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2021.10.01 Seminar - Rong Fan, Yale University - Columbia BME Seminar Series - Fall 2021

https://www.youtube.com/watch/Ru_Jv2yDH9Q

00:00:10.480 okay go right ahead

00:00:13.120 hello welcome uh good morning to our bme

00:00:16.560 seminar series

00:00:18.480 hosted by the department of biomedical

00:00:21.359 engineering

00:00:22.720 now today we

00:00:24.480 continue to offer this lecture in a

00:00:26.720 hybrid format

00:00:28.720 with both a virtual and live

00:00:31.279 audience

00:00:33.200 the speaker will speak for approximately

00:00:36.320 40 minutes so there will be 15 to 20

00:00:38.640 minutes for q a

00:00:40.879 now for the virtual

00:00:42.840 audience throughout the presentation

00:00:46.640 please use the q and a feature at the

00:00:49.039 bottom of the screen

00:00:50.960 it's important not to not to use the

00:00:53.440 chat feature with the q a feature

00:00:59.359 as many questions

00:01:01.440 as possible at the end and of course the

00:01:04.159 live audience

00:01:06.080 can also ask questions

00:01:09.200 for now let us

00:01:10.840 welcome professor

00:01:13.200 wrong fan

00:01:14.560 dr farm is a professor of biomedical

00:01:17.280 engineering

00:01:18.400 and pathology at yale

00:01:20.880 he received a teaching chemistry at

00:01:23.200 berkeley he is

00:01:27.520 before joining the faculty of yale in

00:01:30.799 2010

00:01:33.600 his current research interest is in

00:01:36.079 developing

00:01:37.680 a single cell and spatial only

00:01:40.479 technologies to study

00:01:43.200 functional cellular heterogeneity

00:01:46.799 and intracellular signaling

00:01:49.439 in human cancers and the immune system

00:01:53.200 he has done seminole he has made seminal

00:01:56.719 contributions to the field particularly

00:01:59.280 in uh spatial

00:02:01.200 transcriptomics

00:02:03.200 he co-founded isoplexis

00:02:05.680 singleton biotechnology

00:02:08.560 and agnes of stomachs

00:02:10.720 he is the recipient of a number of

00:02:13.280 awards

00:02:14.640 including the nsf career award and the

00:02:18.000 practical fellowship

00:02:20.000 for science and engineering

00:02:22.400 so welcome

00:02:47.920 yeah okay so thank you so much ken um

00:02:51.200 for the introduction you know thank you

00:02:53.120 uh everyone for having me here

00:02:56.000 and kind of getting me out of my tiny

00:02:58.959 house and after this year and a half and

00:03:01.599 i i almost felt this unreal okay see see

00:03:04.720 so many people here in the same room

00:03:07.680 and so what i'm gonna talk about today

00:03:10.480 is um

00:03:12.239 it's not just a spatial omics

00:03:15.360 so our latest research efforts in my

00:03:17.920 laboratory but a little bit kind of how

00:03:20.319 i end up here as a biomedical engineer i

00:03:22.800 think many of you guys are very

00:03:24.959 fortunate you have biomedical

00:03:26.720 engineering

00:03:28.159 a major you can choose when i was

00:03:30.400 undergrad no okay

00:03:33.440 so

00:03:34.560 um

00:03:36.239 i'm gonna kind of kick off my talk uh

00:03:38.879 with the

00:03:40.000 this is my uh

00:03:41.680 kind of disclaimer

00:03:43.440 and

00:03:44.239 first of all to really

00:03:46.720 uh so say happy birthday to you guys i

00:03:49.519 think it's a 20th anniversary

00:03:52.560 and yeah happy birthday to you

00:03:55.920 and so this also the 20 years i think

00:03:59.120 after i arrived in u.s

00:04:01.599 and so the reason why

00:04:04.319 i'm able to come over here after this

00:04:06.560 kind of year and a half stuck in a home

00:04:09.200 positive because the advance of the size

00:04:12.159 that made amazing vaccine all right

00:04:15.120 and then flip vaccinate i'm able to come

00:04:17.199 here here

00:04:18.798 and

00:04:19.600 so

00:04:20.320 i'm going to start my talk actually also

00:04:23.360 from

00:04:24.240 the story about vaccine about 15 years

00:04:26.880 ago and

00:04:29.759 that was a very very promising vaccine i

00:04:32.400 think everyone

00:04:33.759 uh hoped that going to work and a

00:04:35.440 complete cure

00:04:37.280 that there's also pandemic that's an

00:04:39.360 aids hiv

00:04:41.440 i think a merc developed a vaccine

00:04:44.240 this t-cell vaccine and the successfully

00:04:46.880 pushed to on away all the way to

00:04:48.720 interface three clinical trial

00:04:50.960 and in phase one phase two all patients

00:04:53.360 or

00:04:54.320 volunteers develop anticipated email

00:04:56.880 response

00:04:58.080 but still completely failed and

00:05:00.320 afterwards and the experts got together

00:05:02.479 discuss why i think of many different

00:05:04.960 reasons for sure i think human monkey is

00:05:07.039 slightly different they gotta understand

00:05:08.639 better how the

00:05:10.720 vaccine works seem uh in human

00:05:14.160 and rather than just the monkey but one

00:05:16.639 thing that got my attention is right

00:05:18.560 here so

00:05:19.680 there's a the acid

00:05:22.240 which is still the gold standard

00:05:24.400 nowadays in a vaccine industry it's a

00:05:26.560 kind of

00:05:27.520 single parameter l-spot acid to look at

00:05:30.160 all different uh

00:05:31.759 activated t cells

00:05:33.520 and but biologists immunologists back to

00:05:36.400 that time order recognized that's not

00:05:38.639 enough okay you really need to look at a

00:05:41.039 large panel of proteins secreted from

00:05:44.080 single t cell to really understand the

00:05:46.000 quality of that t cells

00:05:48.800 but unfortunately no technologies exist

00:05:51.280 i think it will allow you to do so

00:05:53.520 and that time i i just switched my

00:05:55.840 career from

00:05:57.199 physical science to biomedical

00:05:59.039 engineering to narrative biomedical

00:06:01.199 engineering so kind of about medical

00:06:03.280 research

00:06:04.479 and i knew very little about biology or

00:06:07.360 medical science that i thought okay this

00:06:09.440 is something seems like we really need

00:06:11.919 to have

00:06:13.039 in the future from the vaccine

00:06:14.479 development let me go ahead and develop

00:06:16.880 this tool

00:06:18.479 and so but you really need to look at a

00:06:21.520 single cells in this case so multiple

00:06:24.000 proteins because it is the capability

00:06:27.039 of every cell to produce multiple

00:06:29.360 solutions so if you have

00:06:31.280 cytokine a and a b and a c produced by

00:06:34.080 three different cells that doesn't count

00:06:36.960 so single cell analysis back to 2006

00:06:40.800 that's basically

00:06:42.960 so ver very little about the single cell

00:06:45.840 analysis you can do

00:06:48.560 very few technologies you can use

00:06:51.440 and so

00:06:52.880 i think a few papers array in early

00:06:55.560 2007 so if you can

00:06:58.639 measure just a couple proteins from one

00:07:01.759 cell that's a science paper okay

00:07:03.599 probably 2007.

00:07:05.919 and i think a nancy uh uh alberton also

00:07:10.319 was one of the pioneers i think working

00:07:12.319 on single cell

00:07:14.560 so electrophoresis using the chem using

00:07:17.759 the analytical chemistry approach

00:07:20.240 but you don't get enough throughput uh

00:07:22.160 at all you can just get a white cell and

00:07:24.319 do electrophoresis literally you are not

00:07:26.880 able to do extremely high plaques

00:07:29.199 you are not able to look at that many

00:07:31.599 proteins you need to

00:07:33.199 measure to understand the biology and

00:07:35.520 you are not able to measure hundreds or

00:07:37.360 thousands of single cells in parallel

00:07:40.639 so i think what i propose back to that

00:07:43.280 time is okay

00:07:44.720 can we

00:07:45.840 miniaturize the dna microwave which i

00:07:48.240 learned in the on the protein micro

00:07:50.639 which i learned as the first thing when

00:07:52.720 i joined caltech uh jim heath's lab it's

00:07:56.479 basically

00:07:57.440 which is a microarray-based fertilizer

00:07:59.919 i was thinking can we making the light

00:08:02.240 the microarray much much smaller and

00:08:04.720 highly ministerized to put in a tiny

00:08:07.199 tiny chamber

00:08:08.560 uh the volume is about one nanoliter if

00:08:11.280 you have one cell in one nano liter

00:08:13.680 chamber

00:08:14.639 i think you guys probably caught

00:08:15.840 yourselves

00:08:17.199 all the time you know okay typically one

00:08:19.680 million cells per ml

00:08:21.599 if i have one cell per one nanoliter

00:08:24.319 actually have the equivalent

00:08:26.560 volume per cell

00:08:28.560 that means okay if that cell is

00:08:30.160 producing the same amount of proteins

00:08:32.320 you should have the same concentration

00:08:34.000 so

00:08:34.719 okay if that's the case that should work

00:08:37.039 if you can really miniaturize the

00:08:38.640 microarray so this is the microwave i

00:08:41.279 proposed to do multiplex uh protein

00:08:44.560 analysis

00:08:45.839 uh in particular protein secretion but

00:08:48.000 actually you can also license the cell

00:08:49.519 to look at intracellular phosphorus

00:08:50.959 proteomics as well

00:08:53.200 and so that time i actually reached out

00:08:56.399 to merck vp working on that clinical

00:08:58.640 trial but they said okay we completed

00:09:00.800 this continuing that trial we're not

00:09:02.560 gonna

00:09:03.519 kind of do anything further

00:09:05.760 with those samples but fortunately i met

00:09:08.160 a tony rivers and uh so tony was working

00:09:11.120 on

00:09:11.839 cancer immunotherapy using uh cpo4 and

00:09:14.560 the and the later in the famous pd1 he

00:09:17.360 chewed that trial he started very first

00:09:19.680 the key through the trial and i met with

00:09:22.959 tony and we started to use this

00:09:25.519 technology to look at a tcr engineer t

00:09:28.399 cells to show human melanoma

00:09:30.560 i think in the paper publisher 2011

00:09:32.800 demonstrate indeed that's totally true

00:09:35.680 okay if you can see poorly functional t

00:09:38.080 cells as predicted

00:09:40.399 and those polar functional t cells gonna

00:09:42.959 give you much better clinical outcome in

00:09:45.440 patients

00:09:47.920 so in melanoma patients traded with

00:09:50.720 the uh the tcr engineer t-cells there's

00:09:53.279 a mark one

00:09:54.959 multi-one engineer um

00:09:57.920 these are uh adaptive transfer t-cells

00:10:01.680 and so

00:10:03.600 so so that's in the beginning so people

00:10:06.000 started to think about can we

00:10:08.399 look at hundreds or thousands of single

00:10:10.720 cells but also

00:10:12.320 uh extremely high plaques for proteins

00:10:15.120 first but people also try to do

00:10:17.440 uh kind of different transcripts and

00:10:19.600 other bio biological analytes

00:10:22.640 and so when i joined the yale 2010

00:10:26.720 and i i was very proud of this device i

00:10:29.440 developed caltech and i took this device

00:10:31.519 to my clinical collaborator at yale

00:10:34.560 and i still like this device but but

00:10:36.959 they had no idea how to use this uh this

00:10:39.760 beautiful device with that spaghetti

00:10:41.680 stuff

00:10:42.560 on the left

00:10:44.079 and and then i realized actually this is

00:10:46.480 an engineering problem since i'm in an

00:10:49.120 engineering school now i should take on

00:10:52.160 that challenge

00:10:53.600 and

00:10:54.640 uh so about like a half a year after i

00:10:57.920 joined um i joined the yale i think

00:11:00.399 mario roddler who i reached out to even

00:11:03.040 when i was a postdoc to discuss

00:11:05.279 this t-cell poly functionality

00:11:07.519 analysis and and he basically a proposal

00:11:10.640 on a theory for the functional t cells

00:11:13.440 correlates with

00:11:15.120 the uh sort of

00:11:17.079 immunodurability and the potency and the

00:11:19.279 durability in t-cell mediated immunity

00:11:23.040 and he invited me to a very nice

00:11:25.120 conference in greece and so i don't know

00:11:28.160 if anyone being there you can't

00:11:29.680 recognize this is a mykonos

00:11:32.480 and

00:11:33.680 and at that conference i was speaking

00:11:36.000 back to back with scott tanner and

00:11:38.720 and after scott's talk and gary nolan

00:11:43.279 was there and uh he he was sitting in

00:11:45.600 the second row of that that conference

00:11:47.519 room

00:11:48.480 and he thought wow that's transformative

00:11:50.720 okay that's how come actual site have

00:11:53.600 started okay uh cyto started to be

00:11:56.000 adopted by

00:11:57.839 by immunologists and that's how the

00:11:59.839 entire field um kind of emerged uh this

00:12:03.920 sort of high plex proteomic single cell

00:12:06.800 analysis

00:12:08.880 so after my talk i was

00:12:11.440 uh i was talking to uh derek bush and

00:12:14.800 that was his response yeah maybe and and

00:12:17.920 i realized why because the device is so

00:12:20.639 complicated with those spaghetti stuff

00:12:23.519 and i really need to

00:12:25.680 kind of sit down think about how to

00:12:27.279 redesign a device and really achieve

00:12:29.600 high throughput now also uh high plaques

00:12:32.320 and uh uh samara rather give give me a

00:12:35.680 list of honor proteins relevant to these

00:12:38.320 activation functions about 42 40 to 45

00:12:42.000 different proteins

00:12:43.760 but then i can measure all of them i

00:12:45.519 think that's extremely challenging

00:12:47.920 uh so over the uh the about five years

00:12:51.519 after i joined the yale and so i

00:12:54.160 gradually

00:12:55.600 kind of redesigned the whole device and

00:12:57.519 applied the technology to different

00:12:59.279 biological questions i think not just

00:13:01.279 the t-cells but also

00:13:03.440 in native immune cells

00:13:05.440 as well as cancer cells actually the

00:13:08.160 cancer cells in the bone marrow in the

00:13:10.320 leukemic bone marrow can produce many

00:13:13.440 different cytokines to to to drive

00:13:16.639 the inflammatory bone marrow micro

00:13:18.639 environment and then driving the

00:13:20.160 pathogenesis

00:13:22.720 so uh so

00:13:25.519 i think around this same time i think my

00:13:27.600 postal advisor jim heath also

00:13:30.399 uh so taking the technology a little bit

00:13:32.480 to look at intracellular phosphorus

00:13:33.920 proteinomics as well so the technology

00:13:36.800 is not limited to secretor proteins

00:13:39.760 but i think my

00:13:41.120 focus in my in my own laboratories has

00:13:43.680 been yeah how to characterize the

00:13:45.920 immunoso activation states using the

00:13:49.120 highly multiplexed protein secretion

00:13:51.360 assay

00:13:52.560 and so if you are curious

00:13:54.880 what the device looks like now

00:13:57.600 and

00:13:58.560 this is a much much simpler okay

00:14:01.519 you don't have that spaghetti stuff

00:14:03.839 anymore

00:14:05.120 and there's just a bunch of open micro

00:14:07.519 troughs if you can if you know how to

00:14:09.440 use pipette you should be able to

00:14:10.959 disperse the cells

00:14:12.560 to the surface of that device and put a

00:14:14.880 glass line on top the glass slide has

00:14:17.600 bunch of

00:14:19.519 antibiotic stripes and within each

00:14:22.000 chamber you have a whole set of

00:14:24.639 antibiotic stripes to measure up to 42

00:14:27.760 different cytokines

00:14:29.680 and a single cell level so you can image

00:14:31.920 which chamber has one cell which has two

00:14:34.000 or three so basically you can look at

00:14:36.880 single cell secretion single cell

00:14:39.120 protein armic profile but also you can

00:14:42.160 also see how when the two cells there

00:14:44.480 how they talk to each other so if you

00:14:46.240 can decipher

00:14:47.920 the secret conversation between the

00:14:49.839 cells by measuring the proteins produced

00:14:52.480 by those two cells in the same chamber

00:14:55.519 and so the technology was uh uh used by

00:14:59.120 uh i think both novartis and kai pharma

00:15:01.839 on the cartesian therapy companies

00:15:04.240 actually novartis reached out to us

00:15:06.079 first

00:15:07.279 i just want to show you one example

00:15:09.760 and so the i think the kai pharma

00:15:13.440 use the single cell proteomics uh

00:15:15.760 technology we developed to characterize

00:15:18.160 the pre-infusion car t cell products

00:15:21.360 right before

00:15:22.959 you give back to the patients

00:15:25.199 and they found indeed okay the ability

00:15:28.320 for every car t cells to co-produce

00:15:31.199 multiple cytokines as defined here as

00:15:34.160 poor functional strength index

00:15:36.320 correlates very well with the clinical

00:15:38.560 outcome of those patients all the

00:15:40.639 non-responders

00:15:42.399 most of them have much lower psi for the

00:15:45.360 functional strength index

00:15:47.279 and the beginning even before you give

00:15:49.920 the car t cells back to the patient if

00:15:52.000 you look at

00:15:53.360 the responders versus non-responders and

00:15:55.680 the p-value is statistically significant

00:15:58.560 so if our immunologists we're going to

00:16:00.639 look at many other things like

00:16:03.279 whether or not

00:16:04.560 those cells are producing interferon and

00:16:07.199 whether or not you have

00:16:08.880 helper cells versus a toxic t cells

00:16:12.079 and but none of them gives you no

00:16:14.560 correlation with the clinical outcome

00:16:16.959 except this poly functional strength

00:16:18.720 index

00:16:19.920 i think the idea i realized actually

00:16:22.079 pretty straightforward

00:16:23.680 pretty intuitive so if if you're asking

00:16:26.959 what the non-t-cell is going to do in a

00:16:28.720 job okay learn the t-cells can a hammer

00:16:31.360 and t-cells give them

00:16:33.120 an antigen-specific stimulation and see

00:16:35.600 what they can do right so that's much

00:16:38.079 more direct measurement of the t-cell

00:16:40.240 function rather than you look at all the

00:16:42.079 profiles okay the analogy is just like

00:16:45.199 for me speaking here you look at my hair

00:16:48.079 look at my skin color you see okay this

00:16:49.920 is the asian from china maybe he's not a

00:16:52.240 good speaker but why not put him on a

00:16:54.720 stage let him speak okay the same thing

00:16:56.880 that's what i think

00:16:58.320 what's the best way to evaluate in the

00:17:00.160 t-cell function here

00:17:02.880 so i think about a couple years uh later

00:17:05.839 so that's another major breakthrough in

00:17:07.679 the field so

00:17:09.760 not only in the proteins

00:17:11.839 you can look at transcripton scale on a

00:17:14.799 genes and a single cell level but also

00:17:17.280 extremely high through rules

00:17:19.520 so i think back to 2011 in my laboratory

00:17:22.640 i also started to work on the single

00:17:24.640 cell transport on sequencing

00:17:26.720 but until uh

00:17:28.760 2015 i think

00:17:30.720 the two papers published back to back

00:17:33.600 to show you can actually a molecular

00:17:35.919 barcode

00:17:37.120 on a transcript from the same cell and

00:17:39.600 pull

00:17:40.559 the cda together to to do

00:17:43.280 uh poor this uh sequencing by

00:17:45.520 computational reconstructed single cell

00:17:48.400 gene expression then you'll finally

00:17:51.600 achieve not extremely high throughput or

00:17:54.000 massively parallel single cell

00:17:55.520 transcriptone

00:17:57.200 profiling so the two papers published

00:17:59.600 back to back 2015

00:18:04.080 from two different groups but you you'll

00:18:06.000 find that one person i think is here in

00:18:08.320 the authorship that's dave white so

00:18:10.559 basically dave

00:18:12.400 developed all the droplet microfluidic

00:18:14.480 systems so if the micro food is really

00:18:16.799 enabling

00:18:18.160 this massive parallel single cell oh mix

00:18:22.480 so in my laboratory we're able to

00:18:24.480 combine i'm not showing the the protein

00:18:26.720 data in this case but we're able to

00:18:28.400 combine

00:18:29.600 the t cell protein data and the single

00:18:32.480 cell transcripton to to really pinpoint

00:18:35.360 the mechanism

00:18:36.880 underlying this poly functional strength

00:18:39.039 index or poly functionality of

00:18:41.919 single-car t-cells so i found something

00:18:44.880 very very striking

00:18:47.120 so immunologists know okay that the

00:18:49.520 t-cells can polarize into type 1 type 2

00:18:54.240 so th1 th2

00:18:56.400 some of them like th17 but you should

00:18:58.640 now see

00:18:59.760 so if the hybrid type 1 slash type 2 you

00:19:03.679 may see that transient state

00:19:05.760 but we found that car t cells upon

00:19:07.840 antigen specific activation are

00:19:10.480 most of the hybrid type 1 type 2

00:19:13.440 phenotype that's a very interesting

00:19:16.080 but on the other hand think about those

00:19:17.919 are the t cells made by scientists okay

00:19:20.320 they're not existing

00:19:22.799 in sort of the natural immune system of

00:19:25.440 normal healthy individuals they're

00:19:27.840 they're made by scientists engineers so

00:19:30.640 they're kind of like aliens or monsters

00:19:33.200 they can do something

00:19:35.120 charlie january's textbook does not tell

00:19:37.200 you so

00:19:39.120 but on the other hand this kind of

00:19:40.720 confirms of those t cells those car t

00:19:43.919 cells are extremely poorly functional

00:19:46.960 so the question is whether on the polar

00:19:48.720 functionality and the underlying

00:19:50.720 maximums really dictate

00:19:52.799 the clinical outcome so this paper will

00:19:55.039 show from just a healthy donor derived

00:19:57.200 car t cells and then we'll try try to

00:19:59.679 ask whether or not

00:20:01.360 napoleon functionality of those car t

00:20:03.520 cells really predicts the clinical

00:20:05.919 response

00:20:07.280 so the clinical trial we we participate

00:20:10.320 in is that so all if you look at all the

00:20:13.679 clinical

00:20:15.120 trials or cardio immunotherapy in all

00:20:18.000 acute lymphoplastic leukemia

00:20:21.360 and chronic lymph

00:20:23.840 blastic leukemia and non-hodgkin's

00:20:25.840 lymphoma

00:20:27.280 and so all patients responded extremely

00:20:30.320 well almost like a 90 of the patients

00:20:32.799 responded but after a couple years okay

00:20:35.760 within five years i think uh

00:20:38.080 50 percent of those responders developed

00:20:40.480 the relapse

00:20:42.000 and so

00:20:43.520 uh this collaboration with pen which

00:20:46.159 cardio used horse and steve grubb

00:20:49.360 uh wait we look at all the sort of car t

00:20:52.240 cells in the pre-infusion product across

00:20:54.480 the uh about 20 different patients

00:20:57.840 so we found indeed okay now responders

00:21:01.280 the relapse okay what is most

00:21:03.760 interesting here is in a relapse so long

00:21:06.240 story short so if no relapse patients

00:21:09.520 they have the

00:21:11.360 very potent type 1

00:21:13.679 response or type 1 function in their car

00:21:16.880 t cells as manufactured

00:21:19.120 but they don't have a type 2 function so

00:21:23.200 so it turns out type 2 function is

00:21:24.960 really required to keep the patients

00:21:27.760 under long-term remission so that that's

00:21:31.120 a major finding here it's very

00:21:33.280 counterintuitive for most

00:21:34.799 immunobiologists

00:21:36.320 so now we're validating this result in

00:21:39.520 even much much larger cohort like 80 to

00:21:42.000 100 patients

00:21:43.679 at a pen so it's hard to do this

00:21:45.840 experiment because we are doing

00:21:47.840 like a five-year follow-up of those

00:21:50.000 patients you know car t-cell

00:21:52.080 therapy relative to neo i think one of

00:21:54.720 the

00:21:55.760 first cohorts i think are traded by car

00:21:58.480 t that's about like five to six years

00:22:01.360 now

00:22:02.320 uh so uh

00:22:04.000 yeah so i think aided that's probably

00:22:05.840 all the patients we can find uh to

00:22:07.919 validate this this result

00:22:11.360 so this is not limited to car t cells

00:22:13.840 actually we also look at turmeric

00:22:16.000 infistine t cells

00:22:17.760 uh in this case we are not able to do uh

00:22:20.720 uh sort of antigen specific stimulation

00:22:24.400 uh we just kind of stimulate uh on

00:22:27.720 specifically or not specifically

00:22:31.200 however we observe exactly the same

00:22:34.080 change of

00:22:35.760 the polar functional response t cells

00:22:38.960 as long as you have those t cells in the

00:22:40.880 tumor and then you're given a meal check

00:22:43.120 from the inhibitor therapist those

00:22:45.360 patients gonna respond extremely well

00:22:47.840 if you don't have no

00:22:49.440 the high quality t cells in a tumor

00:22:52.240 and even though you give them

00:22:53.679 immunotherapy drug uh they still cannot

00:22:56.400 respond and so

00:22:58.320 uh so that i think there's another way

00:23:01.200 so before treatment you can predict the

00:23:03.600 clinical response i know in this field

00:23:05.679 people constantly look at mutational

00:23:07.280 burden and a harder versus cold but we

00:23:10.799 show actually the corridor of those t

00:23:12.880 cells

00:23:14.080 in the tumor matters most as compared to

00:23:16.960 all other

00:23:18.080 matrix

00:23:20.320 so

00:23:21.280 this is the the diagram i use the over

00:23:24.640 and over i think in the past 15 years

00:23:26.799 when i wrote my natural brand so when

00:23:28.799 you look at a tumor micro environment

00:23:31.200 the t cells there

00:23:32.880 and the tumor cells extremely

00:23:34.320 heterogeneous

00:23:35.679 but that's still not a full story okay

00:23:38.320 you you you have them but you have them

00:23:41.200 in the well-defined spatial context

00:23:44.640 uh so i think joanna wrote this uh

00:23:47.760 review article or perspective article uh

00:23:50.640 more than 15 years ago

00:23:52.960 showing okay the the tumor vasculature

00:23:55.679 and the and the and the immune fissures

00:23:58.400 and the lymphocytes

00:24:00.000 and and the different tumor subtypes and

00:24:03.360 and the invasive versus the dormant and

00:24:05.679 the

00:24:06.720 really

00:24:07.679 full well-defined spatial uh interaction

00:24:11.120 network

00:24:12.320 and so i think my uh former graduate

00:24:14.960 student i think uh who's in the audience

00:24:17.039 right now i think a poster with uh

00:24:19.120 professor liang

00:24:20.559 and and uh and the yandi does beautiful

00:24:22.799 work to look at the interaction between

00:24:24.880 just the two types of cells now and the

00:24:27.200 third cells

00:24:28.640 uh in this case you already have the

00:24:31.360 micro vasculature developed

00:24:33.919 from the human endothelial cells but

00:24:36.559 you're putting human

00:24:38.440 glioblastoma tumor cells x variable from

00:24:42.080 the patients into

00:24:43.840 uh the micro vasculature say how they

00:24:45.919 interact

00:24:47.120 and then we found okay that's a very

00:24:49.520 complex or tumor subtype specific

00:24:52.799 and so all those

00:24:54.720 different branches if you are doing

00:24:56.799 single cell sequencing you know

00:24:58.240 something called a monocle you can look

00:25:00.240 at a different differentiation

00:25:02.080 trajectory

00:25:03.760 so this is what we show

00:25:06.159 so different the differentiation

00:25:07.679 differentiation is trajectory each data

00:25:10.080 here is a single cell

00:25:11.919 and for the uh

00:25:13.919 uh so from the tumor samples

00:25:17.039 that give you the highest the

00:25:18.559 co-localization with the micro

00:25:20.159 vasculature uh most of the cells are in

00:25:23.279 this branch and a little bit in this

00:25:25.039 branch and the cells that are

00:25:27.679 that do not care the microvasculature

00:25:30.799 that are in this branch and then we know

00:25:32.640 okay these two branches are

00:25:35.360 basically uh pro neuron tumors and also

00:25:39.279 uh autonomous incoming tumors

00:25:41.679 pro neuron tumors

00:25:43.520 are

00:25:44.559 sort of no tumor stem progenitor cells

00:25:46.880 they're rare like perivascular knees so

00:25:49.279 mesenchymal tumor cells tend to migrate

00:25:51.600 along the micro vessels

00:25:53.600 but the classical tumor cells don't care

00:25:55.600 okay they just will grow by themselves

00:25:58.080 so this is a perfect correlation but you

00:26:00.559 really don't know which tumor cells here

00:26:03.360 interact with

00:26:04.880 what

00:26:05.760 endothelial cells and so you still need

00:26:08.880 sort of a spatial context

00:26:11.039 and this is a much much simplified model

00:26:13.279 but the real tumor is much more

00:26:14.960 complicated so can we

00:26:17.760 develop something to really map down the

00:26:21.039 entire tumor in a spatial tissue context

00:26:23.520 and also across

00:26:24.960 entire genomes or transcriptal scale

00:26:29.279 and so

00:26:31.279 if you're working on single cell

00:26:33.360 sequencing

00:26:34.640 and a phototax genomics website you'll

00:26:37.440 probably have seen this diagram over and

00:26:39.520 over and uh which describes the data

00:26:42.720 structure for bulk iron sequencing

00:26:45.760 and a single cell sequence and a spatial

00:26:47.600 sequencing right

00:26:48.960 so i

00:26:49.840 i yeah i'm stuck home kind of for a year

00:26:52.400 and a half but i still love travel

00:26:54.799 uh so i tend to use this analogy so if

00:26:57.760 you look at the map here this is

00:27:00.159 literally not a map okay this is just in

00:27:02.640 the shape of our country but you know

00:27:04.480 that's usa

00:27:06.400 and if you do single cell sequencing

00:27:08.400 instead of you can get all the different

00:27:10.159 states and then maybe in new york city

00:27:12.159 in new york because you get a cell

00:27:14.000 subtypes there

00:27:15.840 and but you can

00:27:18.320 you just can't use this one plus this

00:27:20.640 one to drive around enjoy your trip

00:27:22.720 right so you really need a full map with

00:27:25.279 all the states cities and how they're

00:27:27.279 connected

00:27:28.559 and to to to find the location you want

00:27:31.279 to go and to enjoy your trip so biology

00:27:34.559 works exactly the same way okay you you

00:27:37.279 know what cell types there you know

00:27:39.360 overall shape of the country

00:27:41.760 that's not enough you really need a very

00:27:44.480 detailed and a single cell level in a

00:27:47.120 spatial tissue contacts information

00:27:50.880 so over the past five to ten years i

00:27:53.200 think in the spatial omex technology

00:27:55.360 merged to address this challenge can we

00:27:58.320 rather profile individual cells and and

00:28:01.919 directly in a in a t-shirt context

00:28:04.799 there are two

00:28:05.919 major different technology uh directions

00:28:08.559 or different

00:28:09.760 categories one is

00:28:11.600 you can do imaging okay people

00:28:14.240 do

00:28:14.960 fish for decades but

00:28:17.520 i was talking to steve just a half an

00:28:19.279 hour ago and

00:28:20.640 like a decades ago you can do just a one

00:28:24.320 uh gene you do fish and it's hard to do

00:28:27.520 multiple

00:28:28.960 and you can do

00:28:30.720 ifc immunochemical standing

00:28:33.520 for one protein markers extremely to do

00:28:36.480 uh even just a two or three

00:28:38.880 and but i i was super impressed i think

00:28:42.080 in the past five to ten years i think a

00:28:44.080 folks in the field in a in a microscopy

00:28:47.039 imaging field

00:28:48.480 really pushing a boundary and in

00:28:50.880 particular for sp for

00:28:52.960 sm of fish that demonstrate can get up

00:28:55.840 to entire transcript on scale like the

00:28:58.320 10 000

00:28:59.679 genes mapped out but that's extremely

00:29:02.159 tedious and time consuming experiment

00:29:05.520 however that doesn't really give you the

00:29:07.840 ability to scale and to to get a high

00:29:10.480 content and a large

00:29:12.480 volume and also a large sample number

00:29:16.240 i really think in a breakthrough

00:29:18.720 came out when

00:29:20.399 the spatial

00:29:22.000 mapping was uh down with high fructose

00:29:25.360 sequencing so basically you can use the

00:29:27.120 illumina sequencing

00:29:29.039 but to reconstruct the spatial

00:29:31.520 gene expression uh profile

00:29:34.320 so in this case i think there are uh

00:29:37.440 most of technologies are very very

00:29:40.399 similar i'm gonna kind of walk you

00:29:42.320 through

00:29:43.200 very briefly the technology landscape in

00:29:45.520 this ngs based

00:29:47.600 spatial transcription sequencing

00:29:50.159 and so the landmark

00:29:52.080 paper came out 2016

00:29:54.960 when professor joaquin lombard

00:29:57.200 published this work in science showing

00:29:59.120 you can

00:30:00.559 use dna microarray

00:30:02.880 to capture messenger eyes from the

00:30:05.279 tissue section sitting on top of the dna

00:30:07.760 microarray

00:30:09.039 and then you're making a cda on the

00:30:12.399 microwave spots and and and then pour on

00:30:15.760 a cda

00:30:17.039 uh

00:30:17.840 and and do parent sequencing and then

00:30:20.480 you can computational reconstruct the

00:30:22.559 gene expression profile because every

00:30:24.720 single spot gives you a specific address

00:30:27.039 code

00:30:27.919 uh so about two years later i think 10x

00:30:31.279 genomics acquired that technology

00:30:34.159 and so 2019 about two years ago that was

00:30:38.480 the moment the

00:30:40.000 the whole entire field exploded

00:30:42.799 and i think the slide sequel published

00:30:45.679 earlier that year and then later as the

00:30:47.679 hdst they used the bs instead of the dna

00:30:51.679 microarray spots to caption the cda to

00:30:54.480 capture the messenger from the tissue

00:30:56.960 and take genomics launching the first

00:30:59.039 commercial product

00:31:00.799 and so we upload our paper uh

00:31:04.799 about that time as well

00:31:06.720 and so so the next year i think the the

00:31:09.600 technology uh including the

00:31:12.000 commercialized division

00:31:13.760 uh has been demonstrated forever pe t

00:31:16.240 show

00:31:17.039 and this year this is even more exciting

00:31:19.200 i think three technologies came out

00:31:22.159 to show you can get a uh even like a one

00:31:25.440 micron a spatial resolution

00:31:28.320 by further shrinking the size of the

00:31:30.559 spots the three technologies called

00:31:34.080 sterosic and a sick scope and a pixel

00:31:36.480 sick

00:31:37.519 and so i think

00:31:39.440 however all those technologies are more

00:31:41.919 or less in the same principle i think a

00:31:44.960 corner by professor yukin londonberg

00:31:47.440 it's a surface

00:31:48.960 uh

00:31:50.240 surface spark a barcode surface mri

00:31:52.960 capture for spatial transcriptional

00:31:55.200 sequencing so our approach kind of

00:31:57.679 complete the opposite so we don't take

00:32:00.000 any messenger is out of the tissue

00:32:02.399 instead we put the dna

00:32:04.880 barcodes into the tissue and do all the

00:32:07.200 chemistry in the tissue matrix

00:32:09.679 and so way demonstrate even two years

00:32:12.640 ago we can

00:32:14.399 do the entire transcription spatial

00:32:16.799 mapping but we can also map

00:32:18.880 ten tens of proteins so from the first

00:32:21.519 spatial multi-omics

00:32:23.360 and this year we have uh

00:32:26.720 sort from the spatial epi genome we can

00:32:28.960 look at

00:32:29.919 not just the transcriptone or panel

00:32:32.320 proteins and many other new

00:32:34.880 opportunities that can be unlocked

00:32:37.840 uh based on this approach called the

00:32:39.840 basic

00:32:41.200 uh so

00:32:42.960 uh the

00:32:44.159 this paper was published last year if

00:32:46.240 you want to know the details you can uh

00:32:48.720 find out

00:32:49.840 uh the the

00:32:51.360 the sale paper

00:32:53.200 uh i think from november last year

00:32:56.480 what i want to show you is this device

00:32:58.640 actually

00:33:00.559 so this turns out to be the simplest

00:33:03.039 microphone device ever worked with so

00:33:05.039 all right

00:33:06.159 and owner inlets are

00:33:08.640 are pretty big if you know how to use

00:33:10.880 pipette you can just prepare your agents

00:33:13.039 into those inlets i think 50 different

00:33:15.760 inlets

00:33:16.960 you don't need a complicated spaghetti

00:33:19.200 through the

00:33:20.640 tubing system

00:33:22.399 you're just using a global vacuum you

00:33:24.159 can pull the reagents into this region

00:33:28.000 where you have the tissue section

00:33:30.399 so this is really the simplest micro

00:33:32.640 footage i ever worked with

00:33:35.279 and

00:33:36.640 so how the actual works uh is showing in

00:33:39.760 this diagram

00:33:41.200 so you can't take existing tissue

00:33:44.159 glass slide okay you don't have to bring

00:33:46.399 your

00:33:47.200 uh your your device to the micro tom or

00:33:50.159 to

00:33:50.960 the crowd sectioning machine uh you have

00:33:53.919 an existing t-shirt on the slide

00:33:56.240 and you put your microphone device on

00:33:58.159 top of the t-shirt and introducing the

00:34:00.000 first set of dna barcodes

00:34:02.559 a to a 50 and each barcode each oligo

00:34:06.799 uh has

00:34:09.119 no illegal dt to

00:34:11.440 uh to detect the messenger is all

00:34:14.960 uh napoleon tail of the end of the

00:34:17.280 conjugates

00:34:18.560 and so afterwards you do intuition

00:34:22.480 cda synthesis so you already in

00:34:25.839 afterwards you already have cda in a

00:34:27.760 t-shirt

00:34:28.960 but only one direction you don't get a

00:34:30.960 two-directional uh uh address code right

00:34:34.320 and then you remove the first device and

00:34:36.639 put another device uh microfiber device

00:34:39.280 on top with the micro channels

00:34:40.800 perpendicular to the first flow

00:34:43.119 direction to introduce the second set of

00:34:45.359 dna barcodes and then locate them

00:34:47.359 together

00:34:48.719 at the intersection you have the

00:34:50.239 combination of a and a b

00:34:52.159 that combination gives you very unique

00:34:54.800 spatial address code

00:34:56.719 and then you're collecting the sitting

00:34:58.079 at your parent sequencing you can

00:35:00.240 computational reconstruct a spatial gene

00:35:02.640 expression gene expression map

00:35:05.040 uh so if you're playing a trick with the

00:35:06.960 dna antibiotic conjugates you can

00:35:09.520 map down the proteins uh simultaneously

00:35:13.280 uh in the same workflow

00:35:15.599 and so what i'm showing you here is the

00:35:18.000 data we already published from the

00:35:20.160 embryonic mouse brain

00:35:22.240 and so after this the two uh

00:35:25.200 microfluidic flow broccolin step

00:35:29.280 somehow can you press down the tissue

00:35:31.200 you can see a little bit kind of imprint

00:35:33.599 into the tissue matrix

00:35:35.520 which is great because you can actually

00:35:37.599 see where the tissue pixels are located

00:35:39.680 so the individual tiny tiny

00:35:42.640 squares and

00:35:44.720 and you can look at on a messenger eyes

00:35:47.440 and on a proteins in this case only 22.

00:35:51.280 if you look at individual proteins for

00:35:53.119 example right here

00:35:54.880 this pandotherial antigen

00:35:57.280 which tells you where the

00:35:58.480 microvasculature in the brain micro

00:36:00.400 microvascular is located i'm not

00:36:02.160 pathology by training there's no way to

00:36:04.720 tell where the microvasculature is but

00:36:07.520 from the sequencing data it's very clear

00:36:09.680 you can see the microvascular network so

00:36:12.320 epichem tells you an endothelial organs

00:36:15.200 start to develop at this stage

00:36:18.160 but from the same sample we have the

00:36:20.480 whole transcriptome map down

00:36:22.640 pixel by pixel and then you can do uh

00:36:25.920 some sort of

00:36:27.200 clustering analysis very much like how

00:36:29.200 you do your single cell rna sequencing

00:36:31.760 you can find the

00:36:33.280 in this case 11 different clusters and

00:36:35.839 also what genes determine

00:36:38.640 each cluster i just want to bring your

00:36:41.200 attention again to this cluster cluster

00:36:43.680 too

00:36:44.560 and it looks like in the network i just

00:36:47.520 showed you before in a previous slide

00:36:50.160 and then when you look at what genes are

00:36:52.480 associated with this cluster they are

00:36:54.720 hemoglobin genes they are red blood

00:36:56.560 cells so basically those are the red

00:36:58.880 blood cells stuck in the micro vessels

00:37:00.800 okay

00:37:01.839 biologically may be not so interesting

00:37:04.079 but i think this is this is kind of very

00:37:06.560 cool you know from different data kind

00:37:09.200 of proteins

00:37:10.400 and the transcriptone you can see how

00:37:12.800 they really match each other so well

00:37:17.680 okay so we also apply a much smaller

00:37:21.440 tissue pixel size uh to map

00:37:24.800 a specific ranging of normal spring i

00:37:27.760 would say random ranging because we

00:37:29.440 didn't know much development about that

00:37:31.440 time we should put our device right here

00:37:34.320 to map down uh this uh this area of the

00:37:37.520 tissue

00:37:38.560 and when i look at the image my poster

00:37:41.440 showed me i thought okay you got a

00:37:43.839 piece of tissue fiber

00:37:45.680 from your king wife t-shirt okay

00:37:48.079 now the

00:37:51.200 that happens very often if you work with

00:37:53.359 microfluidics and i say okay don't worry

00:37:56.160 let's still go ahead and get your

00:37:57.760 sequencing data

00:37:59.119 it turns out that's not a piece of

00:38:01.839 fiber that's actual layer of cells

00:38:05.440 defined by some markers for example

00:38:08.160 female that's melanocytemarker

00:38:10.720 so actually have a layer of melanocytes

00:38:13.119 lying around some structure that's not

00:38:16.000 i felt basically what you are seeing

00:38:18.720 is an early stage no eye fail or

00:38:21.119 iphysical development and after just a

00:38:24.160 one day you'll begin using a optical

00:38:26.480 vesicle

00:38:27.599 so i think of develop development of

00:38:30.000 biology sorry they know so at this stage

00:38:32.880 the melanocycle

00:38:36.960 so melanocyte epithelial melanocytes are

00:38:41.040 just a one layer of cells

00:38:43.440 and so what we really demonstrate here

00:38:45.920 is

00:38:46.880 the 10 micron pixel size difference it

00:38:48.880 can resolve just a single layer of the

00:38:51.599 cells

00:38:52.560 directly in a t-shirt

00:38:56.320 so what is even more powerful in terms

00:38:58.800 of computational data analysis we found

00:39:01.200 is

00:39:02.480 you can integrate the spatial tissue

00:39:05.359 pixel data the whole transcriptone data

00:39:08.000 and the singles are sequencing data in

00:39:09.839 the same data set to perform

00:39:11.920 unsupervised clustering and afterwards

00:39:14.960 you see all the

00:39:16.880 uh trans uh owner special pixels conform

00:39:20.560 to the different clusters

00:39:22.720 and then you you you can do sort of your

00:39:25.200 own genealogy analysis for each cluster

00:39:28.000 to find what cell types associated with

00:39:31.040 those clusters and then go back to see

00:39:33.839 where they are right so you can see

00:39:35.839 especially

00:39:37.599 many of those clusters are extremely

00:39:39.599 distinct and if you know the tissue

00:39:42.000 pathology tissue histology you know what

00:39:44.240 type of cells what type of tissue

00:39:45.920 associated with that cluster

00:39:48.480 and

00:39:49.599 also you can do another

00:39:51.520 approach called label transfer you

00:39:53.680 integrate the single cell sequencing

00:39:55.599 data and

00:39:56.800 and the transcript and uh

00:40:00.079 and and a spatial transcriptome together

00:40:03.200 and single cell sequencing data will

00:40:05.200 annotate it you know

00:40:07.280 on the different cell types you'll just

00:40:09.040 say transferring the cell type or cell

00:40:11.040 lineage label

00:40:12.720 to the spatial

00:40:14.560 expression and then you can see where

00:40:17.119 they are

00:40:18.160 i just show you a couple of examples

00:40:20.880 for example some

00:40:22.839 oligodendrocytes based on the

00:40:25.599 single cell sequencing data they are all

00:40:27.440 oligodendrocytes

00:40:29.040 however when we look at our

00:40:32.319 pixels spatial pixels looks like there

00:40:35.280 are two different subsets and when you

00:40:37.280 go to look at a special distribution

00:40:39.680 indeed

00:40:40.800 there are three different regions okay

00:40:43.040 uh there are all oligodendrocytes but

00:40:45.520 they are from different

00:40:47.040 regions in a tissue

00:40:48.880 you can look at many other cell types as

00:40:50.880 well and they make perfect sense like a

00:40:53.359 connective tissue this is a ganglion

00:40:55.839 neuron and also you see some uh vessels

00:40:58.960 uh and and also the red blood cells

00:41:01.280 stuck in a vessel

00:41:03.200 and so whether or not the technology

00:41:05.280 works for the effort to show okay if you

00:41:08.240 really want to push in a boundary to

00:41:10.160 apply the technology to the

00:41:12.079 archival clinical tissue specimens

00:41:14.240 that's very important question so it

00:41:16.480 demonstrated that worked i think about a

00:41:18.160 year ago

00:41:19.359 and but reason the way further democracy

00:41:22.720 that works but actually works just

00:41:25.599 just a peripheral i think the data

00:41:27.359 quality is as good as the fresh frozen

00:41:30.240 t-shirt and there's a humanly

00:41:32.440 informational way we mapped out the fop

00:41:36.160 sample you can see some clusters i think

00:41:39.599 the data is much more complicated i i i

00:41:42.960 just want to bring your attention to the

00:41:44.560 quality of the data here

00:41:47.040 at a 10 micron pixel size level we're

00:41:50.319 able to get more than 2500

00:41:52.960 genes per pixel and almost 10 000 uh

00:41:56.480 transcripts per pixel this is as good as

00:41:59.119 the fresh frozen samples which we're

00:42:01.440 very very happy about

00:42:03.839 and so

00:42:05.200 also we apply this to human brain tissue

00:42:08.240 i think it is a collaboration with

00:42:09.920 professor liang and uh

00:42:12.800 maybe later i think a young and a

00:42:15.200 professional i can tell you a more

00:42:16.880 exciting story from this but we're so

00:42:19.520 happy that technology works so well

00:42:22.079 in this kind of post-modern

00:42:25.119 archive human brain tissue samples

00:42:29.359 so i think everyone in this field got so

00:42:32.400 excited earlier this year because nature

00:42:34.560 methods should spatially especially

00:42:36.800 resolve the transcriptomics as the

00:42:38.880 method of year

00:42:40.240 in the same issue i think uh they also

00:42:42.640 hide the artwork saying oh multi-o makes

00:42:45.440 codes spatial as well

00:42:47.680 and so but what is beyond what we have

00:42:51.359 demonstrated in that paper

00:42:53.119 uh and uh so

00:42:55.200 the leaders in a failed artist

00:42:57.520 the industry leaders they really believe

00:43:00.560 uh with all the different spatialomix

00:43:02.640 technologies uh you're gonna see in the

00:43:05.359 next wave of biology uh revolution

00:43:08.480 and some people even believe you don't

00:43:10.640 need a single cell sequencing anymore in

00:43:12.720 the future that's what i do bitching

00:43:14.400 really believe maybe i have slightly

00:43:16.480 different opinion i really think you

00:43:18.000 need both

00:43:19.359 but i can't deny so how much

00:43:22.240 impact how huge the impact will be

00:43:24.800 once all those facial technologies are

00:43:27.040 broader uh applied uh to different uh uh

00:43:31.200 different biological and biomedical

00:43:33.280 research uh problems

00:43:35.839 and so what do we have further

00:43:37.680 demonstrating in a past a couple months

00:43:40.640 is okay number one you can do proteins

00:43:43.359 but how many proteins you can you can do

00:43:46.480 and so i would say i don't know the

00:43:48.400 answer is honestly i don't know but i

00:43:50.640 show you here

00:43:52.240 up to 300 proteins the total durable

00:43:54.800 actually only uses 10 of the sequence in

00:43:57.680 depth to do that 300 proteins in theory

00:44:00.560 probably can do even 3 000 but

00:44:03.680 yeah for small f i think it's difficult

00:44:06.160 to get so many different antivirus

00:44:08.720 so this is data from human console

00:44:11.440 and so you can see the spatial clusters

00:44:14.880 from the protein data owner you can see

00:44:17.599 very nice clusters that

00:44:20.560 match the the the tissue histology in

00:44:23.920 the tissue morphology where those uh

00:44:26.079 b-cell follicles are located you'll see

00:44:28.720 uh even a lysone and a dark zone

00:44:32.240 and from the same image from the same

00:44:34.800 tissue way also sequencing the whole

00:44:36.560 transcriptome we can perform

00:44:38.160 unsupervised the classroom of the whole

00:44:40.400 transcripton i think that clusters in a

00:44:42.640 spatial context

00:44:44.240 match each other reasonably well

00:44:48.000 so you can also look at individual

00:44:50.000 proteins for

00:44:51.839 on a b cell for b cells or t cell city

00:44:55.280 334 so in the t cell zone those uh the b

00:44:59.440 cell follicles also you can look at a

00:45:01.760 functional uh protein markers like igg

00:45:04.880 igm ig uh igd

00:45:07.760 and so

00:45:09.440 uh

00:45:10.240 so 300 i'm not able to show you all of

00:45:12.480 them but just to give you a little bit

00:45:14.560 idea how how rich in the data you can

00:45:17.520 get out of this

00:45:18.960 hypox spatial uh protein uh profiling

00:45:23.680 uh in conjunction with naho

00:45:25.760 transcriptional sequencing

00:45:27.599 so this is interesting data from the

00:45:30.000 vaccine again so we

00:45:33.599 we did this high flax protein and a and

00:45:37.040 a transcript on co-sequencing

00:45:39.520 and from a scheme biopsy sample they

00:45:42.000 supposed the uh modena vaccine i think

00:45:45.119 the second dose and we took a little bit

00:45:48.160 of skin

00:45:49.119 out of the vaccine side vaccination side

00:45:52.480 and look at all the b cell uh on the

00:45:54.480 immune cells and also the the

00:45:57.200 softener the skin on the skin epidermal

00:45:59.839 cells as well

00:46:01.359 and i'm not going to go into the details

00:46:03.839 but you just can't see how how beautiful

00:46:06.960 this

00:46:07.760 kind of spatial gene expression

00:46:09.359 clustering and a spatial protein ohm

00:46:11.920 clustering

00:46:13.520 and so next just a couple of uh

00:46:17.839 minutes i hope i can show you

00:46:20.079 this is

00:46:21.200 way beyond

00:46:22.720 just a transcriptome and a couple of

00:46:25.280 proteins you can

00:46:27.040 look at the

00:46:28.880 epigenetic uh organization of um

00:46:33.200 so directly in a t-shirt

00:46:35.440 uh so my poster yeah and uh

00:46:38.720 and he's a he's an amazing engineer

00:46:41.839 but in this case actually he figured out

00:46:43.920 all the molecular biology stuff and he's

00:46:46.560 now teaching me the epigenetics

00:46:49.520 and so

00:46:51.200 we we

00:46:52.640 applied the same cross-flow barcoding

00:46:54.880 approach to look at now chromatin

00:46:57.599 accessibility

00:46:59.280 and instead of using oligodt to look at

00:47:03.359 the transcripts through the canon

00:47:04.800 messenger

00:47:06.160 wheels

00:47:07.119 tm5 transposes to probe all the open

00:47:10.000 chromatin loci loci

00:47:12.480 and afterwards you in certain dna only

00:47:15.119 go to the open chromatin region

00:47:17.680 and then like gain a barcode a and like

00:47:20.240 a barcode b and then you have the space

00:47:22.319 in a spatial address code so when you

00:47:24.480 collect the owner genome dna in a

00:47:26.480 sequence

00:47:27.520 you can identify where they are in a

00:47:30.240 tissue

00:47:31.280 and so what you are seeing here is the

00:47:34.079 reference data

00:47:35.599 from the encode database and this is

00:47:37.839 from our aggregate

00:47:39.680 uh sequencing data but you can also see

00:47:41.920 individual pixels uh from

00:47:45.040 this this is embryonic mouse lever

00:47:48.079 and so if you look at the entire mouse

00:47:50.319 umbrella

00:47:51.359 you based on the spatial chromatin

00:47:54.400 accessibility data

00:47:56.319 uh you you already can do very nice uh

00:47:59.359 clustering and to identify different uh

00:48:02.800 tissue types so it's a lever this is

00:48:04.800 spinal cord

00:48:06.400 but you see very fine very complicated

00:48:08.559 structure in the brain because at that

00:48:10.400 stage i think a brain is the most well

00:48:13.040 developed

00:48:14.079 you see all uh many different neuronal

00:48:16.960 subtypes and the brain tissue types over

00:48:19.040 there they all can be captured very well

00:48:22.160 by the spatial

00:48:23.839 chromatin accessibility mapping

00:48:28.240 so again you can compare the data

00:48:30.720 to the encoder reference data

00:48:33.200 the different uh different organs uh

00:48:35.760 from the embryo embryonic mouse uh

00:48:38.960 mouse tissue and they all match very

00:48:41.839 well but

00:48:43.040 you see we have much more granular

00:48:44.960 information because we mapped out pixel

00:48:47.680 by pixel rather than your

00:48:49.920 dissecting the entire organ uh to do

00:48:53.040 uh

00:48:53.920 a toxic

00:48:55.680 and so again we're playing the same

00:48:58.000 trick uh to integrate

00:49:00.400 the spatial uh

00:49:02.720 uh

00:49:03.440 a toxic data

00:49:05.200 and a spatial and a single cell

00:49:06.880 transcriptone sequencing so using single

00:49:09.520 cell transcriptional sequencing you can

00:49:11.040 get us different cell types and lineages

00:49:14.240 and then you'll see where the spatial

00:49:16.079 pixels uh sort of co-localize with the

00:49:19.440 cluster you know okay that's the type of

00:49:21.839 cell

00:49:22.800 you have in that pixel and then you can

00:49:25.440 go back to see where

00:49:27.119 uh

00:49:29.040 you can go back to see where those cell

00:49:30.800 types are located

00:49:32.480 but keep in mind what you are seeing

00:49:34.480 here is not expression but you are

00:49:36.559 seeing

00:49:37.760 the

00:49:38.720 chromatin uh accessibility state okay uh

00:49:42.160 what i'm showing here for example in the

00:49:44.319 the red blood cells they're enriching

00:49:46.400 the liver that makes perfect sense

00:49:48.240 because at that stage actual liver

00:49:51.040 is the major hematopoiesis organ

00:49:53.920 not in a bone marrow

00:49:55.760 and

00:49:57.680 from

00:49:59.119 using the same technology we're also

00:50:01.040 looking at a human tonsil again

00:50:04.160 and you can see on the t b cell genes

00:50:07.200 t cell genes

00:50:08.960 but again we're now seeing a gene

00:50:11.359 expression but actually we're seeing

00:50:13.280 spatial and chromatin accessibility

00:50:15.520 state associated with different cell

00:50:17.440 types t cells b cells

00:50:19.440 this is something i think no one else

00:50:21.280 really can see

00:50:23.440 so something

00:50:24.839 biological uh

00:50:27.359 super exciting

00:50:29.440 but no one can really imagine you can

00:50:31.520 see at this level

00:50:33.760 uh probably i should try to finish up

00:50:36.480 very quickly i just want to show you

00:50:39.119 what can i further extend this to look

00:50:41.119 at the specific chromatin modification

00:50:44.160 rather than global or chromatin

00:50:45.760 accessibility

00:50:47.680 and so again with uh

00:50:50.079 my posterior sha and he

00:50:53.200 uh use the different antibodies to

00:50:56.160 target a different chromatin uh histone

00:50:58.559 modification first and then applying the

00:51:01.440 transpose hdm5

00:51:03.760 so very similar but you just add the

00:51:06.720 antibodies to

00:51:08.480 uh to target a specific histone

00:51:10.240 modifications so what you're seeing here

00:51:12.960 is for three different histones and a

00:51:15.520 uh kind of several tissue sections from

00:51:17.760 the same mouse uh embryo

00:51:20.160 and when you look at at data quality

00:51:22.000 it's extremely good it's even better

00:51:24.160 than you know best single cell kind of

00:51:26.640 attack data

00:51:28.559 and so if you compare

00:51:31.760 uh the the clustering okay based on the

00:51:34.720 chromatin modification uh profile

00:51:37.760 to the encode reference data

00:51:40.240 the they do match quite well okay lever

00:51:42.640 there's a lever here it's a har this is

00:51:45.119 nahar

00:51:46.480 and but again you'll see much more

00:51:48.319 granular information

00:51:50.400 when you compare our data to the encode

00:51:53.359 reference data

00:51:54.960 but you know those are several sections

00:51:57.119 right you immediately get an idea so

00:51:59.599 different histone controls slightly

00:52:01.680 different tissue

00:52:03.359 development different different regions

00:52:05.839 of nature

00:52:07.280 and you'll probably want to ask whether

00:52:09.280 or not it's a multivalent uh

00:52:11.839 histone uh histone control

00:52:15.280 histone modification control the the

00:52:17.599 development of for example in the

00:52:19.119 different brain

00:52:20.640 tissue types now answer is true

00:52:23.359 and you already can can see that

00:52:25.839 probably you can do better job if you

00:52:27.680 can

00:52:28.640 computationally integrate them

00:52:30.800 uh together

00:52:34.160 uh so this is uh

00:52:36.480 so if one of the histones were analyzed

00:52:38.480 they just give you

00:52:39.920 uh so better view

00:52:42.000 of uh the different tissue regimes and a

00:52:45.520 different history modification profiles

00:52:48.800 analyzed

00:52:49.920 and so you can see the clustering based

00:52:52.079 on uh software global

00:52:54.640 sequencing profile

00:52:56.400 from this histone modification you can

00:52:59.040 also see individual genes predicted uh

00:53:01.839 from that history modification

00:53:03.359 associated with different tissue regions

00:53:04.800 you can see very fine resolution

00:53:07.200 for tiny tissue tiny features of often

00:53:10.240 brain tissue as well

00:53:11.760 so i'm gonna kind of skip the uh

00:53:15.839 those slides uh but very very exciting

00:53:18.559 data uh from adult mouse brain

00:53:22.000 uh we

00:53:23.200 we did a uh nakata and tag to look at a

00:53:27.119 different histones controlling

00:53:30.160 the cortical layer formation

00:53:32.480 but for the interest of time i'm going

00:53:34.079 to skip those

00:53:36.160 but just kind of can already emphasize

00:53:40.000 how exciting this felt i think over the

00:53:42.400 past a couple of years and the way

00:53:44.400 further

00:53:45.359 bring to the table is way beyond a

00:53:48.559 spatial transcriptome and so

00:53:51.839 how i think what the basic is i think i

00:53:54.480 was really inspired by the speech given

00:53:57.200 by our president last year uh how he

00:53:59.760 defined what uh

00:54:01.440 um what is america so

00:54:04.319 uh so it's possibilities so i believe in

00:54:07.359 the same thing so the basic means

00:54:10.079 unlimited possibilities okay it's not

00:54:13.119 another spatial transfer of technology i

00:54:15.520 never believe from the very beginning

00:54:18.400 so actually that's a platform to develop

00:54:21.040 many many more spatialomix technologies

00:54:23.920 to unlock

00:54:25.359 new opportunities for biomedical

00:54:27.440 research in the future so i was in the

00:54:29.680 limit is your imagination i think you

00:54:32.559 guys probably know better molecular

00:54:34.480 biology you can think of many many more

00:54:37.520 things you can do with this

00:54:39.839 this platform technology

00:54:42.000 so thank you very much for your

00:54:43.520 attention and uh

00:54:44.640 [Applause]

00:54:49.440 yeah

00:54:50.799 if two seconds

00:54:52.400 okay sorry

00:54:54.160 i was trying to say if two seconds i

00:54:55.839 have i want to advertise wait we do have

00:54:58.400 the junior factor position open this

00:55:00.880 year in my department in the field of

00:55:03.040 neural engineering

00:55:04.880 if anyone ready to go and i want to join

00:55:07.520 yale

00:55:08.720 yeah

00:55:09.599 uh right

00:55:10.799 send me email

00:55:16.319 okay

00:55:17.040 uh we have some time for some questions

00:55:19.599 i'm going to try to use the microphone

00:55:20.880 here so that everybody can hear us

00:55:29.280 hi dr thanks for your great talk so i

00:55:32.079 have two questions the first one is even

00:55:35.040 though the pixel size is 10 micron it

00:55:37.520 could be still there are two cells

00:55:39.760 sharing the same pixel and your their

00:55:43.040 both of their transatomic information

00:55:45.520 will be collected is there a way to

00:55:47.839 distinguish it and also if a cell is

00:55:50.960 occupying two pixels you are gonna

00:55:54.880 organize the information afterwards

00:55:57.280 during the analysis

00:55:59.040 and the second

00:56:00.400 question is so the this very cool

00:56:03.200 technique is for the fixed tissue

00:56:05.920 uh if but if we

00:56:07.760 want to track the cell motion

00:56:10.079 and then use the technique to map the

00:56:13.760 like cell motion and the spatial like

00:56:16.559 transcriptomic information is there a

00:56:18.960 future direction for the spatial

00:56:21.920 temporal

00:56:23.200 technique thank you

00:56:25.119 yeah thanks i think the first question

00:56:27.359 is written cell type decomposition i

00:56:30.240 think

00:56:31.440 quite a few papers already the

00:56:33.119 population has failed uh to show how to

00:56:35.839 do decomposition of either the visum

00:56:38.400 data or slicing data

00:56:40.720 based on the same thing can be applied

00:56:42.480 to our data

00:56:44.880 but i think there there's a much better

00:56:46.960 way to do that

00:56:49.359 i think on a uh

00:56:51.520 i think a different pipeline's published

00:56:53.359 right now they just do uh sort of blind

00:56:56.319 decomposition so they don't

00:56:58.640 look at what you actually have in each

00:57:01.119 pixel

00:57:02.160 they're just a computational

00:57:03.920 kind of kind of deconvolute uh the the

00:57:07.440 transcriptional profile in those pixels

00:57:10.240 or spots

00:57:12.640 and that that worked to some degree

00:57:15.359 but what we are trying to do now is uh

00:57:18.480 really integrate the spatial imaging

00:57:21.760 and the spatial transcription sequencing

00:57:24.000 so you can see for example in that pixel

00:57:26.400 okay there's one t cell one b cell or

00:57:28.720 one

00:57:29.520 t cell even half b cells so you can do

00:57:32.079 much better the decomposition so from a

00:57:34.799 guide that supervises the decomposition

00:57:37.359 all your sub machine learning to better

00:57:39.599 refine

00:57:40.799 the result of your decomposition or

00:57:42.960 deconvolution that's what i'm thinking

00:57:45.040 so it's totally durable with the current

00:57:47.119 approach but i think there are much

00:57:49.280 better ways to do

00:57:50.880 in the future so the second question is

00:57:53.280 no so uh

00:57:54.880 sort of the the

00:57:57.040 spatial temporal profile yes

00:58:00.000 um

00:58:00.799 i think a computational you can you can

00:58:03.040 do so

00:58:04.400 uh using something like r velocity and

00:58:07.359 you look at a tracing

00:58:09.520 so nascent rna versus maturity and a

00:58:12.559 splicing pattern you you can you can

00:58:15.920 so

00:58:16.720 so do spatial rna velocity and we're

00:58:20.160 trying that uh wait i don't have no i

00:58:23.520 don't have the answer right now but i i

00:58:25.839 really think that's durable

00:58:27.839 um

00:58:29.280 yeah but if you are talking about

00:58:31.119 individual cells you can watch how they

00:58:33.760 actually move how they actually

00:58:35.520 differentiate

00:58:37.040 the data i'm now showing you but

00:58:38.880 actually collected that before on a

00:58:41.119 tissue spatial mapping was

00:58:43.359 so you can do live cell imaging how the

00:58:45.839 cell moves around or how the cells

00:58:48.160 divide to give rise to earth

00:58:50.319 and and daughter cells

00:58:52.400 and then you'll fix them in situ or fix

00:58:55.359 them on a slide

00:58:57.359 and then apply this cross-flow barcoding

00:59:00.400 to sequence individual cells but you

00:59:02.720 know own a history okay before that

00:59:05.200 snapshot right so you can go back and

00:59:07.920 connect that history to your

00:59:10.000 transcriptome data

00:59:13.119 dr fond we have one question we have

00:59:15.040 time for one more question from the

00:59:16.480 virtual audience here it's from lewis

00:59:19.040 single

00:59:20.160 it says excellent talk professor one of

00:59:22.240 the limitations with vision for our

00:59:23.839 group is that it has not been optimized

00:59:25.680 in skin has dbitc been applied to

00:59:28.480 multiple tissues other than brain in

00:59:30.160 particular skin if not would you

00:59:31.920 anticipate issues with its use in skin

00:59:33.839 without further optimization many things

00:59:37.200 uh

00:59:37.920 yeah this is this is a great question so

00:59:40.799 whether or not the technology is uh kind

00:59:43.680 of broader applicable to different

00:59:45.839 tissue types uh my short answer is yes

00:59:49.119 but on the other hand

00:59:50.640 uh i think

00:59:52.319 i i do believe i think for different

00:59:54.640 teachers you need to do different

00:59:56.319 optimization

00:59:58.079 uh so uh i think in my own laboratory we

01:00:02.000 haven't uh we haven't done uh all kinds

01:00:05.040 of t-shirts yeah probably

01:00:07.200 10x genomics can do so

01:00:09.440 uh but we have pretty good data from

01:00:12.240 uh from brain i think a human

01:00:14.480 and a mouse and also skin and uh and the

01:00:17.359 lymph nodes

01:00:18.720 and tonsil

01:00:20.319 and

01:00:21.599 uh

01:00:22.960 i think it written some data from

01:00:25.280 yeah i think beautiful data from skin as

01:00:27.680 i mentioned

01:00:29.359 and the lever as well

01:00:31.200 but the very difficult t-shirt to look

01:00:33.119 at in a bone marrow that's on that's

01:00:35.040 right on top of my

01:00:37.040 uh

01:00:38.079 my list

01:00:39.200 to to do spatial mapping

01:00:41.440 but of course i think for different

01:00:43.200 tissues you need to

01:00:44.799 uh i think a tissue processing optim and

01:00:48.319 an optimization for spatial

01:00:50.319 transcriptone that's very very important

01:00:52.720 equally important

01:00:54.240 uh as compared to the the assay itself

01:00:59.520 all right um i think we need to wrap up

01:01:01.520 yes

01:01:04.240 so thank you uh

01:01:06.079 professor

01:01:07.119 uh fantasy

01:01:09.200 wonderful

01:01:10.480 talk unless

01:01:12.640 just one announcement there will be a

01:01:15.040 seminar two weeks

01:01:17.520 from today for the benefit of the

01:01:20.240 audience online speaker would be

01:01:23.040 professor jim well

01:01:25.040 from

01:01:26.319 internet

01:01:28.079 i think i was asked to announce that he

01:01:30.880 will be

01:01:32.960 speaking

01:01:36.079 on

01:01:40.319 that

01:01:42.319 with that let us thank our speaker again