:41:00.936 Versus others.

NOTE Confidence: 0.881540801428571

00:41:00.936 --> 00:41:04.116 So first of all our compound is a non

NOTE Confidence: 0.881540801428571

00:41:04.116 --> 00:41:06.664 covalent inhibitor by most of the other

NOTE Confidence: 0.881540801428571

00:41:06.664 --> 00:41:09.969 work in this area been covalent inhibitors.

NOTE Confidence: 0.881540801428571

00:41:09.970 --> 00:41:12.318 Up until recently covalent

NOTE Confidence: 0.881540801428571

00:41:12.318 --> 00:41:15.253 inhibitors were considered to be.

NOTE Confidence: 0.881540801428571

00:41:15.260 --> 00:41:17.905 Not desirable because you're always

NOTE Confidence: 0.881540801428571

00:41:17.905 --> 00:41:20.550 worried about off target activity.

NOTE Confidence: 0.881540801428571

00:41:20.550 --> 00:41:23.084 But here is how other people progress.

NOTE Confidence: 0.881540801428571

00:41:23.090 --> 00:41:25.370 So a lot of these things are peptidic.

NOTE Confidence: 0.881540801428571

00:41:25.370 --> 00:41:28.874 Generally we don't like peptidic inhibitors

NOTE Confidence: 0.881540801428571

00:41:28.874 --> 00:41:33.159 because they can be proteolysis by many.

NOTE Confidence: 0.881540801428571

00:41:33.160 --> 00:41:35.604 Proteolytic enzymes that exist

NOTE Confidence: 0.881540801428571

00:41:35.604 --> 00:41:40.326 in humans so but this is some of

NOTE Confidence: 0.881540801428571

00:41:40.326 --> 00:41:43.791 the compounds and EC 50 of 720.

NOTE Confidence: 0.881540801428571

00:41:43.791 --> 00:41:47.577 Remember we're 50 or 80 nanomolar.

NOTE Confidence: 0.881540801428571

00:41:47.580 --> 00:41:49.274 This is the COVID moon shot that

NOTE Confidence: 0.881540801428571

00:41:49.274 --> 00:41:50.998 got quite a bit of publicity.

NOTE Confidence: 0.881540801428571

00:41:51.000 --> 00:41:52.836 This is just the icy 50.

NOTE Confidence: 0.881540801428571

00:41:52.840 --> 00:41:56.505 They obtained an assay 2400

NOTE Confidence: 0.881540801428571

00:41:56.505 --> 00:42:00.748 compounds and the best IC50 they

NOTE Confidence: 0.881540801428571

00:42:00.748 --> 00:42:04.018 obtained is basically 100 nanomolar.

NOTE Confidence: 0.881540801428571

00:42:04.020 --> 00:42:04.760 At 30,

NOTE Confidence: 0.881540801428571

00:42:04.760 --> 00:42:07.720 we had made no more than 30 compounds

NOTE Confidence: 0.881540801428571

00:42:07.811 --> 00:42:10.169 and we were at 18 nanomolar.

NOTE Confidence: 0.881540801428571

00:42:10.170 --> 00:42:12.754 Another peptide peptide peptide,

NOTE Confidence: 0.881540801428571

00:42:12.754 --> 00:42:16.630 but this is a PAX lovin.

NOTE Confidence: 0.881540801428571

00:42:16.630 --> 00:42:21.005 So Pax Lovid is this neurometrix alvir,

NOTE Confidence: 0.881540801428571

00:42:21.010 --> 00:42:24.272 but you have to include a SIP

NOTE Confidence: 0.881540801428571

00:42:24.272 --> 00:42:25.204 inhibitor ritonavir.

NOTE Confidence: 0.881540801428571

00:42:25.210 --> 00:42:28.745 So ritonavir is an HIV protease inhibitor.

NOTE Confidence: 0.881540801428571

00:42:28.750 --> 00:42:30.000 Not something you probably want

NOTE Confidence: 0.881540801428571

00:42:30.000 --> 00:42:32.068 to take for a long time and have

NOTE Confidence: 0.881540801428571

00:42:32.068 --> 00:42:33.348 their side effects of that.

NOTE Confidence: 0.881540801428571

00:42:33.350 --> 00:42:34.610 Of course you're not going to take

NOTE Confidence: 0.881540801428571

00:42:34.610 --> 00:42:35.928 packs a little bit for a long time.

NOTE Confidence: 0.881540801428571

00:42:35.930 --> 00:42:37.610 So I guess it's OK,

NOTE Confidence: 0.881540801428571

00:42:37.610 --> 00:42:40.970 but on the other hand having to

NOTE Confidence: 0.881540801428571

00:42:40.970 --> 00:42:44.920 have the SIP inhibitor to keep the.

NOTE Confidence: 0.881540801428571

00:42:44.920 --> 00:42:48.178 Protease inhibitor from being chewed up.

NOTE Confidence: 0.881540801428571

00:42:48.180 --> 00:42:48.694 Metabolically.

NOTE Confidence: 0.881540801428571

00:42:48.694 --> 00:42:51.264 Is clearly not desirable because

NOTE Confidence: 0.881540801428571

00:42:51.264 --> 00:42:54.040 you don't want to be, you know,

NOTE Confidence: 0.881540801428571

00:42:54.040 --> 00:42:55.802 can have drug, drug interactions.

NOTE Confidence: 0.881540801428571

00:42:55.802 --> 00:42:58.126 This is our compound.

NOTE Confidence: 0.881540801428571

00:42:58.130 --> 00:42:59.465 Again, by comparison,

NOTE Confidence: 0.881540801428571

00:42:59.465 --> 00:43:01.690 other things that you know.

NOTE Confidence: 0.881540801428571

00:43:01.690 --> 00:43:03.685 I'm obviously a little bit prejudiced here,

NOTE Confidence: 0.881540801428571

00:43:03.690 --> 00:43:08.194 but this to me is a tough molecule.

NOTE Confidence: 0.881540801428571

00:43:08.200 --> 00:43:09.650 All the stereo chemistry going

NOTE Confidence: 0.881540801428571

00:43:09.650 --> 00:43:11.100 to be tough to synthesize.

NOTE Confidence: 0.881540801428571

00:43:11.100 --> 00:43:12.960 You have high cost of goods.

NOTE Confidence: 0.881540801428571

00:43:12.960 --> 00:43:15.216 It's peptic. You worry about that.

NOTE Confidence: 0.881540801428571

00:43:15.220 --> 00:43:16.760 It is a covalent inhibitor,

NOTE Confidence: 0.881540801428571

00:43:16.760 --> 00:43:18.660 covalently modifies the cyano,

NOTE Confidence: 0.881540801428571

00:43:18.660 --> 00:43:20.560 but it's probably reversible.

NOTE Confidence: 0.881540801428571

00:43:20.560 --> 00:43:21.610 Are covalent.

NOTE Confidence: 0.881540801428571

00:43:21.610 --> 00:43:24.235 There have been a synthesis

NOTE Confidence: 0.881540801428571

00:43:24.235 --> 00:43:26.740 issues with the compound.

NOTE Confidence: 0.881540801428571

00:43:26.740 --> 00:43:28.064 It's also intrinsically not

NOTE Confidence: 0.881540801428571

00:43:28.064 --> 00:43:29.719 as potent as our compound.

NOTE Confidence: 0.881540801428571

00:43:29.720 --> 00:43:34.870 It's a EC 50 or 740 whereas we're at you

NOTE Confidence: 0.881540801428571

00:43:34.870 --> 00:43:38.040 know 10 times more potent with there's no,

NOTE Confidence: 0.881540801428571

00:43:38.040 --> 00:43:40.771 we don't we know from our preclinical

NOTE Confidence: 0.881540801428571

00:43:40.771 --> 00:43:42.877 work on off target and SIP

NOTE Confidence: 0.881540801428571

00:43:42.877 --> 00:43:45.500 activity that we don't have any sip

NOTE Confidence: 0.881540801428571

00:43:45.500 --> 00:43:47.380 problems with the compound either.

NOTE Confidence: 0.906853313333333

00:43:47.380 --> 00:43:50.620 So the rest of the story.

NOTE Confidence: 0.906853313333333

00:43:50.620 --> 00:43:53.462 So why isn't our compound in clinical

NOTE Confidence: 0.906853313333333

00:43:53.462 --> 00:43:56.528 trials and that's a probably takes me

NOTE Confidence: 0.906853313333333

00:43:56.528 --> 00:44:00.107 more than the last time I I have here.

NOTE Confidence: 0.906853313333333

00:44:00.110 --> 00:44:02.630 But the packs of lovin and thermal,

NOTE Confidence: 0.906853313333333

00:44:02.630 --> 00:44:04.928 Trevor got into clinical trials very

NOTE Confidence: 0.906853313333333

00:44:04.928 --> 00:44:07.536 quickly because it was sitting on the

NOTE Confidence: 0.906853313333333

00:44:07.536 --> 00:44:09.895 shelf from the SARS Cove One project.

NOTE Confidence: 0.906853313333333

00:44:09.900 --> 00:44:11.976 They made a minor modification to

NOTE Confidence: 0.906853313333333

00:44:11.976 --> 00:44:13.897 make it have better solubility.

NOTE Confidence: 0.906853313333333

00:44:13.897 --> 00:44:16.760 So it was ready to go and

NOTE Confidence: 0.906853313333333

00:44:16.846 --> 00:44:18.846 so it's off and running,

NOTE Confidence: 0.906853313333333

00:44:18.850 --> 00:44:21.298 I doubt seriously it's the best.

NOTE Confidence: 0.906853313333333

00:44:21.300 --> 00:44:22.512 Drug possible,

NOTE Confidence: 0.906853313333333

00:44:22.512 --> 00:44:25.600 and there's no way, and well,

NOTE Confidence: 0.906853313333333

00:44:25.600 --> 00:44:27.910 time will tell the problem for the

NOTE Confidence: 0.906853313333333

00:44:27.910 --> 00:44:29.288 pharmaceutical companies that they're

NOTE Confidence: 0.906853313333333

00:44:29.288 --> 00:44:31.598 all in the business of making money.

NOTE Confidence: 0.906853313333333

00:44:31.600 --> 00:44:37.126 And so the before the end of last fall.

NOTE Confidence: 0.906853313333333

00:44:37.130 --> 00:44:39.468 People are getting kind of cocky about,

NOTE Confidence: 0.906853313333333

00:44:39.470 --> 00:44:41.880 you know, covid's under control,

NOTE Confidence: 0.906853313333333

00:44:41.880 --> 00:44:44.248 the vaccines are working.

NOTE Confidence: 0.906853313333333

00:44:44.248 --> 00:44:48.218 And then Omicron came along around December

NOTE Confidence: 0.906853313333333

00:44:48.218 --> 00:44:52.829 of last year and that's changed things a bit.

NOTE Confidence: 0.906853313333333

00:44:52.830 --> 00:44:57.074 But we'll see who has the, you know,

NOTE Confidence: 0.906853313333333

00:44:57.074 --> 00:45:00.018 stamina to advance additional protease

NOTE Confidence: 0.906853313333333

00:45:00.018 --> 00:45:02.038 inhibitors into the clinic because

NOTE Confidence: 0.906853313333333

00:45:02.038 --> 00:45:04.727 of the cost of the clinical trials.

NOTE Confidence: 0.906853313333333

00:45:04.730 --> 00:45:06.440 This is a timeline just showing

NOTE Confidence: 0.906853313333333

00:45:06.440 --> 00:45:08.569 the power I think of our approach.

NOTE Confidence: 0.906853313333333

00:45:08.570 --> 00:45:11.765 So June 15th all we had was parent panel.

NOTE Confidence: 0.906853313333333

00:45:11.770 --> 00:45:14.955 By August 3rd we had these six

NOTE Confidence: 0.906853313333333

00:45:14.955 --> 00:45:17.330 and four micromolar compounds.

NOTE Confidence: 0.906853313333333

00:45:17.330 --> 00:45:17.781 By.

NOTE Confidence: 0.906853313333333

00:45:17.781 --> 00:45:20.487 September 2nd we had the proxy

NOTE Confidence: 0.906853313333333

00:45:20.490 --> 00:45:22.284 140 nanomolar compound.

NOTE Confidence: 0.906853313333333

00:45:22.284 --> 00:45:26.470 September 10th we had the corresponding of.

NOTE Confidence: 0.906853313333333

00:45:26.470 --> 00:45:27.394 Benzyl oxy,

NOTE Confidence: 0.906853313333333

00:45:27.394 --> 00:45:30.166 uracil and then we started getting

NOTE Confidence: 0.906853313333333

00:45:30.166 --> 00:45:32.979 some crystal structures October 3rd.

NOTE Confidence: 0.906853313333333

00:45:32.980 --> 00:45:37.215 We had the first crystal structure October

NOTE Confidence: 0.906853313333333

00:45:37.215 --> 00:45:41.477 4th and also the Propoxur compound and

NOTE Confidence: 0.906853313333333

00:45:41.477 --> 00:45:46.298 but the speed here which we got to the.

NOTE Confidence: 0.906853313333333

00:45:46.300 --> 00:45:48.544 These sort of loading animal compounds

NOTE Confidence: 0.906853313333333

00:45:48.544 --> 00:45:51.581 again to get to 18 animal we had

NOTE Confidence: 0.906853313333333

00:45:51.581 --> 00:45:53.783 synthesized about 30 compounds and a

NOTE Confidence: 0.906853313333333

00:45:53.857 --> 00:45:56.708 few of them were things we probably 8

NOTE Confidence: 0.906853313333333

00:45:56.708 --> 00:46:01.780 or 10 of them were real or wild shots.

NOTE Confidence: 0.906853313333333

00:46:01.780 --> 00:46:03.796 And this synthesis was done by a gun.

NOTE Confidence: 0.906853313333333

00:46:03.800 --> 00:46:07.460 Postdoc chunwei and graduate student Lizzie.

NOTE Confidence: 0.906853313333333

00:46:07.460 --> 00:46:10.636 So that's the story and I I hope

NOTE Confidence: 0.906853313333333

00:46:10.636 --> 00:46:13.516 I've told you a little bit about

NOTE Confidence: 0.906853313333333

00:46:13.516 --> 00:46:16.359 what Karen and I do and the.

NOTE Confidence: 0.906853313333333

00:46:16.360 --> 00:46:21.099 Hour of combining the computation with the,

NOTE Confidence: 0.906853313333333

00:46:21.100 --> 00:46:21.982 you know,

NOTE Confidence: 0.906853313333333

00:46:21.982 --> 00:46:23.746 reliable assaying and crystallography

NOTE Confidence: 0.906853313333333

00:46:23.746 --> 00:46:26.179 is such a different world than

NOTE Confidence: 0.906853313333333

00:46:26.179 --> 00:46:28.279 what we lived in 20 years ago.

NOTE Confidence: 0.906853313333333

00:46:28.280 --> 00:46:32.848 So just thanking people in my lab notably.

NOTE Confidence: 0.906853313333333

00:46:32.850 --> 00:46:35.398 And Julian is a long-term associate other

NOTE Confidence: 0.906853313333333

00:46:35.398 --> 00:46:38.420 so he's a senior research scientist.

NOTE Confidence: 0.906853313333333

00:46:38.420 --> 00:46:41.696 Anna and Joe were both associate research

NOTE Confidence: 0.906853313333333

00:46:41.696 --> 00:46:44.639 scientist and other people listed here.

NOTE Confidence: 0.906853313333333

00:46:44.640 --> 00:46:47.292 Karen of course my.

NOTE Confidence: 0.906853313333333

00:46:47.292 --> 00:46:49.281 Wonderful collaborator and

NOTE Confidence: 0.906853313333333

00:46:49.281 --> 00:46:51.452 other Pi collaborators,

NOTE Confidence: 0.906853313333333

00:46:51.452 --> 00:46:57.222 pretty yosi on our Jack projects and Brett,

NOTE Confidence: 0.906853313333333

00:46:57.222 --> 00:47:00.806 Brett and Faron on the COVID project.

NOTE Confidence: 0.906853313333333

00:47:00.810 --> 00:47:02.406 So pleasure to be here with

NOTE Confidence: 0.906853313333333

00:47:02.406 --> 00:47:04.119 you and thank you very much.

NOTE Confidence: 0.739636152

00:47:11.700 --> 00:47:13.460 What a whirlwind journey.

NOTE Confidence: 0.739636152

00:47:13.460 --> 00:47:14.561 Yeah, amazing.

NOTE Confidence: 0.739636152

00:47:14.561 --> 00:47:17.866 Are there any questions here,

NOTE Confidence: 0.739636152

00:47:17.870 --> 00:47:19.214 Emily? Are you monitoring

NOTE Confidence: 0.739636152

00:47:19.214 --> 00:47:21.290 questions in the chat, Tommy?

NOTE Confidence: 0.8061161

00:47:34.810 --> 00:47:37.438 Yeah, these the COVID compounds

NOTE Confidence: 0.8061161

00:47:37.438 --> 00:47:40.630 are all binding to the active

NOTE Confidence: 0.805156937857143

00:47:40.733 --> 00:47:42.669 site of the Proteus.

NOTE Confidence: 0.805156937857143

00:47:42.670 --> 00:47:44.190 So the cysteine, that's a,

NOTE Confidence: 0.805156937857143

00:47:44.190 --> 00:47:45.126 there's a cysteine,

NOTE Confidence: 0.805156937857143

00:47:45.126 --> 00:47:46.374 it's a cysteine protease,

NOTE Confidence: 0.805156937857143

00:47:46.380 --> 00:47:47.672 there's a cysteine it.

NOTE Confidence: 0.805156937857143

00:47:47.672 --> 00:47:50.310 We're sort of in the middle of all

NOTE Confidence: 0.805156937857143

00:47:50.310 --> 00:47:52.206 the structures I showed you and

NOTE Confidence: 0.805156937857143

00:47:52.206 --> 00:47:54.268 that's the active site cysteine.

NOTE Confidence: 0.469477465

00:48:01.700 --> 00:48:02.330 Even fine.

NOTE Confidence: 0.79802995

00:48:07.620 --> 00:48:11.650 Yes, the the Pfizer compound

NOTE Confidence: 0.79802995

00:48:11.650 --> 00:48:15.150 binds in that same site, and it

NOTE Confidence: 0.79802995

00:48:15.150 --> 00:48:18.050 covalently modifies that cysteine.

NOTE Confidence: 0.79802995

00:48:18.050 --> 00:48:21.070 And you? Does not covalent.

NOTE Confidence: 0.23773223

00:48:27.120 --> 00:48:27.450 Yes.

NOTE Confidence: 0.46480277

00:48:33.910 --> 00:48:34.290 Dog.

NOTE Confidence: 0.52170563

00:48:40.210 --> 00:48:42.925 Quite understand, he's asking if

NOTE Confidence: 0.52170563

00:48:42.925 --> 00:48:45.100 in the crystal structure does

NOTE Confidence: 0.52170563

00:48:45.100 --> 00:48:48.380 it bind to the cleavage. Yes,

NOTE Confidence: 0.789376365

00:48:48.390 --> 00:48:51.178 and this is the.

NOTE Confidence: 0.789376365

00:48:51.180 --> 00:48:54.340 The cysteine there cysts 145

NOTE Confidence: 0.789376365

00:48:54.340 --> 00:48:57.500 and this histadine over here.

NOTE Confidence: 0.789376365

00:48:57.500 --> 00:48:59.436 Are the catalytic residues,

NOTE Confidence: 0.789376365

00:48:59.436 --> 00:49:03.388 so our compound sitting right on top of them.

NOTE Confidence: 0.789376365

00:49:03.390 --> 00:49:06.732 And the Pfizer compound covalently modifies

NOTE Confidence: 0.789376365

00:49:06.732 --> 00:49:10.648 that cysteine as do most of the other.

NOTE Confidence: 0.789376365

00:49:10.650 --> 00:49:13.296 There's a very few coat non covalent

NOTE Confidence: 0.789376365

00:49:13.296 --> 00:49:15.666 inhibitors have been reported for this.

NOTE Confidence: 0.789376365

00:49:15.666 --> 00:49:17.892 But we from the getco we wanted

NOTE Confidence: 0.789376365

00:49:17.892 --> 00:49:20.164 to pursue non covalent inhibitors

NOTE Confidence: 0.789376365

00:49:20.164 --> 00:49:22.514 just to avoid the potential

NOTE Confidence: 0.789376365

00:49:22.514 --> 00:49:24.719 issues of covalent inhibitors.

NOTE Confidence: 0.850728121428571

00:49:29.320 --> 00:49:31.310 So you know, we're we're

NOTE Confidence: 0.850728121428571

00:49:31.310 --> 00:49:33.300 extremely familiar with the hyper

NOTE Confidence: 0.850728121428571

00:49:33.374 --> 00:49:35.678 immutability of this virus in the

NOTE Confidence: 0.850728121428571

00:49:35.678 --> 00:49:37.910 spike protein to evade immunity.

NOTE Confidence: 0.850728121428571

00:49:37.910 --> 00:49:41.294 I wonder if you've done sort of low dose

NOTE Confidence: 0.850728121428571

00:49:41.294 --> 00:49:43.900 exposure and if there's a mutational.

NOTE Confidence: 0.850728121428571

00:49:43.900 --> 00:49:46.080 Response to to a protease

NOTE Confidence: 0.850728121428571

00:49:46.080 --> 00:49:47.388 inhibitor like this?

NOTE Confidence: 0.74597426

00:49:48.960 --> 00:49:50.432 Yeah, I haven't maybe.

NOTE Confidence: 0.74597426

00:49:50.432 --> 00:49:53.170 I mean, we haven't to my knowledge,

NOTE Confidence: 0.74597426

00:49:53.170 --> 00:49:55.250 unless Karen's been up to

NOTE Confidence: 0.74597426

00:49:55.250 --> 00:49:57.330 something I don't know about,

NOTE Confidence: 0.74597426

00:49:57.330 --> 00:50:01.154 the SARS Cove 1 protease and SARS Cove

NOTE Confidence: 0.74597426

00:50:01.154 --> 00:50:04.548 2 protease are extremely identical.

NOTE Confidence: 0.74597426

00:50:04.550 --> 00:50:07.022 They're the only differences are quite

NOTE Confidence: 0.74597426

00:50:07.022 --> 00:50:10.329 far from the the protease active site.

NOTE Confidence: 0.74597426

00:50:10.330 --> 00:50:15.398 So it's it's hoped that there won't be.

NOTE Confidence: 0.74597426

00:50:15.400 --> 00:50:17.640 A lot of mutations possible

NOTE Confidence: 0.74597426

00:50:17.640 --> 00:50:19.385 for the Proteus, however,

NOTE Confidence: 0.74597426

00:50:19.385 --> 00:50:21.360 it hasn't been under pressure.

NOTE Confidence: 0.74597426

00:50:21.360 --> 00:50:24.472 So I think with the Pax lovid treatments

NOTE Confidence: 0.74597426

00:50:24.472 --> 00:50:27.686 we will probably begin to see some

NOTE Confidence: 0.74597426

00:50:27.686 --> 00:50:30.530 mutations closer to the binding site.

NOTE Confidence: 0.74597426

00:50:30.530 --> 00:50:33.218 And there there was a recent

NOTE Confidence: 0.74597426

00:50:33.218 --> 00:50:34.562 paper in science,

NOTE Confidence: 0.74597426

00:50:34.570 --> 00:50:39.708 I believe is it science indicating some

NOTE Confidence: 0.74597426

00:50:39.710 --> 00:50:43.406 mutations that might arise in this Proteus,

NOTE Confidence: 0.74597426

00:50:43.410 --> 00:50:46.066 so it was under some pressure that they.

NOTE Confidence: 0.74597426

00:50:46.070 --> 00:50:46.802 Put it,

NOTE Confidence: 0.74597426

00:50:46.802 --> 00:50:49.364 but we haven't looked into that yet.

NOTE Confidence: 0.864771771111111

00:51:00.700 --> 00:51:03.472 So this is a this is a related question,

NOTE Confidence: 0.864771771111111

00:51:03.480 --> 00:51:05.853 but how different is the COVID 2

NOTE Confidence: 0.864771771111111

00:51:05.853 --> 00:51:07.700 protease active site from that

NOTE Confidence: 0.864771771111111

00:51:07.700 --> 00:51:09.615 of other common human proteases?

NOTE Confidence: 0.44774485

00:51:11.290 --> 00:51:16.818 Umm. Well, I would say it's it's the

NOTE Confidence: 0.44774485

00:51:16.818 --> 00:51:20.208 COVID active site is quite unique,

NOTE Confidence: 0.44774485

00:51:20.210 --> 00:51:22.500 but it's virtually identical to

NOTE Confidence: 0.44774485

00:51:22.500 --> 00:51:25.290 the SARS Cove one active site,

NOTE Confidence: 0.44774485

00:51:25.290 --> 00:51:26.956 but I don't think there's been a.

NOTE Confidence: 0.814747040909091

00:51:29.950 --> 00:51:33.373 I don't think that these inhibitors are

NOTE Confidence: 0.814747040909091

00:51:33.373 --> 00:51:35.660 generally inhibiting other proteases.

NOTE Confidence: 0.789001333333333

00:51:39.240 --> 00:51:42.156 So I I haven't heard that,

NOTE Confidence: 0.789001333333333

00:51:42.160 --> 00:51:45.272 so I don't expect it, but if they were,

NOTE Confidence: 0.789001333333333

00:51:45.272 --> 00:51:46.802 it would certainly be, I'd imagine

NOTE Confidence: 0.789001333333333

00:51:46.802 --> 00:51:48.698 it'd be assisting a protease would

NOTE Confidence: 0.789001333333333

00:51:48.698 --> 00:51:50.879 be the ones you'd be looking at.

NOTE Confidence: 0.867015158333333

00:51:53.250 --> 00:51:54.750 Well, we're we're at the hour.

NOTE Confidence: 0.867015158333333

00:51:54.750 --> 00:51:57.557 I can't thank you enough for this

NOTE Confidence: 0.867015158333333

00:51:57.557 --> 00:51:59.866 lucid explanation to a bunch of

NOTE Confidence: 0.867015158333333

00:51:59.866 --> 00:52:01.690 non chemists was really beautiful.

NOTE Confidence: 0.867015158333333

00:52:01.690 --> 00:52:03.590 Also on behalf of healthcare

NOTE Confidence: 0.867015158333333

00:52:03.590 --> 00:52:04.832 workers who, you know,

NOTE Confidence: 0.867015158333333

00:52:04.832 --> 00:52:06.519 see people with COVID all the time.

NOTE Confidence: 0.867015158333333

00:52:06.520 --> 00:52:07.426 It's wonderful work.

NOTE Confidence: 0.867015158333333

00:52:07.426 --> 00:52:10.000 Thank you very much. Thank you.