Rounds we have two speakers today from male to wonderful speakers first or Hegel on my own, introduced and then the cold diesel, who Linda Irwin will introduce. I've known Jorge since before he arrived at Yale. He’s now the Lucille P Marquis, professor, microbial pathogenesis and chair of the Department. In his lab studies bacterial infections, he’s probably best known for his discovery and characterization of the Type 3 secretion apparatus,
which is this microscopic needle that injects proteins into cells. A fantastic story, and in recognition of this work, he’s received numerous awards and been elected to the National Academy of Sciences, but more recently he’s got interested in the Association between cancer and bacteria, and mechanistically, how does that work, and he’s shown, for example, that some bacterial toxins can induce DNA damage. And therefore are potential carcinogens. And so today we’ll hear about this very exciting work.
So Jorge, the floor is yours.

Thanks Dan,

And yeah as then.

Imply microbes and cancer are a lot more intertwined that many would think.

If we start with the obvious that.

So these are the known causes

That amount to that 20%.
But by all accounts this is probably rose underestimate in terms of the influence in the etiology of cancer of microbes. But Microsoft, either toying with cancer in many other ways. For example, the study of microbial pathogens really have provided fundamental knowledge for the understanding of cancer. You, of course, are aware that Uncle genes really were discovered through the study of a chicken ritualize. And today the study of host pathogen
interactions have provided insight into cancer that are extremely important for the fundamental knowledge.

Of infectious diseases as an entity are really a significant challenge in the context of cancer patients. Many of the drugs that we administer to treat cancer or course have immunosuppressive power and increases the susceptibility of patients to infectious diseases and imposes it challenge in many therapeutic set settings.

And of course, the elephant in the room.
The resident microbiome, which in the last five years or so, is quickly emerging as a major factor, both in terms of cancer etiology and cancer treatment. So what I'm trying to tell you here is something that should be obvious and that this is an extremely important aspect of cancer biology and quite frankly, is one of the most exciting times to be involved in this research space. So the that's perhaps the reason why maybe some of us were a bit disappointed when the cancer
00:03:31.412 --> 00:03:33.707 microbiology piece of the Cancer
NOTE Confidence: 0.7699789
00:03:33.707 --> 00:03:35.045 Center was interrupted.
NOTE Confidence: 0.7699789
00:03:35.050 --> 00:03:35.886 In fact,
NOTE Confidence: 0.7699789
00:03:35.886 --> 00:03:39.230 when I was invited to give this talk,
NOTE Confidence: 0.85875857
00:03:39.230 --> 00:03:42.065 I was invited as a member of
NOTE Confidence: 0.85875857
00:03:42.065 --> 00:03:45.610 the Cancer Microbiology Group,
NOTE Confidence: 0.85875857
00:03:45.610 --> 00:03:47.835 which now doesn’t exist.
NOTE Confidence: 0.85875857
00:03:47.835 --> 00:04:03.118 Although I completely understand
NOTE Confidence: 0.85875857
00:04:03.120 --> 00:04:03.118 why the leadership of the Cancer
NOTE Confidence: 0.85875857
00:04:03.120 --> 00:04:06.448 Center to please this step,
NOTE Confidence: 0.85875857
00:04:06.450 --> 00:04:08.315 And although I completely understand
NOTE Confidence: 0.85875857
00:04:08.315 --> 00:04:08.315 microbiology or microbes really are
not the this the so called cancer establishment from which reviewers will be drawn to review the Cancer Center grant.

I’m not really friendly to the concept of Micros, Ann and cancer. For whatever reason, and even other considerations, other currencies that are used in the evaluation of these grants, such as for example in CI grants. You know, people work with my girls that that don’t score high on that because it will be a fundraising malpractice. If you can send your grant when
00:04:44.624 --> 00:04:47.339 I need to send it to NCI,
NOTE Confidence: 0.85875857
00:04:47.340 --> 00:04:49.566 which is much less generous and
NOTE Confidence: 0.85875857
00:04:49.566 --> 00:04:52.020 certainly less friendly to these courses.
NOTE Confidence: 0.85875857
00:04:52.020 --> 00:04:55.140 So I although I totally understand these,
NOTE Confidence: 0.85875857
00:04:55.140 --> 00:04:57.480 I think is is an opportunity
NOTE Confidence: 0.85875857
00:04:57.480 --> 00:04:58.650 loss for leadership,
NOTE Confidence: 0.85875857
00:04:58.650 --> 00:05:01.107 particularly with the really the the history
NOTE Confidence: 0.85875857
00:05:01.107 --> 00:05:03.829 of deal with the tremendous leadership.
NOTE Confidence: 0.85875857
00:05:03.830 --> 00:05:08.765 People like Dundee Moniot or Charles Miller.
NOTE Confidence: 0.85875857
00:05:08.770 --> 00:05:10.846 In the space of Uncle Virus, for example,
NOTE Confidence: 0.85875857
00:05:10.846 --> 00:05:13.849 there is a lot of history here on this space.
NOTE Confidence: 0.85875857
00:05:13.850 --> 00:05:15.880 But life is life and the cancer
NOTE Confidence: 0.85875857
00:05:15.880 --> 00:05:17.980 establishment is the cancer establishment.
NOTE Confidence: 0.85875857
00:05:17.980 --> 00:05:19.730 This is the same establishment
NOTE Confidence: 0.85875857
00:05:19.730 --> 00:05:22.450 that 10 years ago or 20 years ago,
NOTE Confidence: 0.85875857
00:05:22.450 --> 00:05:24.508 worse naughty related to cancer immunology.
00:05:24.510 --> 00:05:27.606 It with people like blow it all the late, allowing all that was advocating for it.

00:05:27.610 --> 00:05:30.018 And he was really honestly looked down.

00:05:30.020 --> 00:05:34.150 I was a close collaborator, the law and he always complained.

00:05:34.150 --> 00:05:36.208 Of course he was shielded by the Ludwig Cancer Center.

00:05:36.210 --> 00:05:38.274 He didn’t have to worry about, but anyway,

00:05:41.710 --> 00:05:45.720 I think he said more of a loss opportunity. I think he said more of a loss opportunity.

00:05:47.685 --> 00:05:49.650 this this decision was made, so enough venting enough Priscilla Teising.

00:05:52.010 --> 00:05:55.122 Let’s get back to business here and in order to put in context a little bit,
what I will tell you briefly is is to consider the general mechanisms by which microbes induce cancer and and there are two types of mechanisms. If you will. The direct Uncle Genesis and that is obvious when a virus is introduces an Uncle gene itself. This is of course. The mechanisms behind HPB or a BB, for example. Or when it when they integration event itself access and origin, because obviously the viruses integrate upstream of some gene that can drive sort of proliferation and growth. That’s that’s direct on Go Genesis,
but arguably more common is the indirect organ Genesis, and this takes several forms. For example the form in which viruses in a cost, immunosuppression and immunosuppression activates for example. Other two more viruses. In the case of Kaposi sarcoma, is an HIV HIV infection. It comes to mind or when viruses triggers chromosome instability or translocation that eventually die. Of course, leads to cancer and other
aspects of the Director Genesis

more related to what I'm being,

I'm going to be telling you today is,

for example, chronic inflammation,

which is very well established to

be linked to to Uncle Genesis.

The production of proinflammatory

cytokines that have growth promoting

abilities combined with oxygen radicals.

They have a mutation or mutagenesis ability

leads to setting the stage for Franco,

Genesis is the case,

for example with Helicobacter

pylori and gastric cancer,

and in addition something that has been

emerging over the last few years and
00:07:46.563 --> 00:07:49.556 that we sort of Pioneer in this area

00:07:49.556 --> 00:07:52.214 is the fact that certain organisms

00:07:52.214 --> 00:07:54.651 really produce direct Gina toxins

00:07:54.651 --> 00:07:57.753 that will drive the oncogenic event.

00:07:57.760 --> 00:08:00.576 So I say alluded these last two are

00:08:00.576 --> 00:08:03.440 the ones more relevant to bacteria,

00:08:03.440 --> 00:08:05.888 which is the type of microbes

00:08:05.888 --> 00:08:08.320 that we study in the lab.

00:08:08.320 --> 00:08:10.552 So bacterial is in this context

00:08:10.552 --> 00:08:12.040 bacterial colonization leads to

00:08:12.105 --> 00:08:13.761 both inflammation and genotoxin

00:08:13.761 --> 00:08:16.245 production and exposures of tissues to

00:08:16.305 --> 00:08:17.985 genotoxin and therefore predisposing

00:08:17.985 --> 00:08:20.085 those tissues to to cancel.

00:08:20.090 --> 00:08:23.121 What I'm gonna be telling you today

NOTE Confidence: 0.79306287
00:08:23.121 --> 00:08:26.088 is the paradigm of two organisms that
NOTE Confidence: 0.79306287
00:08:26.088 --> 00:08:29.354 we study in the lab. Both of them.
NOTE Confidence: 0.79306287
00:08:29.354 --> 00:08:31.066 These organisms are salmonella
NOTE Confidence: 0.79306287
00:08:31.066 --> 00:08:32.350 and campylobacter jejuni.
NOTE Confidence: 0.79306287
00:08:32.350 --> 00:08:34.912 Both of them have been very
NOTE Confidence: 0.79306287
00:08:34.912 --> 00:08:35.766 strongly epidemiological.
NOTE Confidence: 0.79306287
00:08:35.770 --> 00:08:37.940 He associated with the development
NOTE Confidence: 0.79306287
00:08:37.940 --> 00:08:39.676 of cancer Campylobacter jejuni
NOTE Confidence: 0.79306287
00:08:39.676 --> 00:08:41.770 associated with an intestinal lymphoma,
NOTE Confidence: 0.79306287
00:08:41.770 --> 00:08:43.430 and while Salmonella Typhi,
NOTE Confidence: 0.79306287
00:08:43.430 --> 00:08:46.648 one of these family that we study in
NOTE Confidence: 0.79306287
00:08:46.648 --> 00:08:49.240 the lab is really a major cause of
NOTE Confidence: 0.79306287
00:08:49.323 --> 00:08:51.435 Gallbladder cancer and Gallbladder
NOTE Confidence: 0.79306287
00:08:51.435 --> 00:08:55.085 cancer in endemic areas is actually one
NOTE Confidence: 0.79306287
00:08:55.085 --> 00:08:58.410 of the main cancers that affect those.
NOTE Confidence: 0.79306287
00:08:58.410 --> 00:09:01.620 Individuals and it infections with
Salmonella Typhi and associated with a 204 risk of hip, hepatobiliary carcinoma and Gallbladder cancer, so these are important causes of cancer which incidentally are not in that 20% statistic that I told you about. Now, in the case of Campylobacter, what we discovered that was sort of central to understand how these organisms linked to oncogenesis is a characterization of a toxin that we did almost two decades ago.
00:09:36.321 --> 00:09:40.248 actually scary more than two decades ago?
NOTE Confidence: 0.79306287
00:09:40.250 --> 00:09:42.966 That he said toxin that caught our
NOTE Confidence: 0.79306287
00:09:42.966 --> 00:09:45.897 attention because of what you see here in in.
NOTE Confidence: 0.79306287
00:09:45.900 --> 00:09:46.959 In these images,
NOTE Confidence: 0.79306287
00:09:46.959 --> 00:09:49.077 these are cells that are intoxicated.
NOTE Confidence: 0.79306287
00:09:49.080 --> 00:09:51.824 You see them very much expanded with a
NOTE Confidence: 0.79306287
00:09:51.824 --> 00:09:53.955 large nuclei in comparison to control
NOTE Confidence: 0.79306287
00:09:53.955 --> 00:09:56.490 cell at the same excuse me Jorge,
NOTE Confidence: 0.79306287
00:09:56.490 --> 00:09:57.549 your your slide
NOTE Confidence: 0.8167658
00:09:57.550 --> 00:09:59.668 is not. It did not advance.
NOTE Confidence: 0.820451730769231
00:10:00.120 --> 00:10:01.347 Papa you mean?
NOTE Confidence: 0.820451730769231
00:10:01.347 --> 00:10:05.640 I mean what they have you on the 1st slide?
NOTE Confidence: 0.820451730769231
00:10:05.640 --> 00:10:09.060 Oh gosh, that’s that’s not good.
NOTE Confidence: 0.820451730769231
00:10:09.060 --> 00:10:11.780 That can you see them this way now?
NOTE Confidence: 0.820451730769231
00:10:11.780 --> 00:10:14.484 Yeah, that I can see those OK when
NOTE Confidence: 0.820451730769231
00:10:14.484 --> 00:10:17.558 I when I do it that way because OK,
00:10:17.560 --> 00:10:18.580 yeah unfortunately because
00:10:18.580 --> 00:10:20.620 whatever it would have been easier.
00:10:20.620 --> 00:10:23.000 But thank you for letting me know.
00:10:23.000 --> 00:10:25.720 OK so anyway, so here it is.
00:10:28.960 --> 00:10:31.402 OK, so this image is showing
00:10:31.402 --> 00:10:34.754 you the the cells that have been
00:10:34.754 --> 00:10:36.930 intoxicated with this toxin,
00:10:36.930 --> 00:10:39.194 showing this unusual morphology.
00:10:39.194 --> 00:10:42.024 In comparison we control cell
00:10:42.024 --> 00:10:45.352 and the reason these cells have
00:10:45.352 --> 00:10:47.488 that morphology is becaused.
00:10:47.490 --> 00:10:50.698 The cells are stuck on the G2M phase
00:10:50.698 --> 00:10:53.828 of the cell cycle and we found
00:10:53.828 --> 00:10:57.141 that the reason for that is that
00:10:57.141 --> 00:11:00.075 this toxin that we had discovered.
It has a genotoxicity DNA damage in capacity,

NOTE Confidence: 0.76506776

those this is a toxin typical

NOTE Confidence: 0.76506776

toxins have two two types of parts.

NOTE Confidence: 0.76506776

If you will the be part,

NOTE Confidence: 0.76506776

which is what targets the payload to a

NOTE Confidence: 0.76506776

particular cell and the payload part.

NOTE Confidence: 0.76506776

The nucleus is an endonuclease is

NOTE Confidence: 0.76506776

actually an unusual in the nucleus

NOTE Confidence: 0.76506776

in the sense that primary amino

NOTE Confidence: 0.76506776

acid sequence would not overtly

NOTE Confidence: 0.76506776

tell you that this is a new case.

NOTE Confidence: 0.76506776

But when you look at the atomic structure,

NOTE Confidence: 0.76506776

you can make out the catalytic side.

NOTE Confidence: 0.76506776

So so this is a typical case of

NOTE Confidence: 0.76506776

genotoxin that is responsible for for
driving the day on today.

Cancer development and in fact just recently, this has been formally demonstrated in an animal model that this toxin is responsible for Campylobacter jejuni's ability to promote cancer so.

It's kind of awkward to have to advise it like this, but I will go ahead. So the second example is Salmonella Typhi and I need to tell you that the basic about something that I think people things in context again and that is that someone had typhus and exclusive pathogen of humans. It causes typhoid fever.
One of those historical diseases if you will, but important for Genesis is the fact that those that survived the disease, many of them go on to persistently harbored the Organism. Within the Gallbladder and that is where the rubber meets the road and that is the reason why those individuals that are harboring salmonella typing in the areas are prone to develop Gallbladder cancer. And in the case of Salmonella the paradigm is slightly different than the paradigm in Campylobacter jejuni. But it shares it remarkably, is shares more than what would expect.
You need to think in terms of evolution that Campylobacter and Salmonella are they. Couldn’t be more far apart. One is an epsilon bacteria, the other is a gammaproteobacteria. It’s like absolutely no evolutionary connection and yet what is remarkable is that we discover a toxin in Salmonella typhi that we call typhoid toxin. That also has the ability to induce DNA damage, as shown here in this image, and when we characterize this toxin, we were surprised to see that the active subunit of this toxin.
was virtually identical, that the active subunit of the completely unrelated toxin Curry by camping of active June. So this is really a remarkable piece of evolution. This is one of those head turning toxins that actually evolution put it together by fusing two toxins, one. That some of you may be familiar, it called pertussis toxin, what makes you a what is central for the pathogenesis of whooping cough. And then these other talks in that I described earlier. They cite a little distending toxin,
Note: Confidence: 0.8201903
00:14:18.230 --> 00:14:20.253 so this lower part of the talks
Note: Confidence: 0.8201903
00:14:20.253 --> 00:14:22.220 in comes from pertussis toxin,
Note: Confidence: 0.8201903
00:14:22.220 --> 00:14:24.170 and this upper Paradox income from
Note: Confidence: 0.8201903
00:14:24.170 --> 00:14:25.870 side a little extended talks,
Note: Confidence: 0.8201903
00:14:25.870 --> 00:14:27.380 so evolution hook them together
Note: Confidence: 0.8201903
00:14:27.380 --> 00:14:29.324 to make this head turning toxin
Note: Confidence: 0.8201903
00:14:29.324 --> 00:14:30.848 that Salmonella typhi encodes,
Note: Confidence: 0.8201903
00:14:30.850 --> 00:14:33.272 and that it is responsible for the
Note: Confidence: 0.8201903
00:14:33.272 --> 00:14:35.000 genotoxicity of these organisms.
Note: Confidence: 0.8201903
00:14:35.000 --> 00:14:37.064 And easy sent unusual toxin in
Note: Confidence: 0.8201903
00:14:37.064 --> 00:14:39.023 many different ways that I don’t
Note: Confidence: 0.8201903
00:14:39.023 --> 00:14:40.318 have time to go into,
Note: Confidence: 0.8201903
00:14:40.320 --> 00:14:42.574 but one of the remarkable ways in
Note: Confidence: 0.8201903
00:14:42.574 --> 00:14:45.019 which this toxin is unique is that it
Note: Confidence: 0.8201903
00:14:45.019 --> 00:14:47.210 is other patient to the human host.
Note: Confidence: 0.8201903
24
And what do I mean by that? Well, the receptor for these talks, you know the receptors. I should say we discovered two proteins, part of policing, one in epithelial cells and CD 45 in. In immune cells, but what is important here is what does the toxin see on this block of proteins and is the glycan power and we through like Andres and other types of studies for to address these kinds of questions we discovered that what Typhoid toxin likes if you will is glycans terminated in the sitting room.
We know that many Kacian hooked to galactose and and to glucose or setting glucosamine in this particular fashion. And why is this relevant? Well, this is important because you may not know these or many of you may know that we humans are actually rather unusual mammals in many ways, and one of the ways in which unusually is in our glycosylation pattern. All our sciullo glycans are terminated in a city neuraminic acid, but all other mammals in fact, like answer, terminated in Blakely, like neuraminic acid,
and the reason is that the enzyme that is responsible for.

Can you see this slide and? Well, whatever I continuously the inside that is responsible for putting these acts. that is responsible for putting these acts.

Oxygen here is mutated in humans. We have a pseudogene there and therefore we are unique in that fashion and typhoid toxin combined likens exclusively terminated in a city in America. We have a pseudogene there and therefore we are unique in that fashion and typhoid toxin combined likens exclusively terminated in a city in America.

And in fact, if you just change one oxidant in any of these glycans that Typhoid toxin likes and you already meaning in in an array make like an array,
NOTE Confidence: 0.76375777
00:16:29.000 --> 00:16:30.800 typhoid toxin does not bind.
NOTE Confidence: 0.76375777
00:16:30.800 --> 00:16:33.390 It also has the ability to distinguish.
NOTE Confidence: 0.76375777
00:16:33.390 --> 00:16:35.580 Just one Atom of oxygen.
NOTE Confidence: 0.76375777
00:16:35.580 --> 00:16:37.685 Remarkable piece of evolution that
NOTE Confidence: 0.76375777
00:16:37.685 --> 00:16:40.764 makes it able to target human cells
NOTE Confidence: 0.76375777
00:16:40.764 --> 00:16:42.994 and have that oncogenic effect.
NOTE Confidence: 0.76375777
00:16:43.000 --> 00:16:45.622 But in addition to having a
NOTE Confidence: 0.76375777
00:16:45.622 --> 00:16:46.496 genotoxin somewhere,
NOTE Confidence: 0.76375777
00:16:46.500 --> 00:16:49.116 typhi is actually has the 241.
NOTE Confidence: 0.76375777
00:16:49.120 --> 00:16:50.599 In other words,
NOTE Confidence: 0.76375777
00:16:50.599 --> 00:16:53.064 is also the chronic inflammation
NOTE Confidence: 0.76375777
00:16:53.064 --> 00:16:56.433 part that plays a role in the
NOTE Confidence: 0.76375777
00:16:56.433 --> 00:16:58.728 Uncle Genesis of Salmonella Typhi.
NOTE Confidence: 0.76375777
00:16:58.730 --> 00:17:01.747 And so it’s something that I think
NOTE Confidence: 0.76375777
00:17:01.747 --> 00:17:04.092 causes chronic inflammation of the
NOTE Confidence: 0.76375777
28
Gallbladder and that chronic inflammation, as is well known, leads to the development of cancer or contributes to development of cancer and the paradigm here is well known where as I said, the production of growth. Promoting cytokines combined with or radical oxygens that Armenta Genic eventually leads to the development of cancer angiogenesis. Growth stimulation and so on and so forth. So the issue is how does salmonella trigger inflammation now on this on? On the surface, this could be a rather simple story
00:17:43.005 --> 00:17:45.957 and you may know that we are in now
with innate immune receptors famously put into the scientific space by the late Charlie Janeway here at Yale and this innate immune receptors have the capacity to recognize bacterial products. They essentially coordinate an inflammatory response and that inflammatory response eventually leads to pathogen rejection and
they acquired immune response.

So this is central to the way we hosts,

But all mammals defend against microbial.

Pathogens now it turns out that then

from these framework it will be very

simple to think that someone other

because he has plenty of LPS.

He has plenty of these product

and is the detection of the

host that drives inflammation.

In other words,

this will be like a host centric view,

but work that we have done in our

lab for the last 15 years or so has
completely turn around this paradigm and discovered that that’s actually incorrect in the case of Salmonella, that salmonella really has a specific adaptations. Evolve by similar to trigger inflammation. So this is a pathogen driven process, not a host driven process, and the reason is very simple or not so simple. Salmonella, like many other microbes, when they encounter a mucosal site, being an intestinal being the Gallbladder mucosa, they need to compete with resident
microbiota who has a foothold on that issue and really put up a good fight. This is actually over. One of our main barriers against bacterial pathogens, particularly in this time, is the resident microbiota. The inflammatory response crosses it causes profound dysbiosis, which is essential for someone else to be able to colonize and replicate. Not only that, inflammation makes nutrients available, electron acceptors camper sourcers that otherwise would not be available in the an inflamed tissue,
and that drives the replication of the aluminum.

Population of salmon are so, so is the inflammatory response that causes even though someone else and intracellular pathogen the bulk of the bacterial replication comes from this lumenal population that is fed from the inflammatory response triggered by this in this bacteria.

Here. So a nice division of Labor. Now how does someone even managed to trigger an inflammatory response?

Mucosal sites which are actually is pretty difficult because mucosal
sites are subject to various stringent negative regulation of his native.
Respected receptors precisely to prevent this microbiota that in theory can also stimulate in Amy receptors to trigger an inflammatory response and for all of us to be working with IBD or Crohn’s disease. To avoid that they’re very precise mechanisms to keep those innate immune receptors in check, and somebody had to trigger inflammation in that environment has does he do it? Well, it does sit through this amazing machine that Dan alluded earlier that
we discovered more than two decades ago. It’s an amazing sort of bacterial injection device if you will. That injects bacterially encoded proteins that. Have the capacity to modulate many signal transduction pathways. And it’s the ability to stimulate those signal transduction pathways and modulate cellular process for the benefit of the pathogen specifically relevant to inflammation. are three of these effective proteins that activate Rho Family GTPases by either being exchange factors of
the Pro Family GPs is or forcefully nocetti phosphatase.
In the case of this particular effector that wouldn’t activate endogenous change factors and activate that, and that leads to the activation of CDC.
and that leads to transcriptional responses that really are proinflammatory and really looked like in 18 responses.
This was a bit puzzling for a number of years because CDC 42 had never been linked to innate immune responses until very recently,
where we sort of cracked this little
puzzle and we discovered that the activation of CDC 42 by Salmonella leads to the formation of a noncanonical signaling complex made by pack one. A target of CDC 42 and these other components. Trap 6 Tab Tak, One Tab 1 Tab 2 that leads to the inflammatory response and what is what explains the whole thing is these signaling complexes identical to the signaling complex that is tripped by narimi receptors. So what someone in essence is doing is going down the signaling pathway.
so that as to avoid the negative regulatory system and trigger essentially an innate immune response. But by non Canonical methods, so he uses other type of mechanism similar to this going downstream of Canonical signaling pathways. But since my time is up I just gonna put up a sort of a summary of these and sort of to give you a flavor or how these effector proteins can go down. Different signaling pathways intersect with signaling pathway. For example this effector can activate the rig I and MD I5. A nucleotide sensing pathway,
00:23:26.556 --> 00:23:29.490 but without the need of nuclear dice.

00:23:29.490 --> 00:23:32.166 It just simply activates regay by interfacing with dream 56 and trim 65.

00:23:34.940 --> 00:23:37.448 Two regulators of this pathway you.

00:23:37.450 --> 00:23:40.327 We could make them activates them and trips this signaling pathway without the need of The Agonist of those receptors.

00:23:42.897 --> 00:23:45.830 and the same applies to another effector here that it actually inhibits an anti-inflammatory pathway.

00:23:45.830 --> 00:23:47.810 So, but since I don’t have time.

00:23:47.810 --> 00:23:52.118 I had to skip it, so I hope that you got a sense of the sophistication by which bacterial pathogens manipulate cells in in ways
that benefit them but doesn’t benefit us.

And through the production of Gina toxins or inflammation,
it leads to the predisposition to cancer and then finally last but not least,
people that were involved in this work obviously and talked to work that was done a number of years ago as well,
Indiana were involved and one whose did all this work and Mary,
Indiana was involved and one whose did all this work and Mary,
whom did all this work and Mary, of course,
had made the pioneering discoveries of the Genotoxin in Campillo Bacter.
Jejuni and set in motion all this work. And thank you very much.
And with that I’m gonna stop sharing if I can.
And.
OK, well thank you very much.
Jorge is very interesting.
Very exciting work.
I don’t know how to swim.
I should know how to stop sharing but you help me on that one.
Yeah, OK.
If people have questions,
you can type them into the chat,
or Renee’s, or way to unmute them.
We can, if you’d like, sure.
I’m ask a quick question. I was very struck by that by what appears to be the convergent evolution of these two nuclease.

Yeah, it’s really very striking.

Is there? What is the advantage of the bacteria to induce cell cycle arrest? What cell cycle arrest actually is also growing inflammatory?

So probably one of the main drivers is the Pro inflammatory response and also in the case of some type is using this activity to target immune cells.

So obviously if you’re a virus and you know you know a thing or two about them and you integrate your
genome in in the host, you’re free.

You know you.

That’s the way you can persist as long as you want.

If you’re somebody that I feel you have.

4761 those are the number of open reading frames,

potential antigens you need to hide.

So the way somebody that he does it is by creating a sort of immunological suppression around the site,

wherein colonizes and these toxin is central for that.

For the persistent infection,
00:26:20.632 --> 00:26:22.184 by targeting immune cells.
NOTE Confidence: 0.8003514
00:26:22.190 --> 00:26:25.310 So so, and in the case of Campylobacter,
NOTE Confidence: 0.8003514
00:26:25.310 --> 00:26:26.014 of course,
NOTE Confidence: 0.8003514
00:26:26.014 --> 00:26:28.830 inflammation is central for the bug and and
NOTE Confidence: 0.8003514
00:26:28.905 --> 00:26:31.647 this proinflammatory aspect of DNA damage.
NOTE Confidence: 0.8003514
00:26:31.650 --> 00:26:33.030 Is probably what evolutionary
NOTE Confidence: 0.8003514
00:26:33.030 --> 00:26:34.065 selected for these,
NOTE Confidence: 0.8003514
00:26:34.070 --> 00:26:34.762 you know,
NOTE Confidence: 0.8003514
00:26:34.762 --> 00:26:36.838 toxins and the in the process.
NOTE Confidence: 0.8003514
00:26:36.840 --> 00:26:38.916 We you know we got clipped.
NOTE Confidence: 0.83454424
00:26:40.490 --> 00:26:41.710 Thank you are there
NOTE Confidence: 0.83454424
00:26:41.710 --> 00:26:43.528 are there other questions for Jorge?
NOTE Confidence: 0.91647124
00:26:50.550 --> 00:26:52.236 Alright, well thank you very much.
NOTE Confidence: 0.83337504
00:26:59.580 --> 00:27:03.090 I think I think Dan froze.
NOTE Confidence: 0.83337504
00:27:03.090 --> 00:27:05.360 You were frozen Dan.
NOTE Confidence: 0.83337504
00:27:05.360 --> 00:27:07.628 Oh, I'm sorry, frozen.
I guess introduce you,

Melinda Kay. Great don’t we love

the advances in technology.

Thank you Doctor Glenn that was fabulous Ann.

I am now delighted to introduce

Doctor Nicole Diesel to present

her research on environmental

carcinogens and thyroid cancer.

Doctor Diesel is an associate

professor of environmental health in

the Yale School Public Health and

she received her PhD in her Masters

in industrial hygiene from the Johns

Hopkins School of Public Health.

Her environmental exposure assessment
strategies aimed to reduce exposure

misclassification for epidemiological.

Studies and in advance understanding

of the relationship between exposure

chemicals in the risk of cancer

in other adverse health outcomes,

she serves as the Pi of a study funded

by the American Cancer Society and

investigating exposure to flame retardants,

pesticides,

and other persistent pollutants in

thyroid cancer risk and of note,

she is the winner of the Yale Cancer

Center 2020 Research Prize in population.

Science for her research on this topic,
so we're delighted for your presentation.

Doctor diesel.

Take it away.

OK, thank you so much Melinda for the generous introduction.

Very pleased to be here to share some of my recent work with you.

I really enjoyed Doctor Galanes presentation looking at exposure to microbial pathogens and the associated toxins, and I'll be switching gears a little bit to look at work looking at the Epidemiology of exposures to chemical toxins and thyroid cancer risk.

OK, so I've advanced my slide and someone
can let me know if there's any issue there.

I first wanted to take a moment just to tell you about the motivation of my research and the research I'll be presenting today and talk about environmental risk factors for cancer. We know that third of cancers are attributable to modifiable factors. We often think of things related to diet, alcohol, tobacco, these so-called lifestyle factors. But this also includes infections which we just heard about as well as pollution. So how much of cancer cases can we attribute to this pollution? While a doll and Peto in their landmark...
study estimated about 7% of cancer deaths could be attributable to occupation,
pollution and industrial products, in many experts agree that this percentage is likely grossly.
Under arrest Maded due to the extremely limited data on the commercial chemicals that we encounter in our day-to-day lives. So in the United States there are 80,000 chemicals that are licensed for commercial use, and of those only 200. So not even a percentage of them have been screened adequately for carcinogenicity.
I find it really striking. Another reason why this is so important is that you know many of these exposures are outside individual control. These are things in air pollution or water supply, the food supply, our workplaces, so we really rely on the government to protect us from exposure to these potentially harmful chemicals and our regulatory system really is quite inadequate to serve this purpose. The way it’s structured. Chemicals have to be proven harmful rather than proven safe at the outset,
so it normally requires researchers like myself and others in my fields who study chemicals you know for decades before we acquire enough evidence to demonstrate harm for particular chemical. Also importantly, we know these exposures are not distributed equitably across populations and that populations experiencing other social disadvantages are often disproportionately exposed to certain pollutants, and some of these points are highlighted in a forthcoming book chapter that I worked on with Doctor.
Orwin edited by Charlie Fuchs.

So turning to the specific research I want to talk about today, which is related to thyroid cancer, thyroid cancer is one of the fastest growing malignancy’s. It has nearly tripled over the past few decades. You can see in these graphs of SEER cancer incidence data. You can also know by looking at the Y axis that females have three times the incidence compared to males. Can thyroid cancer, you know, has a very good prognosis. It’s more than 90% survival after 20 years.
However, survivors face many physical, psychological and financial challenges. With the prolonged treatments, increased surveillance risk of second primary cancer and other quality of life issues. So this increase is likely certainly due at least in part to improvements and changes to diagnostic techniques, imaging techniques and an fine needle biopsy's. So there's some debate about what proportion can be attributed to this increased diagnostic scrutiny, but many analysis suggests that about half of this.
Trend can be linked to these diagnostic changes, leaving half for environmental or lifestyle factors.

I’ve hypothesized that increasing exposure to thyroid hormone disrupting environmental chemicals such as these polybrominated diphenyl ether flame retardants or PVD ES may be partially driving this increasing trend. So I’ll just talk a little bit more about these people. These are actually a lot of thyroid hormone disrupting environmental chemicals in use in the environment. These flame retardants were widely added.
Too many different products.
The polyurethane foam in mattress is
an couch, cushions and vehicle seats,
including baby car seats.
They were also added to electronics
like phones, cell phones, televisions,
computers and the reason they were
added was to meet a flammability
standards such that if these products
you know caught fire they would burn.
More slowly,
which is a good thing from a
public health perspective.
However,
these chemicals once added to these products,
did not stay bound in the matrices as indicated by their manufacturers and instead have migrated out into our homes. At home environments, cars, workplaces, etc. So due to this widespread use as well as disposal and improper disposal of these chemicals, they aren’t ubiquitous and more than 90% of the population here in the US and globally are exposed to these chemicals. And this also they are extremely persistent once they get into their homes or our bodies, they do not degrade very easily, so they stick around for years and decades. So due to concerns about this
persistence and potential toxicities, these particular group of chemicals, the PDE’s were phase outs were initiated over the last. Past decade, however, exposures do continue for the reasons I described. Their persistence, you know, their presence in products made before then. As well as their presence in the food supply and elsewhere. One other group of chemicals that will be talking about today are the polychlorinated biphenyls or PCB’s.
These were also used widely in electrical equipment, hydraulic machinery construction materials.

These were banned in 1979, so again, you might say why? Why are we even studying these now? Well, there’s still around and they’re still around in our our bodies. Our bloodstreams in the environment, and in fact here in Connecticut there’s been some renewed concern about these legacy chemicals. They were commonly used in buildings, including schools constructed in the 1950s to 1970s.
and many of these schools now are in need of repairs and renovations, and there have been some notable schools in Connecticut that I’ve had PCB levels exceeding safe levels. Closures of schools you know, insufficient funds to do a proper and safe remodeling or renovations, and again, often these are in. Kind of environmental justice communities. So another reason to study these legacy chemicals as they get phased out, new chemicals come to take their place, and many of those are also also have similar properties and so understanding.
These may help us inform greener chemistry or future regulations of other chemicals. So we hypothesize that these PV East could be contributing to that increasing trend in thyroid cancer. Here is a graph showing increasing exposure over a similar time period where we saw thyroid cancer cases start to go up. You can see about a doubling every five years of these particular chemicals. So looking at more recent data, I, as I mentioned, these have been somewhat phased out.
You can see that well levels have come down since those some of those earlier years, but then they really have somewhat plateaued. Or are, you know some particular congeners of these? In this family of chemicals are still increasing slightly an we see similar. Trends with the PCB’s that levels have come down since they were banned, but then they reached this plateau in the population because of their persistence and then as new chemicals come on we may be introduced to those on top of these exposures.
Hey and so why?
Why do we think these may be linked to thyroid cancer?
These chemicals are established thyroid hormone disruptors.
Their endocrine disruptors and over here I have an image of our thyroid hormone thyroxine and then the PCB’s and the PVD ES and their general chemical structure so you can see immediately how structurally similar these chemicals are.
Shut thyrax, and we’ve got the two. Aromatic rings and then while thyroxine has iodine, these chemicals have other halogens.
They have either chlorine or bromine’s. Just to further illustrate when for example this particular PDE gets metabolised, it gets this hydroxyl group added. And now even more closely resembles Thyrax in so the in vitro studies have shown that these chemicals can competitively binds with thyroid transport proteins and results in reduced circulation of thyroid hormones, which could then result in dysregulation of the transport and signaling pathways, potentially leading to overproduction of hormones to compensate.
proliferation in the thyroid and potentially neoplasia.

So as you know the hypothalamus, pituitary, thyroid axis is this very well choreographed system.

These perturbations or dysregulation of these systems can perhaps trigger some of these.

Some proliferation of the thyroid and potentially lead to thyroid cancer.

I'm just showing this slide to also illustrate that some chemicals have some additional hypothesized mechanisms, such as.

Some have been shown to be capable to directly bind to DNA,
leading to mutations and could potentially lead to carcinogenesis that way. So before we launched our study, there had only been two other studies examining this hypothesis. This idea that these PPDS could be linked to thyroid cancer. So the first two rows of this table or the two prior epidemiologic studies in the third row was the study that I lead. A couple things to point out here is that the case is the studies that came before us had moderate study populations, and ours was larger. We also looked at more...
chemicals and importantly,
we looked at single and
multi pollutant models so.
So what I mean by that is that in
the real world you know we’re not
exposed to one chemical at a time,
where typically exposed to groups of
chemicals or mixtures of chemicals
and traditional environmental.
Epidemiologic studies have looked
at chemicals just one at a time,
and in my work we’re looking at
these so-called mixtures using
different modeling techniques
to look at the joint effect of
exposures to multiple chemicals.
Similarly for the PCB’s, the other chemicals there were also only two previous studies before we did ours. Also the other studies were a bit smaller and we also looked at mixture modeling. One other one shortcoming, I wanted to point out actually in reference to at least one of the other studies is that our study was a case control study. So we did collect serum samples to do our. Environmental chemical measurements after diagnosis. Whereas one other study collected pre diagnosis samples, we think you know.
So we’re using this post diagnosis sample to try to capture exposures in the past. While it’s not optimal, we think this is actually a pretty strong and reasonable assumption, because we know that these chemicals have half lives of years and decades. Ends may well reflect past exposure.

OK, so just a few more details about the study we conducted. I LED a study within a study and that larger study was the Connecticut thyroid cancer case control study, which was led by Yahweh Chung, our former colleague.
here at the Yale Cancer Center. We focused on women because they have that three times higher risk. I showed earlier about 90% of our cases were white, so we focused on the white population because our numbers were really small for looking at other demographics. I do think now this is something I would like to follow up on more in another population, we focused on papillary thyroid cancers. That’s about 85% of the new cases or papillary. We also collected very detailed
information about demographics, lifestyle, diet. Many other risk factors that we can control for other factors. We collected the blood sample at the time of the interview and then measured the participants blood samples for 11 different peyivan 32 PCBS, which this analysis also gave us. Some pesticides like DDT, which are also structurally similar to these. These classes of chemicals. And again we looked at both pollutants, one at a time, like like most studies do and then multi pollutant models. OK, so here’s some results from
our study population. These are factors that differed between cases and controls, so our cases had a lower educational attainment compared to controls. They did have a history of benign thyroid disease. That’s a strong risk factor for thyroid cancer. Alcohol consumption was actually higher, lower, lower in cases. This is one of the few cancers where alcohol actually has been consistently shown to have a protective effect.
An cases also had a history of thyroid cancer and higher BMI, which has been shown now in several studies indicating another possible risk factor that can also be interrelated to like endocrine disrupting chemicals and also.

OK, so here are some results from our single pollutant models where we looked at one chemical at a time. These are increasing categories of exposure within each of these different pollutants. You know, odds Ratio 1 means no effects, and anything above one would indicate an Association with thyroid cancer.
So you can see here that there's really not much going on with these individual models. If anything, the odds of thyroid cancer seem to be lower than those who are exposed compared to the reference group of low exposure. The medium and high groups are not at an elevated odds of thyroid cancer except for this one chemical.

So when we move to our multi pollutant models, the results are also somewhat null. We have two multi pollutant models.
00:47:31.598 --> 00:47:33.450 here using Bayesian modeling,
NOTE Confidence: 0.79854375
00:47:33.450 --> 00:47:36.216 which I won’t get into here.
NOTE Confidence: 0.79854375
00:47:36.220 --> 00:47:39.556 But here you can see that it’s the
NOTE Confidence: 0.79854375
00:47:39.556 --> 00:47:43.168 picture is still pretty null except for.
NOTE Confidence: 0.79854375
00:47:43.170 --> 00:47:46.404 In this case we have this other,
NOTE Confidence: 0.79854375
00:47:46.410 --> 00:47:49.030 a different chemical PDE 100.
NOTE Confidence: 0.79854375
00:47:49.030 --> 00:47:52.306 Was associated with elevated odds of
NOTE Confidence: 0.79854375
00:47:52.306 --> 00:47:55.730 thyroid cancer using both those models.
NOTE Confidence: 0.8645845
00:47:57.760 --> 00:48:00.888 And then finally we did this one more
NOTE Confidence: 0.8645845
00:48:00.888 --> 00:48:03.478 mixture type approach of principle,
NOTE Confidence: 0.8645845
00:48:03.480 --> 00:48:06.978 components analysis and in this work
NOTE Confidence: 0.8645845
00:48:06.978 --> 00:48:11.159 we found that people who had had this.
NOTE Confidence: 0.8645845
00:48:11.160 --> 00:48:14.796 Combination of exposures which was higher.
NOTE Confidence: 0.8645845
00:48:14.800 --> 00:48:19.280 PBDE 153. An lower PDE 209 had an
NOTE Confidence: 0.8645845
00:48:19.280 --> 00:48:22.669 elevated odds of thyroid cancer.
NOTE Confidence: 0.8226875
00:48:26.300 --> 00:48:29.850 So then moving on to the PCB use in this
00:48:29.942 --> 00:48:33.134 for this one because we had so many,
00:48:33.140 --> 00:48:35.040 we had 32 different chemicals.
00:48:35.040 --> 00:48:37.574 I'm just going to present some some
00:48:37.574 --> 00:48:39.599 groups of structurally similar PCB’s,
00:48:39.600 --> 00:48:41.754 which was another approach we used
00:48:41.754 --> 00:48:44.160 to look at groups of chemicals.
00:48:44.160 --> 00:48:48.120 So in this in this model this kind of
00:48:48.120 --> 00:48:52.358 we're just looking at one group at a time.
00:48:52.360 --> 00:48:55.096 Odds ratios are hovering around 1:00,
00:48:55.100 --> 00:49:01.422 so again pretty null findings. Not.
00:49:01.422 --> 00:49:03.960 However, it said the most intriguing part of
00:49:03.960 --> 00:49:08.056 this study was when we took a closer look at.
00:49:08.056 --> 00:49:12.348 the groups of people,
people who are exposed.

During peak production, who were born during peak production, so presumably would have their highest exposure in very early life. They consistently had higher odds of thyroid cancer, including this group of PCB’s that were particularly structurally similar to thyroid hormones, so this was quite intriguing to me, suggesting maybe the timing. Of exposure could be important. So just to summarize,
some of the key takeaways from both. Of these studies. Strengths were that we looked at this larger population and incorporated these different models to account for Co exposure to multiple pollutants. The results were generally null. You know, we did see a few chemicals here and their associated with elevated odds of thyroid cancer. Particularly, this was more consistent when we looked at the group of women who were born during peak production of PCBS. However, this we only have 3 studies now.
For these, each of these groups of chemicals so. There's really insufficient evidence to rule them out, and I think there can be some improvements to the study design to try to look at this more carefully. I think looking at early life would be important, and using a prospective design where we could have samples collected could help you know. Really, try to nail nail down if anything is going on here. And then finally I just want to talk
about how where I’m taking this work.
I have now expanded this work in adults to looking at children.
So with my collaborator Xiaomei MA, also very active in the Cancer Center.
We are looking at environmental exposures and pediatric thyroid cancer,
We are looking at environmental exposures and pediatric thyroid cancer,
so here’s some incidents.
Data on pediatric thyroid cancer.
It has also been increasing over time.
An children are less likely.
To be.
Targeted for increased screening and diagnosis and imaging,
so these trends are are concerning,
so we have some projects underway to try to look at environmental exposures in this more vulnerable population.

And with that I would like to acknowledge all my wonderful collaborators and my funding from American Cancer Society as well as the Yale Cancer Center for getting me started in this line of research. Thank you.

Thank you Doctor Diesel, that was fantastic. A little alarming. I would say when we start to think about how many you know, carcinogens exist in our environment
in the fact that I’m intrigued by the policy statement that we have to show harm before anything can be done and have these substances banned. Do you think there’s any potential to being able to reverse that or change that policy? Or will it take years and more data to do so? Yeah, so a lot of the chemicals were kind of grandfathered in when we established the Environmental Protection Agency in 1970. There is a new act that is supposed to reverse this burden of proof, but I don’t think it’s going to be retroactive, so I am encouraged to with
the current administration that we may start to move towards a different model.

Also, in Europe they have stronger precautionary policies where if there's a safer alternative you have to use it. And you know not to wait until we prove something with certainty to take some sort of action.

And you know not to wait until we prove something with certainty to take some sort of action.

Great, right? So there's a couple of chat questions I'll just quickly read them. Heard a Chow asked about any data on Agent Orange and thyroid cancer. Yeah, so Dioxin's is one of the constituents of Agent Orange. Well, Agent Orange.
So various herbicides?

And then? Dioxin’s

That’s a great question,

’cause they’re also very structurally similar to the other chemicals

I presented, but I’d have to,

and some of the chemicals we looked at.

Some of the groups were dioxin, like.

I’m not, I’m not sure of any specific studies coming to mind,

but it seems likely that it may follow a similar.

Well, they’re structurally similar

to the other other chemicals. OK,

great and then Jeffrey Townsend
00:54:11.100 --> 00:54:14.129 has a question where you do see elevated odds of thyroid cancer?
NOTE Confidence: 0.85703105
00:54:16.230 --> 00:54:18.906 Do you have any evidence discriminating between the two hypotheses of effects that occur due to hormone disruption compared to effects that might be arising due to induction of carcinogenic mutation?
NOTE Confidence: 0.85703105
00:54:29.436 --> 00:54:31.140 Do you see ways to do this? Yeah, that’s a great question.
NOTE Confidence: 0.85703105
00:54:36.870 --> 00:54:38.726 type of mechanistic work.
NOTE Confidence: 0.85703105
00:54:41.890 --> 00:54:43.865 There’s been a lot more
mechanistic work in that area,

but I’d be open to suggestions for how this could hopefully maybe inform some mechanistic studies.

I think it would be, you know, I really think that. The study could inform mechanistic work and vice versa.

Yeah, that’s a great great point. And then Ashida had mentioned in regards to the policy of showing harm that Europe does the reverse of the US. Do they see as a different trend? Actually, thyroid cancer cases
are going up globally and the trends in exposure are consistent. Actually, they were first observed in Sweden where they have breast milk banks and they saw these flame retardants going up in human milk samples which caused a lot of alarm. At that time we didn’t know if they were carcinogenic or not, but given that you know babies were going to be exposed to these chemicals, triggered this whole area of research on these flame retardants and other chemicals.
and then I just have one final question. The email that we all received last week about benzene being in some of the hand sanitizers for our COVID-19 protection? Do you have any thoughts or comments on that? Yeah, I read that. I think benzene is a known human carcinogen. However, it is present in many sources, so I would really want to understand how risky this is. I think we need to know how much. Benzene and how does that compare to putting gasoline in your car?
you know or being walking near the roadway
so I didn’t raise too many alarms yet,
but I would need.
I feel like I need more data to
be able to reach that conclusion.
And I mean, the so yell health,
environmental, safety and health
said like let’s be precautionary.
Let’s just get rid of these sanitizers,
and I think that’s, uh,
you know, very sensible.
Approach OK great.
Well
thank you so much Dan.
00:56:57.410 --> 00:56:59.522 Do you have any other closing comments? I'll just thank both our speakers today. Two terrific talks. I learned a lot. Thank you. Yes thank you. Have a great day. Thanks.