

WEBVTT

NOTE duration:"00:23:18.3810000" language:en-us

NOTE Confidence: 0.917355597019196

00:00:01.130 --> 00:00:21.130 Thank you for the introduction. Thank you all for coming so today. I'm going to be talking about sex. Specific differences in colorectal cancer metabolism. A lot of the work will be presenting to you today has really just been acquired over the past couple of months. By my very hard working team in my lab, so it would be really interesting to get your.

NOTE Confidence: 0.711733102798462

00:00:21.930 --> 00:00:22.620 As well.

NOTE Confidence: 0.918101191520691

00:00:24.540 --> 00:00:44.540 So colorectal cancer is a third most commonly diagnosed cancer in women and men in the US and the incidents of mortality rate has been declining over the past 30 years and that's due to improvements in colonoscopy screening and removal of precancerous polyps in earlier detection. However, if we look at the 2 sides of the.

NOTE Confidence: 0.735537469387054

00:00:45.340 --> 00:00:50.090 Right so I took the Colon, which is from the cecum is workpoint huge.

NOTE Confidence: 0.877644896507263

00:00:51.920 --> 00:01:11.920 From there, she came up to the right product flat hepatic flexure, and also the left side from the sigmoid up to the splenic flexure. We actually see a difference in outcomes for patients depending on where their primary tumor is located where right sided code, which will cancer patients actually have a poor out.

NOTE Confidence: 0.910695672035217

00:01:12.720 --> 00:01:25.850 And this was highlighted in a recent meta analysis, where they looked at 1.5 million patients. Dakota rectal cancer in general oncology. A couple of years ago and again there sore that right sided colorectal cancer patients have a poor outcome.

NOTE Confidence: 0.908458828926086

00:01:26.760 --> 00:01:46.760 If we have a quick look at the biology of the Colon and the 2 sides of the Colon. We do see some differences in the prevalence of molecular features in the right side of the Colon. We do see that humans are more likely to have be reputations are more likely to have microsatellite instability.

NOTE Confidence: 0.859939634799957

00:01:47.560 --> 00:02:07.560 The argument they phenotype and also have gene expression patterns are linked to higher metabolism and also in infiltration with these cancer molecular subtypes. One and 2 on 3 rather but interestingly we also see is that women have lower rates of colorectal.

NOTE Confidence: 0.860280930995941

00:02:08.360 --> 00:02:28.360 Yeah, prevalence of right sided colorectal cancers. It's also seen that women develop colorectal cancer about 10 years later than men and we believe there is a degree of protection from estradiol, which lowers their risk, but then after menopause they again from colorectal cancer.

NOTE Confidence: 0.870992064476013

00:02:29.710 --> 00:02:49.710 So there are some protective links to estradiol and colorectal cancer. We see that it can be linked to activation of estrogen Receptor Bata, which causes pro upper totally signaling inhibition of inflammatory signals and is also linked to modulation of cellular proliferation and the cell cycle?

NOTE Confidence: 0.85498058795929

00:02:50.510 --> 00:03:10.510 Getting patients with right sided colorectal cancer that the arbiter expression is slower and also decreases with higher stage interestingly estradiol is also linked to cholesterol and bile acid regulation where estradiol downregulates cholesterol and bile acid metabolism. And it's thought that secondary bile acid levels have been much.

NOTE Confidence: 0.855161190032959

00:03:11.580 --> 00:03:31.580 In the Colon due to estradiol protect protection secondary bile acids are very interesting in the context of colorectal cancer because they are going to promote DNA damage and reactive oxygen species and also modulate and want and bitter containing signaling and come contract to coach of cancer and they?

NOTE Confidence: 0.882210314273834

00:03:32.380 --> 00:03:40.440 A high profile papers recently we should also linked secondary bile acids to a lower immune response in liver cancer and liver metastases.

NOTE Confidence: 0.852698147296906

00:03:42.350 --> 00:04:02.350 So given the estradiol might be protected for women against developing color to cancer before manacles and estradiol does have these links to estrogen Receptor Beta Sigma 9 and by lasted metabolism. And we have put the Sizer after menopause by lasted production increases and can cause a higher prevalence of right sided colorectal cancers.

NOTE Confidence: 0.89357590675354

00:04:03.700 --> 00:04:23.700 So to go about this study, we have 2 main aims first of all we want to identify bile acid metabolites in tumor tissues from men and women with colorectal cancer and then in concert with this actually carry out a more systems level approach looking at all the potential metabolites that might be present in colorectal cancers.

NOTE Confidence: 0.893222689628601

00:04:24.500 --> 00:04:37.640 Find more in women before excited colorectal cancer and those that could potentially affect tumor growth and therapeutic responsiveness and we also want to link all of these metabolites to patient outcomes.

NOTE Confidence: 0.884998321533203

00:04:39.230 --> 00:04:59.230 So, in order to measure metabolites, we use a tool called metabolomics and this is a systems level evaluation of all the metabolites. It could be present within a sample. So when we talk about metabolites to talk about those entities that products of food, ingestion, and those are synthesized in ovo.

NOTE Confidence: 0.906775295734406

00:05:00.030 --> 00:05:20.030 Classes such as amino acids and sugars and fatty acids and they're very much regulated by upstream genome regulation of enzymatic reactions, but that also regulated by the gut microbiome. It's also possible that very small perturbations to your local environment can affect my tab.

NOTE Confidence: 0.901014566421509

00:05:21.080 --> 00:05:41.080 Things like stress things like lifestyle changes, if you have shift work patterns. If you have a change to die at this can massively change your metabolome and we can also measure another set of metabolites within samples that come from the environment, so these are chemicals are not naturally produced in your body but can enter deuce.

NOTE Confidence: 0.897702991962433

00:05:41.880 --> 00:06:01.880 Druggys cosmetic application environmental pollutants and food additives and all of these different factors interact together to give each person an actual defining metabolic phenotype or mataba type and as you can imagine this big can be quite difficult if you're carrying out of study, but what it does do is.

NOTE Confidence: 0.902181506156921

00:06:02.680 --> 00:06:09.190 And disease heterogeneity and patient susceptibility to disease and also variation in response to treatments.

NOTE Confidence: 0.892750322818756

00:06:11.600 --> 00:06:31.600 So this is just the setup of my mass spectrometer in my lab over at the school of public health here. We have a liquid chromatography, hyphenate is too high resolution. Kitov mspec trimeter and this instrument actually allows us to do. The system to level analysis, looking at all of the metabolites. It could be present in our sample.

NOTE Confidence: 0.893682718276978

00:06:32.400 --> 00:06:52.400 Based approach and this allows us to identify new metabolize and also new metabolic pathways that may be correlated with the disease. It's also possible to carry out the targeted more hypothesis driven method where we target, say a handful of up.

NOTE Confidence: 0.883425951004028

00:07:14.000 --> 00:07:34.000 Aspect rummage spectrometry imaging instruments to enable us to do this and this is an example of one of the images that you can generate so we have 2 different types of column chemistry, which allow us to analyze both polar metabolome, so these are Water, soluble metabolites things like amino I season chicken.

NOTE Confidence: 0.851619005203247

00:07:34.800 --> 00:07:54.800 And also we first phase analysis, which allows us to look at the nonpolar metabolome to things like fatty acids and triglycerides. So we applying Alma Tableaux Mika Technologies to first identify bile acid metabolites intimate issues for men and women with colorectal cancer.

NOTE Confidence: 0.835355460643768

00:07:55.900 --> 00:08:15.900 So to enable us to do this we ever see had to obtain some samples from patients so Mike OPI Doctor Khan, who is a social conchology. Ascona Medison collaborated with doctor Philip 80 about Morial Sloan Kettering Cancer Center and he acquired a very large.

NOTE Confidence: 0.880249083042145

00:08:16.700 --> 00:08:36.700 I think from the 1990s, which had 760 colorectal cancer patients so he collected primary tumors and also page liver metastasis. I think we have around 150 pairs of these tissues also mucosa muscular. I send out the types of metastases as well all.

NOTE Confidence: 0.914208471775055

00:08:37.500 --> 00:08:57.500 Watch frozen immediately in liquid nitrogen and store dot -80 basically from the 90s to now they hadn't been touched and this is a really valuable resource for Metabolomic Studies and also microbiome analysis because they haven't been typically placed in FFP, which we can't analyze using our instrumentation so.

NOTE Confidence: 0.883529126644135

00:08:58.300 --> 00:09:01.390 To obtain a resource such as this.

NOTE Confidence: 0.881399869918823

00:09:02.330 --> 00:09:22.330 So for aim one we went very stringent at first, and we had some inclusion criteria for the patients. You wanted to include in our study so first of all we took samples from patients where they just had the right sided colorectal cancer and left sided we didn't take any rectal samples or.

NOTE Confidence: 0.887929499149323

00:09:23.130 --> 00:09:43.130 Samples for this analysis, we also looked at your stage one to 3 as we stage 4 patients they were most likely treated with chemotherapeutics before those samples were taken which can affect our metabolic analysis. We also went for patients that were aged over 55 to first and get rid of any effects of estradiol.

NOTE Confidence: 0.914445579051971

00:09:43.930 --> 00:09:53.260 What we ended up with was about 220 samples from this cohorts where we had about 55 per group per sex and location in the Colon.

NOTE Confidence: 0.799205183982849

00:09:55.790 --> 00:10:15.790 Some giving her a very poor diagram that I made of the liver any tested but this is just to show you how the bile acids that I quantified are formed, so we have primary bile acids. Koulik acid in general, deoxycholic acid are metabolise from cholesterol in the liver there conjugated to Taurean and grace.

NOTE Confidence: 0.799353539943695

00:10:16.590 --> 00:10:36.590 Really glycine in humans, then transported through the bio into the daughter name where they then undergo hydrolysis by bias or hydra lays in the ileum and Cole on to the prime rib. I lost it again. Koulik acid and Kennedy Oxic, a leak acid and then they get.

NOTE Confidence: 0.866463363170624

00:10:37.390 --> 00:10:57.390 Information by at the microbiome where they D hydroxylated to be secondary bile acids and EC&L and L CA are known to be a genotoxic some of these biases can be excreted in the store. But the majority of them are taken up again for enterohepatic recirculation and this can happen about 5 to 6.

NOTE Confidence: 0.856682360172272

00:10:58.480 --> 00:11:14.910 So when Theum DCA and LCNCNCDCA end up back in the liver. They get re conjugated again and then end up back again in the small intestine and Colon so these were the different metabolites. We're targeting for our target analysis.

NOTE Confidence: 0.859124958515167

00:11:16.110 --> 00:11:36.110 And this is just some of the initial data where we have each of the biases here. The primary unconjugated and the secondary unconjugated and then their turing and glycine conjugates and we'll be comparing here is a full change in bile acid levels when.

NOTE Confidence: 0.863312423229218

00:11:36.910 --> 00:11:56.910 Left sided chambers to right sided tumors and these are for all the stages combined and women and men combined and what we can see is a general increase in most of the bile acids in the right side of the Colon, which we kind of expected what we don't see is any difference to Torrenting Bryson Khan.

NOTE Confidence: 0.792761325836182

00:11:57.710 --> 00:12:04.630 Uh with the Colac acids. These are typically EE conjugate it in the liver to sulfates as well annex treated.

NOTE Confidence: 0.880539834499359

00:12:06.310 --> 00:12:26.310 However, when we start to look at across stage we do start to see some interesting differences and what we see is stage. One is no changes to primary blessed and secondary biglots is for the non conjugated forms. But we do see higher levels of the turing engrossing conjugative primary bile acids.

NOTE Confidence: 0.892204165458679

00:12:27.110 --> 00:12:45.540 Then when we meet to stage 2. We start to see that the non conjugated forms are increased and the Turing and glassing conjugated form start to gradually decrease and we don't see any differences at Stage 3. So then we started to look a little bit closer at sex differences.

NOTE Confidence: 0.896243393421173

00:12:46.660 --> 00:13:06.660 And what you can see here is that actually there is a sex difference in terms of the bile acid localization in stage. One and 2 wear for women. There aren't any differences between left and right sided for stage one. And when we go to stage 2. We start again to see this trend of increase primary bile acids and.

NOTE Confidence: 0.911791443824768

00:13:07.460 --> 00:13:27.460 This in the Torrington Grayson conjugates for the men so we have a working hypothesis that this could be potentially related to changes in the environment of the Colon, which could be changing proliferation and utilization of the.

NOTE Confidence: 0.873255908489227

00:13:28.260 --> 00:13:48.260 Signs so it's stage one is possible that these 2 microbial processes are not happening and at Stage 2. We see this decreases in the Torrington. Greissing conjugates and then this increase in the CA and

CCA and the DCNLCA where you potentially have a working hypothesis that they could be.

NOTE Confidence: 0.934849798679352

00:13:49.060 --> 00:13:53.170 This is a microbial activity at different stages in colorectal cancer.

NOTE Confidence: 0.899844825267792

00:13:55.100 --> 00:14:15.100 So we didn't see any differences in bile acids between men and women with right sided colorectal cancer. But how Publicis was that women before menopause would have lower levels of bile acids compared to after menopause. So we had a very small subset.

NOTE Confidence: 0.869849920272827

00:14:15.900 --> 00:14:35.900 That tumors we had 8 samples from memory for outside the code on cancer and 10 from women with right sided Colon cancer and so we just looked at the levels of the primary and secondary non conjugated and a touring increasing conjugates you can see here, but there is no signifi-

NOTE Confidence: 0.89002788066864

00:14:36.700 --> 00:14:56.700 And I hate to use the word trend, but you can see here that there are lower levels of the bile acids in the women with right sided colorectal cancer, but we need to increase our sample number to see if this is the actual effect or not so we believe that after menopause the bile acid.

NOTE Confidence: 0.867445290088654

00:14:57.500 --> 00:15:00.770 Crease in women with right sided colorectal cancer.

NOTE Confidence: 0.888439059257507

00:15:01.700 --> 00:15:21.700 So, just to summarize aim one we see that both men and women have higher bile acid levels in the right side of the Colon compared to the left and there is seems to be a difference in by lesser distribution. When we go from stage one to 2 and we do see that the bile acid metabolic differences potentially.

NOTE Confidence: 0.894042909145355

00:15:22.500 --> 00:15:42.500 Simulated after age 55, so further assessments with the file. I said work that we want to do is actually to incorporate the clinical information or this information is not in electronic form. So we now have somebody at Sloan Kettering, pulling out things like BMI hormone.

NOTE Confidence: 0.882286310195923

00:15:43.300 --> 00:16:03.300 Surgeries, racial ethnic groups outcome another medical history and we would like to correlate the bile acid levels to patient

outcome. Once we've assessed all these confounders. We also intend to do some receptor expression analysis and correlate with mass spectrometry imaging.

NOTE Confidence: 0.887447118759155

00:16:04.100 --> 00:16:13.720 Station with metabolites and some histopathological features and we currently doing some microbiome analysis with Baylor college core as well.

NOTE Confidence: 0.902421891689301

00:16:15.560 --> 00:16:35.560 So my phone to end 2 where we doing armor systems level approach. I'm not going to go into this in detail but this is just our workflow that we do in the lab. We've been really over the past couple years, optimizing amor population level analysis of samples from a tableau mix because you do get issues with batch effect.

NOTE Confidence: 0.900147318840027

00:16:36.360 --> 00:16:56.360 Quality control, so this is something we've been optimizing in developing kodinar basically we after we obtain our data. We do a variety of multivariate anuna very analysis to find the most important metabolites and get rid of false positives and then we carry out.

NOTE Confidence: 0.870097577571869

00:16:57.160 --> 00:17:09.020 By Nazis and metabolise identification, which is one of the hardest parts of an targeted metabolomics and then we also validate using another platform and quantify the metabolites.

NOTE Confidence: 0.898142337799072

00:17:10.620 --> 00:17:30.620 So some of the differences that we assessed was metabolic differences between normal tissues and tumor. Tissues differences between the right and the left sides of the Colon differences. Of course, stage and also sex specificity and there's about 30 different perturbations within this so I'm just going to show a couple of the results so the first.

NOTE Confidence: 0.887404084205627

00:17:31.420 --> 00:17:51.420 Ways that we've identified that seems to be really interesting is when we compare normal tissues to colorectal cancer tissues and these are pathways related to argina metabolism. So all the metabolites that are circled in orange are increased in men and women with colorectal cancer. Those are those are.

NOTE Confidence: 0.83454567193985

00:17:52.220 --> 00:18:12.220 Only increased in men and those are in purple, increasing women at stage. One only so this cycle here is the urea cycle where Argentinia is transformed into the area and also on Athene on it being transformed into citrulline and arginine socks and.



NOTE Confidence: 0.873418271541595

00:18:13.020 --> 00:18:33.020 Nothing is particularly interesting in the colour. It'll cancer because it's decarboxylated interpret Racine and enters the Poly aiming pathway and honor thing decarboxylase is typically upregulated in colorectal cancer because it is also regulated by.

NOTE Confidence: 0.832281053066254

00:18:34.040 --> 00:18:36.710 APC, which is mutated in colorectal cancer.

NOTE Confidence: 0.865433394908905

00:18:37.620 --> 00:18:57.620 But if we look at this other path way this is also potentially interesting because we see increases in this metabolite asymmetric dimethyl are Janie and this is formed after proteolysis of proteins and methylation of arginine residues an ATM.

NOTE Confidence: 0.896802663803101

00:18:58.420 --> 00:19:18.420 The being that scene in the cardiovascular diseases because it's known to actually inhibit Ender Thi Lio into filial nitric oxide synthase and decrease nitric oxide production where this is particularly interesting colorectal cancer is that it could potentially increase gut permeability and a DMA has been a soul.

NOTE Confidence: 0.86789870262146

00:19:19.220 --> 00:19:39.220 Take Deering so it's possible that a DMA could increase gut permeability and increase microbial translocation as well, what we see is that in women. Actually, a DMA is only increased in right sided colorectal cancers and we do see a slight increase in arguing stage one and are genes name to compete.

NOTE Confidence: 0.810286521911621

00:19:39.260 --> 00:19:59.260 AMA for Enosse in men. We do see an increase in citrulline. So it's possible the ad man. Men is metabolise into Citrulli. Through this enzyme. DDH and it's possible in women that DDH is deficient interestingly just as a side note do.

NOTE Confidence: 0.892476201057434

00:20:00.060 --> 00:20:10.360 Is also regulated by ethics are? Which is controlled by bile acid levels as well. So it's like a sort of overlap between all of the metabolites in these different pathways, but she was still trying to digest.

NOTE Confidence: 0.903441190719604

00:20:12.180 --> 00:20:32.180 Another pathway uhm this is the last one. I'm going to mention but which is also interesting in terms of women with colorectal cancer is a fatty acid metabolism. And what we see actually is that fatty acids are decreased in women with colorectal cancer, but we see and in.

NOTE Confidence: 0.857470571994781

00:20:32.980 --> 00:20:45.010 In the carnitine shuttle. So where hypothesize in here that potentially women have increased transporter fatty acids by the carnitine shuttle and could be potentially used for beta oxidation and Energi.

NOTE Confidence: 0.872125148773193

00:20:47.150 --> 00:21:07.150 So, just to summarize our aim 2. We see multiple metabolic pathways that are altered in colorectal cancer that we see that we will stay Jancek specific specificity and we see interestingly metabolites are related to any regulation and also got permeability and we also see changes to energem it.

NOTE Confidence: 0.836823403835297

00:21:07.950 --> 00:21:12.620 It's a fatty acid and the carnitine shuffle in women with right sided colorectal cancer.

NOTE Confidence: 0.910368800163269

00:21:13.730 --> 00:21:33.730 So our future work is to investigate these metabolic pathways. A lot more closely as we've only really receive. This data over the past few months and we want to use more of a multi level approach by looking at gene expression changes as well, and also validating with any publicly available data to see if we see the same effects. We also want to look.

NOTE Confidence: 0.921193659305573

00:21:34.530 --> 00:21:54.530 The council, aggressiveness and patient outcomes and then eventually go along the lines of therapeutic intervention. We currently as well trying to validate these work by acquiring a number of samples from patients who are seen at Yale, New Haven Hospital by collecting both tissue samples and.

NOTE Confidence: 0.882947623729706

00:21:55.330 --> 00:22:15.330 And potentially would like to move on to looking at blood based markers as well. But we do see this systemic effects of increased by licensing women with right sided color. It'll cancer and we want to understand the relationship of all of these different factors within the different pathway changes that we are seeing.

NOTE Confidence: 0.879189848899841

00:22:16.130 --> 00:22:30.250 We're looking, and he developed projects within endocrine disrupting chemicals in the color rectal cancer and relationship to your beta and also pharmaco metabolomics to have predicted metabolites of patient response.

NOTE Confidence: 0.851413786411285

00:22:32.140 --> 00:22:52.140 So I would like to acknowledge other members of my lab who had been working on the current accounts of projects. You pink eye and grab tray, you since left to start a faculty position position in Glasgow Varieur. We went over Alvary Santos Neto and also link.

NOTE Confidence: 0.859742045402527

00:22:52.940 --> 00:23:12.940 Paying collect the patient samples my collaborator doctor, Khan at school Madison and also doctor Chung's corner. Medison and public health is helping us with the outcome work and then of course, my collaborators at sign Kettering and the funding sources from women's Health Johanssen.

NOTE Confidence: 0.754822611808777

00:23:13.740 --> 00:23:18.350 NCI as well. Thank you for attention.