Rounds we have two speakers today from male to wonderful speakers first or Hegel on my own, 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.
00:00:56.720 --> 00:00:59.218 So Jorge, the floor is yours.

00:00:59.220 --> 00:01:00.096 Thanks Dan,

00:01:00.096 --> 00:01:03.162 thank you very much for the introduction.

00:01:05.258 --> 00:01:09.152 Imply microbes and cancer are a lot

00:01:09.152 --> 00:01:13.076 more intertwined that many would think.

00:01:13.080 --> 00:01:18.484 If we start with the obvious that.

00:01:20.900 --> 00:01:22.346 by microbial infections.

00:01:22.350 --> 00:01:25.558 The you know of all these examples of

00:01:25.558 --> 00:01:28.609 gastric cancer and helicobacter anogenital,

00:01:28.610 --> 00:01:30.056 cancer and HPV,

00:01:30.056 --> 00:01:32.948 and so on and so forth.

00:01:32.950 --> 00:01:35.704 So these are the known causes

00:01:35.704 --> 00:01:38.250 of microbial causes of cancer.

00:01:38.250 --> 00:01:40.660 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 course, infectious diseases as an entity
are really a significant challenge in the context of cancer patients.

Many of the drugs that we administer have immunosuppressive power and increases the susceptibility of patients to infectious diseases and imposes it challenge in many.

In many therapeutic set settings.

And of course, the elephant in the room.
The resident microbiome, which in the last you know 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
microbiology piece of the Cancer Center was interrupted.

In fact, when I was invited to give this talk, I was invited as a member of the Cancer Microbiology Group, which now doesn’t exist. And although I completely understand why the leadership of the Cancer Center to please this step, they had to tend to an impending Cancer Center grant.

That obviously didn’t take many of these things, and it is clear that you know cancer, 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 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
I need to send it to NCI, which is much less generous and certainly less friendly to these courses. So I although I totally understand these, I think is is an opportunity loss for leadership, particularly with the really the the history particularly with the really the the history of deal with the tremendous leadership. People like Dundee Moniot or Charles Miller. In the space of Uncle Virus, for example, there is a lot of history here on this space. But life is life and the cancer establishment is the cancer establishment. This is the same establishment that 10 years ago or 20 years ago, worse naughty related to cancer immunology.
It with people like blow it all the late, allowing all that was advocating for it. And he was really honestly looked down. I was a close collaborator, the law and he always complained. Of course he was shielded by the Ludwig Cancer Center. He didn’t have to worry about, but anyway, I think he said more of a loss opportunity. But I totally understand why this decision was made, so enough venting enough Priscilla Teising. 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
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 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

capabilities 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
that we sort of Pioneer in this area

is the fact that certain organisms really produce direct Gina toxins that will drive the oncogenic event.

So I say alluded these last two are the ones more relevant to bacteria, which is the type of microbes which we study in the lab.

So bacterial is in this context bacterial colonization leads to both inflammation and genotoxin production and exposures of tissues to genotoxin and therefore predisposing those tissues to cancel.

What I’m gonna be telling you today
is the paradigm of two organisms that we study in the lab. Both of them. These organisms are salmonella and campylobacter jejuni. Both of them have been very strongly epidemiological. He associated with the development of cancer Campylobacter jejuni associated with an intestinal lymphoma, and while Salmonella Typhi, one of these family that we study in the lab is really a major cause of the lab is actually one of the main cancers that affect those. 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 toxin that we did almost two decades ago.
Actually scary more than two decades ago?

That he said toxin that caught our attention because of what you see here in.

In these images, these are cells that are intoxicated.

You see them very much expanded with a large nuclei in comparison to control cell at the same excuse me Jorge,

your your slide is not. It did not advance.

Papa you mean?

I mean what they have you on the 1st slide?

Oh gosh, that’s that’s not good.

That can you see them this way now?

Yeah, that I can see those OK 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 the.
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 because.
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, those this is a toxin typical toxin of we call AB. Toxins have two types of parts. If you will the be part, which is what targets the payload to a particular cell and the payload part. The nucleus is an endonuclease is actually an unusual in the nucleus in the sense that primary amino acid sequence would not overtly tell you that this is a new case. But when you look at the atomic structure, you can make out the catalytic side. So this is a typical case of genotoxin that is responsible for for
00:11:48.518 --> 00:11:52.268 driving driving the day on today.

00:11:54.500 --> 00:11:57.930 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.

00:12:00.460 --> 00:12:04.243 So the second example is Salmonella Typhi and I need to tell you that someone had typhus and exclusive pathogen of humans. It causes typhoid fever.

00:12:04.243 --> 00:12:07.158 It’s kind of awkward to have to advise it like this, but I will go ahead.

00:12:10.540 --> 00:12:13.308 So the second example is Salmonella Typhi and I need to tell you that someone had typhus and exclusive pathogen of humans. It causes typhoid fever.

00:12:13.308 --> 00:12:16.240 it like this, but I will go ahead.

00:12:16.240 --> 00:12:18.388 So the second example is SalmonellaTyphi and I need to tell you that someone had typhus and exclusive pathogen of humans. It causes typhoid fever.

00:12:18.388 --> 00:12:21.296 Typhi and I need to tell you that someone had typhus and exclusive pathogen of humans. It causes typhoid fever.

00:12:21.296 --> 00:12:23.819 the the basic about something that I think people things in context again.

00:12:23.819 --> 00:12:25.883 think people things in context again.

00:12:25.883 --> 00:12:28.340 and that is that someone had typhus.

00:12:28.340 --> 00:12:30.115 and exclusive pathogen of humans.

00:12:30.120 --> 00:12:31.584 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,
so this lower part of the talks in comes from pertussis toxin, and this upper Paradox income from side a little extended talks, so evolution hook them together to make this head turning toxin that Salmonella typhi encodes, that it is responsible for the genotoxicity of these organisms. And easy sent unusual toxin in many different ways that I don’t have time to go into, but one of the remarkable ways in which this toxin is unique is that it is other patient to the human host.
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 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 is that we humans are actually rather unusual mammals in many ways, and one of the ways in which terribly unusual 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, 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. 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. And in fact, if you just change one oxidant in any of these glycans that Typhoid toxin likes and you already meaning in an array make like an array,
typhoid toxin does not bind. It also has the ability to distinguish. Just one Atom of oxygen. Remarkable piece of evolution that makes it able to target human cells and have that oncogenic effect. But in addition to having a genotoxin somewhere, typhi is actually has the 241. In other words, is also the chronic inflammation part that plays a role in the Uncle Genesis of Salmonella Typhi. And so it’s something that I think causes chronic inflammation of the
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.
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. Uh, like polysaccharide peptidoglycan flagella. You name it, many bacterial products can be detected by this innate immune receptors. Them 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,

not just humans.

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
NOTE Confidence: 0.858762
00:18:53.537 --> 00:18:55.362 completely turn around this paradigm
NOTE Confidence: 0.858762
00:18:55.362 --> 00:18:57.422 and discovered that that’s actually
NOTE Confidence: 0.858762
00:18:57.422 --> 00:18:59.734 incorrect in the case of Salmonella,
NOTE Confidence: 0.858762
00:18:59.734 --> 00:19:01.166 that salmonella really has
NOTE Confidence: 0.858762
00:19:01.166 --> 00:19:02.240 a specific adaptations.
NOTE Confidence: 0.858762
00:19:02.240 --> 00:19:04.736 Evolve by similar to trigger inflammation.
NOTE Confidence: 0.858762
00:19:04.740 --> 00:19:07.659 So this is a pathogen driven process,
NOTE Confidence: 0.858762
00:19:07.660 --> 00:19:09.750 not a host driven process,
NOTE Confidence: 0.858762
00:19:09.750 --> 00:19:12.252 and the reason is very simple
NOTE Confidence: 0.858762
00:19:12.252 --> 00:19:13.920 or not so simple.
NOTE Confidence: 0.858762
00:19:13.920 --> 00:19:16.000 Salmonella, like many other microbes,
NOTE Confidence: 0.858762
00:19:16.000 --> 00:19:18.496 when they encounter a mucosal site,
NOTE Confidence: 0.858762
00:19:18.500 --> 00:19:20.168 being an intestinal being
NOTE Confidence: 0.858762
00:19:20.168 --> 00:19:21.419 the Gallbladder mucosa,
NOTE Confidence: 0.858762
00:19:21.420 --> 00:19:24.048 they need to compete with resident
NOTE Confidence: 0.858762
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 GT Paces by either being exchange factors of
the Pro Family GPs is or forcefully

00:21:44.030 --> 00:21:46.364 In the case of this particular

In the case of this particular effector that wouldn’t activate

and that leads to the activation of CDC.

00:22:02.047 and really looked like

00:22:03.109 in 18 responses.

00:22:00.063 that really are proinflammatory

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
00:22:14.722 --> 00:22:17.013 puzzle and we discovered that the
00:22:17.013 --> 00:22:19.834 activation of CDC 42 by Salmonella leads
00:22:19.910 --> 00:22:22.334 to the formation of a noncanonical
00:22:24.618 --> 00:22:26.622 A target of CDC 42 and
00:22:26.622 --> 00:22:28.210 these other components.
00:22:28.210 --> 00:22:29.226 Trap 6 Tab Tak,
00:22:29.226 --> 00:22:32.097 One Tab 1 Tab 2 that leads to the
00:22:32.097 --> 00:22:34.217 inflammatory response and what is
00:22:34.217 --> 00:22:36.889 what explains the whole thing is
00:22:36.889 --> 00:22:38.641 that these signaling complexes
00:22:38.641 --> 00:22:40.651 identical to the signaling complex
00:22:40.651 --> 00:22:42.913 that is tripped by narimi receptors.
00:22:42.920 --> 00:22:45.286 So what someone in essence is doing
00:22:45.286 --> 00:22:47.365 is going down the signaling pathway
00:22:47.365 --> 00:22:49.662 this is the whole thing.
so that so 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,
but without the need of nuclear dice.

It just simply activates regay by interfacing with dream 56 and trim 65.

Two regulators of this pathway you.

We could make them activates them and trips this signaling pathway without the need of The Agonist of those receptors.

Two regulators of this pathway you.

We could make them activates them and trips this signaling pathway without the need of The Agonist of those receptors.

Two regulators of this pathway you.

We could make them activates them and trips this signaling pathway without the need of The Agonist of those receptors.

We could make them activates them and trips this signaling pathway without the need of The Agonist of those receptors.

We could make them activates them and trips this signaling pathway without the need of The Agonist of those receptors.

So, but since I don’t have time.

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, 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.

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 asking a quick question.

I was very struck by that by what appears to be the convergent evolution of these two nucleases.

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 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. You can’t do that right? 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,
by targeting immune cells.

So, and in the case of Campylobacter, inflammation is central for the bug and and this proinflammatory aspect of DNA damage. Is probably what evolutionary selected for these, you know, toxins and the in the process.

Thank you are there are there other questions for Jorge? Alright, well thank you very much.

I think I think Dan froze. You were frozen Dan. 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 to environmental chemicals in the risk of cancer and other adverse health outcomes, 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. These so-called lifestyle factors. But this also includes infections which we just heard about as well as pollution. While Doll and Peto in their landmark
A 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 underestimated. 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. And 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.
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 malignancies. It has nearly tripled over the past few decades. 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 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 an 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,
00:34:56.470 --> 00:35:00.382 did not stay bound in the matrices as
NOTE Confidence: 0.8233529
00:35:00.382 --> 00:35:03.368 indicated by their manufacturers and
NOTE Confidence: 0.8233529
00:35:03.368 --> 00:35:07.820 instead have migrated out into our homes.
NOTE Confidence: 0.8233529
00:35:07.820 --> 00:35:09.748 At home environments, cars,
NOTE Confidence: 0.8233529
00:35:09.748 --> 00:35:10.613 workplaces, etc.
NOTE Confidence: 0.8233529
00:35:10.613 --> 00:35:12.911 So due to this widespread use
NOTE Confidence: 0.8233529
00:35:12.911 --> 00:35:15.981 as well as disposal and improper
NOTE Confidence: 0.8233529
00:35:15.981 --> 00:35:18.417 disposal of these chemicals,
NOTE Confidence: 0.8233529
00:35:18.420 --> 00:35:21.312 they aren’t ubiquitous and more than
NOTE Confidence: 0.8233529
00:35:21.312 --> 00:35:26.136 90% of the population here in the US and
NOTE Confidence: 0.8233529
00:35:26.136 --> 00:35:30.320 globally are exposed to these chemicals.
NOTE Confidence: 0.8233529
00:35:30.320 --> 00:35:34.324 And this also they are extremely persistent
NOTE Confidence: 0.8233529
00:35:34.324 --> 00:35:39.260 once they get into their homes or our bodies,
NOTE Confidence: 0.8233529
00:35:39.260 --> 00:35:42.620 they do not degrade very easily,
NOTE Confidence: 0.8233529
00:35:42.620 --> 00:35:47.084 so they stick around for years and decades.
NOTE Confidence: 0.8233529
00:35:47.090 --> 00:35:50.444 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 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 is 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 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.

So these are measurements taken from blood samples from a blood bank. In the US.

You can see about a doubling every five years of these particular chemicals.

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 and 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 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 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 hypothesized mechanisms, such as chemicals have some additional hypothesized mechanisms, such as.
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.

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, who was 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 pollutants, 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 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.
A 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. So the medium and high groups are not at an elevated odds of thyroid cancer except for this one chemical, this PB 153. When we move to our multi pollutant models, the results are also somewhat null. We have two multi pollutant models.
here using Bayesian modeling, which I won’t get into here. But here you can see that it’s the picture is still pretty null except for. In this case we have this other, a different chemical PDE 100. Was associated with elevated odds of thyroid cancer using both those models. And then finally we did this one more mixture type approach of principle, components analysis and in this work we found that people who had had this combination of exposures which was higher. Combination of exposures which was higher. PBDE 153. An lower PDE 209 had an elevated odds of thyroid cancer. 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, we had 32 different chemicals.

00:48:33.140 --> 00:48:35.040 I'm just going to present some some groups of structurally similar PCB's, which was another approach we used to look at groups of chemicals.

00:48:37.574 --> 00:48:39.599 So in this model this kind of approach, we're just looking at one group at a time. Odds ratios are hovering around 1:00, so again pretty null findings. Not seeing a link between exposure and thyroid cancer.

00:48:41.754 --> 00:48:44.160 The most intriguing part of this study was when we took a closer look at the groups of people, however, it said the most intriguing part of this study was when we took a closer look at. The the groups of people,
people who are exposed. During who were younger during peak production, who were born during peak production of PCB’s. 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. OK. So just to summarize,
00:49:57.994 --> 00:50:00.400 some of the key takeaways from both.

00:50:00.400 --> 00:50:03.430 Of these studies.

00:50:03.430 --> 00:50:05.929 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. 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 pre diagnosis 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 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.
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
NOTE Confidence: 0.86721903

start to move towards a different model.
NOTE Confidence: 0.86721903

Also, in Europe they have stronger
NOTE Confidence: 0.86721903

precautionary policies where if there's
NOTE Confidence: 0.86721903

a safer alternative you have to use it.
NOTE Confidence: 0.86721903

And you know not to wait until we
NOTE Confidence: 0.86721903

prove something with certainty to
NOTE Confidence: 0.86721903

take some sort of action.
NOTE Confidence: 0.7947095

Great, right? So there's a couple of chat
NOTE Confidence: 0.7947095

questions I'll just quickly read them.
NOTE Confidence: 0.7947095

Heard a Chow asked about any data on
NOTE Confidence: 0.7947095

Agent Orange and thyroid cancer.
NOTE Confidence: 0.7947095

Yeah, so Dioxin’s is one of the
NOTE Confidence: 0.7947095

constituents of Agent Orange.
NOTE Confidence: 0.7947095

Well, Agent Orange.
NOTE Confidence: 0.7947095

Had you know these defoliant chemicals?
NOTE Confidence: 0.7947095
00:53:36.540 --> 00:53:37.902 So various herbicides?
NOTE Confidence: 0.7947095
00:53:37.902 --> 00:53:39.900 And then? Dioxin’s
NOTE Confidence: 0.81728315
00:53:42.160 --> 00:53:43.660 that’s a great question,
NOTE Confidence: 0.81728315
00:53:43.660 --> 00:53:45.535 ’cause they’re also very structurally
NOTE Confidence: 0.81728315
00:53:45.535 --> 00:53:47.213 similar to the other chemicals
NOTE Confidence: 0.81728315
00:53:47.213 --> 00:53:49.208 I presented, but I’d have to,
NOTE Confidence: 0.81728315
00:53:49.208 --> 00:53:52.099 and some of the chemicals we looked at.
NOTE Confidence: 0.81728315
00:53:52.100 --> 00:53:56.160 Some of the groups were dioxin, like.
NOTE Confidence: 0.81728315
00:53:56.160 --> 00:53:58.687 I’m not, I’m not sure of any
NOTE Confidence: 0.81728315
00:53:58.687 --> 00:54:00.400 specific studies coming to mind,
NOTE Confidence: 0.81728315
00:54:00.400 --> 00:54:02.320 but it it seems likely that
NOTE Confidence: 0.81728315
00:54:02.320 --> 00:54:04.280 it may follow a similar.
NOTE Confidence: 0.81728315
00:54:04.280 --> 00:54:06.180 Well, they’re structurally similar
NOTE Confidence: 0.81728315
00:54:06.180 --> 00:54:08.990 to the other other chemicals. OK,
NOTE Confidence: 0.85703105
00:54:08.990 --> 00:54:11.100 great and then Jeffrey Townsend
NOTE Confidence: 0.85703105
has a question where you do see elevated odds of thyroid cancer? 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? Do you see ways to do this? Yeah, that’s a great question. I don’t really do this type of mechanistic work. I know the thyroid hormone disruption hypothesis. 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
00:55:19.044 --> 00:55:21.270 are going up globally and the
NOTE Confidence: 0.8658378
NOTE Confidence: 0.8658378
00:55:23.440 --> 00:55:25.565 Actually, they were first observed
NOTE Confidence: 0.8658378
00:55:25.565 --> 00:55:28.171 in Sweden where they have breast
NOTE Confidence: 0.8658378
00:55:28.171 --> 00:55:31.041 milk banks an they saw these flame
NOTE Confidence: 0.8658378
00:55:31.041 --> 00:55:33.241 retardants going up in human milk
NOTE Confidence: 0.8658378
00:55:33.241 --> 00:55:35.552 samples which caused a lot of alarm.
NOTE Confidence: 0.8658378
00:55:35.552 --> 00:55:38.016 At that time we didn’t know if
NOTE Confidence: 0.8658378
00:55:38.016 --> 00:55:40.300 they were carcinogenic or not,
NOTE Confidence: 0.8658378
00:55:40.300 --> 00:55:42.701 but given that you know babies were
NOTE Confidence: 0.8658378
00:55:42.701 --> 00:55:45.779 going to be exposed to these chemicals,
NOTE Confidence: 0.8658378
00:55:45.780 --> 00:55:46.890 that sort of.
NOTE Confidence: 0.8658378
00:55:46.890 --> 00:55:48.740 Triggered this whole area of
NOTE Confidence: 0.8658378
00:55:48.740 --> 00:55:51.024 research on these flame retardants
NOTE Confidence: 0.8658378
00:55:51.024 --> 00:55:52.497 and other chemicals.
NOTE Confidence: 0.8658378
00:55:52.500 --> 00:55:52.860 Great
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 COVID-19 protection? Do you have any thoughts or comments on that? Yeah, I read that I read some of the materials. I think benzene you know 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? Like putting gasoline in your car,
you know or being walking near the roadway
NOTE Confidence: 0.8349844

so I didn’t raise too many alarms yet,
NOTE Confidence: 0.8349844

but I would need.
NOTE Confidence: 0.8349844

I feel like I need more data to
NOTE Confidence: 0.8349844

be able to reach that conclusion.
NOTE Confidence: 0.8349844

And I mean, the so yell health,
NOTE Confidence: 0.8349844

environmental, safety and health
NOTE Confidence: 0.8349844

said like let’s be precautionary.
NOTE Confidence: 0.8349844

Let’s just get rid of these sanitizers,
NOTE Confidence: 0.8349844

you know, let’s take an action
NOTE Confidence: 0.8349844

before we have all the answers,
NOTE Confidence: 0.8349844

so I think that’s, uh,
NOTE Confidence: 0.8349844

you know, very sensible.
NOTE Confidence: 0.8349844

Approach OK great.
NOTE Confidence: 0.8349844

Well
NOTE Confidence: 0.803357

thank you so much Dan.
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.