This Week in Virology

*with **Vincent** Racaniello, Ph.D.*

Episode 131: A REOstat for cancer

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Vincent:
Hey everybody, I am Vincent Racaniello, and it's time to talk about viruses. Joining me today, right here at the TWiV studio is Dickson Despommier. [Small talk omitted.] Also joining us today from western Massachusetts is Alan Dove. [Small talk omitted.] Rich Conduit isn't with us today, he is at the pox virus invitational golf tournament, which is in Gainsville. This time of year all the pox virologists gather to play golf. [jokes omitted[1]]

But we have a special guest today, we're really happy to have Dr. Brad Thompson, the chief executive officer of Oncolytics Biotech. Welcome to TWiV, Brad.

Brad:
Oh thanks very much.

Vincent:
You're here because one of our listeners, Bill, is an aficionado of using viruses to treat cancers. And he's been asking us, I think almost two years now, and so finally we've come around to have you on. And we're going to talk about your company and how it uses reoviruses to treat tumors. But before we do that I'd like to find out a little bit about you. You have a Ph. D. Tell us just briefly your background, how you came to be at Oncolytics Biotech.

Brad:
Well my undergraduate and Ph. D are in microbiology, so classical microbiology which I still have a great fondness for. And then I came back to Alberta, and like many good Albertan kids worked in the oil industry for a while. Unless you do that you aren't really socially acceptable here [laughs in background], but honestly after a couple of years of that I was just like "I have to get back to something interesting". And I apologize to any rock geologists out there that I just offended but the oil industry is very different than what I'm used to, which is more discovery-based fun stuff. From there I went and did a lot of fermentation research and then manufacturing and scale-up work in biologics and then founded a gastroenterology company, which was spot-on with my expertise. We were doing a number of different infectious diseases-- hospital-acquired infectious diseases that

1 Especially Alan's puns

are GI related, and then I had this nice opportunity to come along to work in this particular company. I was literally sitting in my office one day and then a college in the government phoned me up and said there is this very interesting research group at the University of Calgary, you're a microbiologist you'll understand half of what they're about to say to you. And they're looking at developing an interesting new viral vector for treating cancer. And normally I would have probably tried to find an excuse to not talk to another university group about something I didn't know about, but I just had melanoma myself and my mom had just died of adenocarcinoma of the lung and my favorite uncle had just died of head-and-neck cancer. All in about a six week period. So they caught me at a moment where my awareness of oncology was a little higher than it had been. And I do know microbiology, so that's a good thing. And so they came over and gave me a visit and we talked for probably six or seven hours on that first visit. And they showed me just animal model after animal model that they had done. And they were all good, solid-- not jury-rigged animal models-- they were all good, solid relevant animal models, which quite surprised me and I was intrigued that you could actually do something in this particular area for something that meant something to me personal at that point. It kind of caught my attention! So I went home to my wife-- we were running two phase 3 studies in my previous company-- and I say "hey, I'm gonna quit this and go do a preclinical thing again and I'll be paying myself a dollar a month to start because we don't have any money." And she just shrugged and and looked at me and went "hey, great, good for you". And, fortunately she has been the traditionally breadwinner in our family, so I [interrupted]

Dickson (5:58)
--She's still in the oil industry, I take it.--

Brad: (6:01)
She's an investor, so she does a lot of energy investing. And so I had a bit of latitude there from a personal side to do those kind of things. But the whole area just really grabbed my attention. And then I started digging into it, and all of the sudden I find out that there's all these people that I had known when I was in school and whatever who had all hopped over to the "dark side", as people would think of it, and were looking at these different viral vectors early on. I mean Grant McFadden, who's been on this show, was a postdoc down the hallway from me when I was doing my PhD. And and and and and. I mean it's really a tight-knit community, honestly, and it was kinda interesting. And when we started looking into it in more detail there was absolutely no regulatory pathway, nobody knew what the real technical questions were, nobody knew where we were going to trip up, which is exciting-- That's the fun part of doing anything is being first or among a group of people being first. And, here we fast-forward eleven years later, or twelve years later now almost, we're in a phase III that's going to be in eleven or twelve countries in a couple of months. Uh, I've got a couple of other randomized studies running at phase II. I'll have another two running by the fall, so by this fall we'll have five coincident randomized studies in different indications running. You know you think of that whole path from day zero to here-- it's been exciting, it's been fun, it's been challenging. And it's just something that I'm honestly seriously glad that I did.

Vincent: (7:48)
So when we told Rich you were gonna be on he mentioned it to Grant. Then I guess you and Grant knew each other at some point in the past, right?

Brad: (7:58)

Yeah. He was a pure virologist working down the hallway with our favorite pox virus, vaccinia, as a postdoc. He was just finishing off his postdoc when I was finishing off my PhD. My PhD is more bacterial orientated. I was on the other opposing camp down the hallway. He was on the virus end, I was on the [inaudible because of **Dickson** laughing] end.

Vincent: (7:57)

Now you're in the viral end, now.

Brad: (8:02)
Yeah, well I'm quite happily in the viral end. And I've actually done a lot more viral work than I have bacterial. And this area is just a good example of the elements of virology that you can use. I mean you have all these different viruses and-- and everyone always says that since it's a virus it must be the same, which couldn't be further from the truth, which we all know on this line. But you know they're different sizes, they're different immune presentations, they have different mechanisms of action, different replication cycles, et cetera et cetera. Different tropisms for tissue, you have all these different things. And I think that is really a unique element of this particular area. You know we're going to come up with a suite of therapeutics that includes different viral vectors, different engineering tricks that people have done with them. And, in the end I think we'll come up with a suite of products that address a lot of different cancers. No one of these products is going to address everything. And I think you just exploit the things that we have learned along the way as a group and apply that. We'll almost be able to tailor what we're looking at in a few years. I mean who would have though size would have mattered so much when you're talking ranges of 20 to 200 nanometers? Well it does. And who would have thought that immune response could completely block one virus be completely invisible to another virus getting into a tumor. Not just to the tumor, but *into* the tumor. I mean all these things we didn't know. And, uh, we've all kind-of learned from each other. Em, in the early days we had Onyx with O-15, which was kind of trail breaking a lot.

Vincent: (10:15)
That was an adenovirus, right?

Brad: (9:49)
It was adenovirus construct, and they just had a *horrible* time making it. I mean who thinks about manufacturing issues in these things? *Terrible* time making it. But you take a look at the thing, they'd made three genetic changes. So you loose about 90% of productivity with every genetic change, as it turns out, and three leads you to something that's not very good. You know, one thousandth isn't very good. And very early on Onyx was flagging to the rest of us, who were way behind them at that time, "pay attention, pay attention to manufacturing." Some of us have-- There have been a few of the companies that have really paid attention to it, and it has payed off hugely. I mean you have processes that when you're running into late stage are rationalized, they're cost-effective, they're consistent, they're everything that you need for a biologic. But it was again learning from our colleagues. I think probably when people look back in ten years from now they'll see that our contribution to that path was that we were to a greater extent than I think anybody else really looking at combination therapies and their effect on tumor permeability to the virus. Who'd have thought that would have been an issue? If you infect the surface of a

tumor it should be no problem-- well, it IS a problem. And we've found that certain agents really increase tumor permeability to viruses. And, you know, taxanes-- it's a universal fail-safe for us. Radiation-- almost universal for us. And, not in humans, but in animals, the whole VEGF family. You know VEGF itself, Avastin, Sutent, that whole family does that quite nicely. And other people are emulating that now-- You're starting to see that showing up in their programs. So everybody is being contributing little bits and pieces along the way. And all of the sudden you have this field and our colleagues at Biovex (who are now part of Amgen) have two phase IIIs in SPAs[2], which are fairly late-on. We've got a phase III in different indication under a SPA and a bunch of phase two's in behind that. You know there is Pox virus in phase 2's, measles virus in phase 2's, and we've got a whole group of people working on different elements that have learned from each other. And I think that's the key thing. Now this collegiality will completely disappear as soon as we start getting competitive. Like, "poof", you know.

Alan (12:26)
Sure

Brad: (12:27)
But for now, every two years we have this virus meeting-- we just had it a couple of months ago in Vegas. And, it's virus oncology and you have like three or four hundred people and this is all we do. And it's collegial. And it's been remarkable-- if you go back four meetings ago, so back 8 years, everybody was doing early-stage phase 1's and re-tinkering and playing this and playing that. And now, you know, you have a panel this time with three or four companies who are finally going to be filing for product approval within two years. That's just an amazing change for a whole sector. But--

Alan (13:03)
That's actually fairly typical for biotech fields. If you look at any of the major therapies that have come out of biotechnology, any of the biologics-- I've been following this for a decade and a half now-- and you always see this initial group of companies, a lot of small start-ups, and a very collegial atmosphere, and everybody figuring out what mistakes to make so that they can learn from them. And then eventually, as you have already predicted, there will be a change in tone but that will come later as the approvals roll in.

Brad (13:31)
Oh, absolutely, and I think that a bit of the first change in tone is really Amgen buying Biovex. Uh, all of the sudden it's not a number of our small players all hanging out with each other. All of the sudden we have a very large player who is now integrating, phagocytosing Biovex.

Alan: (13:33)
Exactly.

Dickson (13:34)
"Engulf and devourer", I think as they put it.

Brad (13:35)
I think so, and I think the Biovex guys also view it that way, too.

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2 The FDA acronym "SPA" is short for "Special Protocol Assessment".

Dickson (13:40)
Right

Brad (13:41)
I mean Amgen is a great company---[interrupted]

Dickson (13:43)
So are we talking about *curing* or just *holding at bay* these tumors that you're going to be talking about?

Brad (13:48)
I think it's going to be a mix. And of course the we get into the argument about when you get rid of a tumor and it recurs whether it is the same tumor or whether it is just reseeding from somewhere else. But I think there are certain tumor types-- certainly that we've seen-- that we've seen complete responses and that are durable for the period of time that you've seen. And certainly more so in metastatic lesions for us. In particular, Reo requires an activated RAS pathway, which has a much higher incidence rate in metastatic disease. And of course mets are likely to be clonal expansions of of a single or a couple of cells stuck together. So they are much more consistent genetically. And so if you get Reo into a metastatic lesion that has a RAS pathway, it will completely clean it out. And it doesn't recur. Where you get into I think more issues about control or getting into partial responses that last while you're treating and then kinda spring back after you quit treating, the primaries seem to be more in that category. Occasionally you get CRs [complete responses] in primaries, but more often you're getting nice aggressive PRs [partial responses], but still PRs. And, uh, you're going to buy people lifespan with that, and you're gonna do some good things for them. But the tumor architecture is I think critical in primaries. You get all these kinda [inaudible] barriers and mixed strata, you know healthy and non-healthy neoplastic tissue. And so I think it depends on what you're looking at.

Dickson (15:30)

The original work of Judah Folkman's group up at Harvard always said that you could cause a tumor to regress right back to the original cell that caused it, but the original cell took advantage of existing circulation. So the approach to limiting the tumor by inhibiting the growth of capillaries only worked for *new* capillaries and not for the old one that was already there. So it would just grow right back again. And I don't know how far that's advanced since he's passed away, unfortunately. But that was the complaint that these were great therapies while you're using them and the moment you stop everything starts to go back to the way it was.

Alan (16:04)
Well I think one of the mistakes that people make in oncology frequently when they're evaluating it is they'll say "well this therapy didn't cure the cancer therefore it's no good." But if you look at the reality of the way tumors are treated in the clinic, em, it's seldom just one approach that's being applied.

Dickson (16:20)
Right

Brad (16:24)
Yeah. It's a sequence of actions that does some times lead to quote "a cure", right? And we see that, like head & neck cancer is a really good example of that. I mean the first time you get head and neck cancer if they can just do surgery they will. Or they'll combine it with radiation and half the time you're cured. You're fine. You know, it works great. The other half the time life isn't so good. And it's usually when it metastasizes And, the expression "cure for cancer" has not done our research and industry a service.

Vincent (17:02)
Let's talk a little bit about reovirus-- That's one of your main oncolytic agents I presume. Our listeners are pretty broad audience, so tell us what it is and why you are using reovirus in a lot of your studies.

Brad (17:20)
Well reo was discovered clinically in 1958 or 1959 in the feces of a small child. And as was typical in that era-- the golden era of microbiology-- people would then go and try to figure out what it did. And you didn't have to wait for 5 years for a permit to grow it up in the lab. I mean they went straight down the [laughing in the background] hallway, threw it on some cells, and grew up some and then started doing things with it. And after four or five years of failing to find out what reo did they ordered up a batch of prisoners in the South-- like they used to-- and treated 27 quote "volunteers" with pretty high dosages inter-nasally of reo and no statistical correlation with anything.

Dickson (18:03)
Tell us what kind of virus it is.

Brad (18:05)
It's a double-stranded RNA virus. It's a relative of rotavirus, which is why it was interesting early. As a non-pathogenic relative or rotavirus is the way I think of it. And so people just lost interest in it. So the started doing research on it because it was a relative of rota but wasn't pathogenic. So the joke that you found a grad student mouth-pipetting it, you know you didn't have to throw him in the containment suit and that kind of stuff [laughing in the background]. And so that went on for 20 or 25 years and people learned a lot about this interesting durable little double-stranded RNA virus. It was easy to grow, which was good for labs, it was very durable, so you could make up a batch and six months later people could still be pipetting out of the common batch in the lab. People like that in labs-- who wants to be spending time making something when you're investigating it? You want to research it. You know those practical things-- it's a good research tool.

Dickson (18:59)
Why is it called "reo", by the way?

Brad (19:02)
"Respiratory enteric orphan virus."

Dickson (19:04)
Ah-ha. It wasn't found in Rio, south America?

Alan (19:09)
No, it's REO.

Dickson
That's just a play on words.

Vincent
I think that was coined by Albert Sabin, too, right?

Brad (19:18)
I believe it was, actually. It's natural habitat is the lining of the lung and the bowels. But it doesn't cause a pathology. Or course I asked the question "why" pretty early.

Dickson
--Sure--

Brad
I haven't found a lot of things in my experience that infect the lining of the lung and bowel that don't cause something. You know a cough, diarrhea, bloody-diarrhea. I mean my previous history-- I mean anything to do with the GI tract I would always go right straight to the bloody diarrhea thing.

Dickson
You bet.

Alan (19:51)
I mean that's partly because we've noticed the things that cause disease.

Brad (19:53)
That's right. And we ignore everything else. But when you actually sit down and look at where reovirus localizes-- the bowel is the primary natural habitat-- and it's a pan-mammalian virus, so which helps. It's a fecal-oral transmission, so fecally contaminated water or food, which is unfortunately all food and water almost. Uh, you get a low-level infection of the crip cells in the bowel. Well why the crip cells? And then you look at it and those cells are bathed in EGF [Epidermal Growth Factor]. And you say "well what does EGF do to a cell that makes reo infect it at a low level?". And of course EGF, we know now, drives the RAS pathway. So if you take any cell, basically, and stick it in a bath of EGF you will drive it into a low level of RAS activation, which is what reovirus needs to give a productive infection. And so you have this one cell class-- it's the same in the lungs-- that the virus will grow in at very low levels. Fecal-oral, into the bowel, replicates, passed out in the feces, reinfection-- that's the cycle. The reason you don't have a pathology is that it takes reo about three days to kill a cell, and those cells are actually forced into an apoptotic death, and not coincidentally-- because I don't believe in coincidences in nature-- in about three days. So they kill the cells at the same time they're dying anyway. So there's no pathology.

Alan (21:15)
So is that why people don't raise neutralizing antibodies against it, or do they?

Brad (21:19)
Uh, very very low mucosal immunity-- the virus doesn't actually cross the gut barrier or the lung barrier. And so you get a very very low level, very transient-- as they always are--

mucosal immunity. And so when you look at humans if you're looking at the [inaudible doubling??] scale, which unfortunately when you date my lab history back-- we did antibody tiders, that's how we did them-- you're looking at tiders of two, four, eight, sixteen, normally and up normally in a patient population. But it's almost 100% of them-- like virtually everybody has a very very low level. Now when we treat people systemically with reo for five days in a row, you can drive those antibody levels up to 20,000.

Dickson (21:59)
So this is good because you're using it as a therapy so that it doesn't cause pathology. So you can actually say that you're not going to do harm, at least. You might not do good, but you won't do any harm by giving this virus along with what you're trying to -- [interrupted]

Brad (22:12)
Yeah, we're just under 500 patients-- when you count our patient population of about 400 and those the NCI has tacked on. And reovirus as a monotherapy on a five-day cycle will give you-- in patients were are likely to have a tumor response, and that's key-- a low-grade degree to a degree-and-a-half fever, low-grade muscle and joint pain, low-grade fatigue, and low-grade nuetropenia and lithopenia, which you'd expect, on day 2 of a 5-day cycle. Or day 3. And it goes away the same day.

Dickson (22:47)
Interesting

Brad (22:48)
And we can mask all those symptoms with Tylenol, Paracetamol in Europe, and Advil.

Dickson (22:53)
So in tumors that are having low expression of RAS is there a way to ramp that up to make it even more susceptible?

Brad (23:00)
Uh, reovirus actually does that. That's actually published later this year. Reovirus actually drives the expression of EGFR

Dickson (23:12)
--I'll be darned.--

Brad (23:13)
so it's a tricksy little fellow.

Vincent (23:15)
So EGF-- epidermal growth factor-- binds its receptor EGFR, and this drive cells to undergo mitosis, right?

Brad (23:24)
Yeah.

Vincent (23:25)
And the RAS pathway is the signaling pathway that's signaling from the receptor binding all the way into the nucleus, making genes that are needed to get the cells to divide So

what you're saying is that reovirus prefers cells in which that pathway is activated, in which to replicate?

Brad (23:42)
Yes.

Alan (23:44)
An conveniently, a lot of tumors have activate the RAS pathway.

Brad (23:47)
Absolutely--

Dickson (23:48)
Right--

Brad (23:49)
I mean cells have that lovely innate double-stranded RNA defense mechanism (it's not immune) that's mediated by PKR. And PKR binds to unique viral sequences on double-stranded RNA and just shuts down-- you don't get protein translation-- and so the virus can't replicate. But when the RAS pathway is constitutively activated it actually deactivates PKR. So basically you just have a permissive cell environment. So

Dickson (24:15)
--For non-viral speakers, PKR stands for

Brad (24:18)
--"Protein kinase R"

Vincent (24:23)
And it's activated by double-stranded RNA when viruses infect cells as part of the innate defense system.

Dickson (24:28)
Got it. So I think we should pause just one moment here and reemphasize the fact that if you're gonna be a virologist you had better know your cell biology.

Brad (24:37)
Yeah, and unfortunately when we are talking with a group of people who-- we have all kind-of done this before-- we all retreat into a foreign language.

Dickson (24:46)
[laughing] Exactly. Every group does it. It's all jargonized. But uh--

Alan (24:51)
Yeah, we actually have a little reminder at the top of the show notes about that, that we're talking to everybody.

Brad (24:55)
Talk plain-speak, and I agree. So-- to strip the science away-- basically all you're doing is taking a cell that normally has a defense mechanism against this type of virus and and

deactivating it, so the virus can replicate and kill it in a few days. So this is a fully-replicative virus. You get about 40,000 progeny virus per cell infected. And so you just need to infect part of the tumor and then the virus will replicate and spread through the rest of the tumor. Of course that would just be some kind of curiosity if it weren't associated with some kind of disease, right? And we could have found all that biology out just by looking at the lung and the bowel and everyone would have went "well, that's neat, that's very interesting". And that would have been the end of it again. But oncology is certainly the area in which you have the most RAS-pathway activity. I mean you're looking at about probably two-thirds to 75%. Any primary carcinoma has a RAS pathway involvement, a lot of lymphomas do, and most metastatic disease. So basically you have a genetic predisposition from a family of things--cause it's not just EGFR it's anything on the RAS pathway will do the same thing. Uh, RAS protein itself, RAF-kinase, everything on that path.

Dickson (26:12)
So why is there colon cancer then?

Brad (26:15)
Well, we've actually treated polyps with Reo. If you give animals-- you know push them into polyps-- and give it to them orally you can clean up polyps quite nicely with reo. It's dosage and frequency of exposure. And of course, there are a lot of colon cancers that are probably not polyp-related. But I would expect that we might have a lot more colon cancer than we do now if-- [interrupted]

Dickson (26:44)
It doesn't breach the epithelial lining, so you wouldn't get it to the primary tumor then.

Brad (26:45)
That's right. If it penetrates the wall it's too late. So in the coincidental infection with reo-- it's very transient-- a couple of weeks after you've been infected in the wild with reo it's completely gone. It's completely cleaned-out.

Dickson (27:01)
I was looking for a positive role for this in cancer monitoring. It would be great if you could prevent bowel cancers like that, but I guess too good to be true.

Brad (27:08)
I mean I would drink this stuff regularly if I had bowel cancer, but I think the *H. pylori* story comes to mind when you're thinking of doing stuff like that.

Dickson (27:20)
That's right.

Alan (27:22)
Great, now a whole industry of alternative health [background laughing from **Dickson**] is going to spring up selling canned reovirus.

Dickson (27:27)
[laughing] That's right. We had that run on tape-worm segments for a while back in the 1920s, but that didn't work either.

Brad (27:35)
Well, the tape-worm is making a comeback. [laughing in the background]

Dickson (27:39)
Well, actually the round-worms, not the tape-worms, the round worms.[laughing]

Brad [27:40]
Oh, yeah, round-worms are [inaudible with all the laughing in the background].

Dickson (27:42)
That's right, we can cure Crohn's disease now.

Vincent (27:46)
Starting with the observation that this virus likes cells in which RAS is activated, and then knowing that a lot of tumors have this activation, what did you have to do to reach the next step-- to say that this might be feasible for using in people?

Alan (27:58)
Well you just went down the hall and found a few prisoners, right? [laughing]

Brad (28:03)
No, that was Dr. Sabin in 1963.

Dickson (28:06)
A few former hockey players would have done just as well.

Brad (28:08)
Yeah-- things that people wouldn't have missed-- absolutely. Or grad students or med students or law students-- the typical profile for clinical trials. It was a pretty serious issue to say that it is safe in the natural infection cycle-- where you're taking maybe 100 viral particles and swallowing it in your food by accident, and being infected somewhere that it doesn't transfer in your body anywhere-- to leaping into injecting now 3 times ten to the tenth active particles a day intravenously for a week on end every month. That's a big jump. And so you had to get through all the manufacturing stuff. I mean people used to grow them on animal cells like horses-- So we had to get them on human cells, cause nobody was going to let us treat people with animal-cell derived product, even back when we started doing this. So you had to go through that whole process. Um, tons of toxicology-- we just did a MASSIVE number of animal toxicology studies with a lot of primates. I think we ended up doing 15 [inaudible]-animal toxicology studies, and looked at cardiac function in primates, and and and and and. I mean just really extensive-- [interrupted]

Dickson (29:20)
What was your big animal model tumor that you used as the proof-of-concept?

Brad (29:25)
Most of the animal model work were for what I think of as unnatural animal models was all rodent-- and so you're looking at [inaudible] the melanoma models. We did do some naturally occurring tumors in canines early on, too. Mostly sarcoma-based, which is the

most common type of tumor that you see in canines. And, uh, everything was fine. Everything was safe. We discovered if you don't have tumors you don't get side effects with Reo. And that kinda makes sense in hindsight-- if you give somebody a big huge does of this and they don't have a tumor for the virus to grow in, and look for the virus then it's gone in half an hour. It's completely cleared. So it's not such a big deal. One the virus inhabits a tumor then you get active viremias, which is virus in the bloodstream. And those viremias can go on for several weeks. And the start of the viremia is when you get that minor side effect profile that we saw. But of course we didn't know that when we started. So we started out like everybody else, because the agencies just [inaudible] by just doing intratumoral. Now nobody knew in those days that the tumors shed virus. We thought they did-- certainly in the animals they did. But the agencies thought that was safer, so our first three studies were intratumoral. And we did an all-comers study-- [interrupted]

Vincent (30:42)
These are in mice, you mean, right?

Brad (33:44)
No, in people.

Vincent (30:45)
This is in people. So we're past the animals, already?

Brad (30:48)
Yeah. Our first clinical study was an all comers in people. We did a dose escalation in tumors. Then we did a small P2 prostate study. So prostate cancer that hasn't metastasized by either the lobe or the prostate gland. And then finally the penultimate from a safety study, which was a glio [glioblastoma] study-- brain cancer. Cause if you're gonna see symptoms of inflammation swelling, the brain is the best place to do it. I mean it's exquisitely sensitive from a clinical prospective at showing off side effects you're not interested in. You can suffer a lot of things in normal tissue that your brain won't put up with. So that was kinda the acid test toxicology study from my perspective. So we got through that and we kinda went "OK, that's great in those intratumoral things. We have to make the leap to systemic". That's when we ended up having to do all that primate work. I mean we hadn't done the primate work until then and so the agency said go back in and do massive long-term exposure in primates. Daily infusions for six months with monkeys. Monitor cardiac function. Monitor this-- [interrupted]

Dickson (31:54)
--Good heavens.--

Brad (31:55)
And each one of those monkeys costs about the same price as about four clinical patients in a clinical study. I mean its a very expensive program--and we knew unnecessary-- but we do it anyway. And so we've got through all that, that was all fine. And the agency then smiled at us and went "You do realize you won't see any side effects unless you put tumors in all those animals." [Laughing in the background] Thanks guys. So we did a tumor-bearing animals toxicology. And that's when you see the low-grade tumors [Transcriber note: I think he meant so say "side effects" rather than "tumors"]. We did it in rat's actually. You just put the sensor chip in the rat. And you put it over a scanner to take its body heat every day. And things like that. And then we did IV [intravenous]. We did an

IV monotherapy study in the UK, and one in the US just to make sure we weren't getting jurisdictional bias. And then that just opened the door. Once we got the monotherapy systemic behind us that just opened the door. We started doing all the co-therapy work and started exploring it. That's when our enrollment exploded. But we're still obsessive about following safety. What I find interesting in this whole field-- if you want I'll put on my "whole field" hat for a second here-- If you take all the gene therapy studies, it doesn't matter whether it is oncology or not, anything that has used a virus vector and all the oncology stuff you're probably having about ten to fifteen thousand patients now worldwide. And we've had probably less than ten deaths that you could associate directly with whatever virus. It's got the lowest side effect profile of a therapeutic area ever reported. And that doesn't matter what the virus is-- the only virus that there seems to be a little question mark beside is adenovirus in certain cases. But it's got a liver tropism, and honestly most of the events are due to a liver tropism. We were very cautious as a whole field, all of us. When you look at the pox virus work, the measles virus work, you look at adenovirus, reo, herpes, we've all been very cautious safety-wise. And what we've come up with is an area safety package-- if you want to think of it that way-- that is probably the best of any therapeutic area I've ever seen. It makes antibodies look horrid. Of course it makes all old-line chemo awful. It's really-- with some very minor exceptions that you just have to watch out for-- really safe.

Dickson (34:21)
Of the 15000 people that have received this kind of therapy how many gone home and never had to go back to the hospital?

Brad (34:31)
In every one of our studies we always have stand-out patients who were supposed to be dead, that were dying when they came into the study, that would be tumor-free and go home. Our very first clinical study, which was [inaudible] 1999 early 2000, I have an [inaudible] patient, last legs, probably six weeks left alive, who comes in every six or eight months and strips down to his underwear in my office and I take pictures of him. But our first glioblastoma study, we had a long-term survivor off of that. Always. But when you take people that are literally the nine toes in the grave and turn them around and their fine it's very encouraging. And we all have those experience in this field. I mean oncolytics isn't alone in this. I mean I'm very familiar with most of my colleagues' studies and there are a lot of people wandering around today, even from early-stage studies, that are doing very well. Now of course the proof is what Biovex is doing in phase IIIs and what we're doing in phase IIIs right now. You know, at the registration level-- big randomized studies, control arms, the whole nine yards. And we'll see.

Vincent (35:49)
So have you started a phase III yet, or are they just beginning?

Brad (35:50)
We are about 8 months actively into our head & neck phase 3. It's just under about 30 sites now, in five countries, and that will be in close to 100 sites in about 4 months.

Vincent (36:04)
How many patients are enrolled in that?

Brad (36:07)

I'm not saying exactly how many to date. It's a two-part study.

Vincent (36:13)
And this will end up being able to use Reovirus for head-and-neck tumors, right?

Brad (36:18)
Yeah, it's second-line. So it's platinum-refractory taxane-naive patients, and it's all metastatic disease. Like everyone has metastatic disease.[3]

Vincent (36:27)
Is it virus or is there--- It's not monotherapy, right?

Brad (36:31)
No, it's carboplatin paclitaxol and reo together. So "CTR" is what the investigators call it [interrupted]

Dickson (36:39)
What about breast cancer?

Brad (36:40)
I've had a couple of nice durable partial responses as a monotherapy with Reo in breast cancer. And they also took care of the liver mets in those breast cancer patients. Same with melanoma patients as a monotherapy. We've had a few like that. It's interesting when you dig into the clinical data-- of course the scientists among us all do this and doctors start glazing over-- but I love digging through clinical data. I just expected we would see differential responses in metastatic disease. And of course nobody believed that when we started because it's kind of heresy in oncology that you'd have something that would work better in mets [metastatic tumors] than in primaries. We're seeing-- if you look across our studies-- about a 40% true clinical response rate in metastatic disease across studies. And about an 80% stable disease or better rate in metastatic disease. And that's lymp, lung, and liver. And liver seems to be the most aggressive. And of course we all exclude brain mets from all these studies, because they're just the wild-card and they really mess up life-span measurements. But that would be the gold standard. I mean if we could do brain mets that would be--- There are almost 300,000 people that die every year in the US from brain metastasis We're actually selecting for brain mets because most of the drugs that we use don't cross the blood-brain barrier, so patients that would have died of something else are now dying of brain mets. To have an agent that's that active against metastatic disease is interesting in itself. Of course, until a couple of years ago, metastatic endpoints weren't accepted by the FDA as and endpoint. It wasn't a disease. It was an outcome of some other disease. But there have been a couple of companies now that have gotten SPAs [FDA special protocol assessments] for metastatic liver disease that are measured separately from the primaries. And so we're wrestling with how to handle one of that in one of our studies, because I think the preponderance of liver responses in particular with reovirus is quite overwhelming. It's just really unusual. Normally you see low single-digit response rates, and we're taking that up to 40%. That's a big difference. And they're durable, too. They're quite long lasting. They last for a long time after you quit treating. They do regress eventually, but it's quite remarkable. It's kinda neat

3 In the Oncolytics Biotech phase 3 update conference call of Sept 2012 Brad said that a few of the patients on study did not have metastatic disease.

Vincent (39:10)
So do you expect after this phase three that you'll be able to go to market with a reovirus for head-and-neck tumors?

Brad (39:18)
Yeah, absolutely. This study was done under a special protocol assessment, so the FDA-- to the degree that you can hold them to that-- signed off on it before we did the study. And so this will count as a single registration study and they've already said that it will count as a single study.

Vincent (39:38)
So are there other viruses out there now that are now being used, that you're going to piggyback onto? Or are you going to be the first?

Brad (39:46)
The only approved virus is in China. The old O-15 vector from Onyx got sold by Onyx to a Chinese company who then got it approved in China. They have limited sales there. So that's the only jurisdiction that I'm aware of where people are *legally* selling virus. There are a couple of jurisdictions were people are illegally selling virus. In the states that if you're looking a local therapies-- injected directly into the tumors-- then Biovex will certainly be the first I think across the finish line.

Vincent (40:22)
What virus are they using?

Brad (40:23)
They're using an engineered herpes virus. If you're a technical speaker it's got a 34.5 deletion to take the neural toxicity part out. And they've used that as an insertion cite for I think a CGSF. So it's really an immune therapy. So you put a virus in and it basically expresses that and you attract in [interrupted]

Vincent (40:47)
So it doesn't actually kill tumor cells, it enhances the immune response against the tumor?

Brad (40:52)
Exactly. They're using it as a payload delivery vehicle more than anything else. And that seems to work quite nicely, actually. Jennerex is doing the same thing, and a couple of other people are doing that same approach.

Alan (41:05)
Yeah, the whole cancer vaccine field has really heated up. And that general virological approach is something that people have been talking about for a while in concert with a [interrupted]

Vincent (41:13)
So you mentioned a lot of studies in various rodents, in primates, you mentioned GMP production of the virus. Was that all done at your company, or was some of it done elsewhere?

Brad (41:26)

For our research we went for a kind-of distributed model, where instead of us setting up wet-labs and trying to recruit everybody, we just went out and set up collaborations-- paid collaborations-- with people in universities and research institutes and hospitals. And we've normally had ten to fifteen of those running simultaneously for the last ten years. We've sponsored a lot of basic research. Our way of doing it is to basically just say "Here's the general area, could you work in it?" and let people loose on it. Academics love that. And we demand that they publish, which makes us a little atypical. I think we've been able to work with very good people by doing it that way. And it's also very cost-effective for the company.

Dickson (42:16)
So what are your funding sources?

Brad (42:18)
We've been public for quite some time. We've raised around 190 million dollars now over the history of the company.

Dickson (42:25)
That's very good, even in *Canadian* dollars. [laughing in background]

Brad (42:27)
Even in *American* dollars, these days.

Dickson (42:30)
Well, that's why I said that.

Brad (42:32)
I'm still getting use to the fact that the American dollar is worth less than the Canadian dollar.

Dickson (42:39)
Well we're not getting used to that.

Vincent (42:43)
What's the size of your company? How many scientists are working there?

Brad (42:47)
We have 19 people total as internal hires. There are probably what I would consider to be five or six of us to be scientists. And I still have myself in that category. So we did the research out-of-house, with input from us. I mean there is a lot of publication, cross-publication there. The manufacturing-- I've got Toll Skelpin [spelling??] manufacturing. Matt Coffey, who's my chief operating officer, does it now. And so he and I have directed a lot of that. But again, we did it in out-facilities that we did for a couple of years. And so what we've done is just had what's in-house what was necessary to actually run programs. So we haven't done a lot of stuff specifically in-house from a wet-lab prospective. You just find the best people outside of the place and contract to work with them. And, of course, clinical studies are always run that way. So most of the people working for me now are clin-reg people working our clinical programs, honestly.

Alan (43:46)

So now what's the plan assuming the phase III goes well and you get the approval? Are you then going to build your own sales force for this whole thing, or are you planning on collaborating with that too?

Brad (44:02)
That's come down to just a numbers issue. People used to partner for soft issues-- soft issues being things like you didn't have the people or the money to do the things that big pharma could do for you. And that went all the way through running big, complicated clinical studies, paying for them and running them, and the sales and marketing side. And so when you were evaluating whether you should run by yourself or partner, you always had to factor in the their-going-to-do-it-faster-than-you, they'll have access to more capital than you, they'll do it better than you. And that was the reason you could justify doing partnerships, honestly. They've downsized so much in the last few years that there is this massive pool of unbelievably skilled, qualified, experienced people out there that can do all those things. So then it comes down to can you access capital? And so really whether you partner or not turns into an access-to-capital question. So if the cost-of-capital is cheaper for me to do out of public financing, which I've done lots of, then you keep running by yourself. If the cost of capital gets more expensive than the partnership then you do the partnership. And that's what is has really come down to. Right now we're just running by ourselves. Most of the big pharma franchises that have oncology are looking at us and other companies in this area with a high degree of interest. So I couldn't predict honestly today whether we'll be partnered or not partnered. It's an interesting process. In the end what we're here for is our shareholders. And in the end what they're interested in is a stock price that's X higher and not half-of-X higher. And any decisions what we make are based on what the eventual outcome on share price are. And as a company that's how it has to be.

Dickson (46:01)
The history of all these biotech companies, not including yours of course, but a lot of them end up as subdivisions of very large [interrupted]

Alan (46:10)
--They tend to get phagocytosed.--

Dickson (46:11)
Exactly. Engulfed and devoured But they lysosomal enzymes don't apparently work, because some of the personnel are still kept, but the facilities now become known as you know like Merck or Pfizer, or these large pharmaceuticals. What are your hopes and expectations for your own company? In let's say ten years from now, how would you like to look?

Brad (46:32)
If you're looking from a shareholder perspective-- [interrupted]

Alan (46:36)
Sorry I'm laughing, I talk to people all the time who can't quite answer questions like that.

Dickson (46:41)
You know you've got to ask the question, though, **Alan**. I mean come on.

Brad (46:45)
When we set this up we tried to align our management's self-interest with our shareholder's self-interest to the greatest degree possible. So what we've always said is "what will be the best for our shareholders will be the best for us". Which means we're incentivized from a stock prospective more than we are from a drawing-salary perspective. And so I'm obsessed with end-game and what that means for share price. That means something to me personally, since we've set it up that way-- I'm the one who set it up. I mean I was setting it up to make sure that it works this way, and it has. But when you look at companies which were bought-- Basically, I mean our friends at Cephalon are experiencing this right now. I mean you had a company that was trading at, I don't know, $55 or $60 per share or whatever it was, forecast-- because there first product is coming off of patent so their royalties are going to disappear-- probably dropping down to thirty or forty dollars next year and all of the sudden a bigger company comes hopping over the fence and hits them with a pretty decent premium, what $73 a share, and they're trading at $76 because everybody thinks it's going to take another $3 to get them. And you know blah blah blah blah. That endgame is a very nice endgame for a company. Being phagocytosed for the right price is a very good endgame. Our friends at Biovex I think would very much agree with that completely. Their shareholders, of which many are my shareholders too, are extremely happy with that endpoint. They got $425M for the core company and another $575M in milestones that will go to the shareholders based on reaching those milestones. Their shareholders think that's a great deal. Their management is tied into that upside, so they think it's a great deal. If we're phagocytosed in a couple or three years I think that's probably a pretty good outcome.

Dickson (48:43)
So who taught you all of this. You know you're talking to scientists and laypeople out there. How did you learn all this stuff? Because I've been around the block a few times and this is a language that most science graduates haven't got a clue about. They discover something and then someone comes along and teaches them all these things. How did you pick all this up? I mean if you don't mind me asking. I mean that's a personal question.

Brad (49:09)
Well, my PhD is bacterial cell wall ultrastructure. Let's get really esoteric. Three people in the world knew what I was doing and they all ended up being on my defense committee. And then we started collaborating with each other because nobody cared, right? I couldn't have picked a more interesting and irrelevant topic. At the same time I had my own EM, literally as a grad student I had my own thing I just burrowed away in there. My prof had 5-year grants so we never had to write grant money. Life was amazing. Well it was RG Murray, kind-of the father of a lot of microbiology, discovered the graham-negative cell wall had peptide glycand. We're talking old stuff here. And Carl Robinow down the hallway who discovered Giemsa staining. You know Phil Fitz-james had discovered parasporal crystals.

Dickson (50:02)
Robert Coke I assume was your senior advisor. [laughing]

Brad (50:07)
And fire had just become common for the use of cooking food.

Dickson (50:10)
Well, in Canada that's a recent invention. [laughing]

Brad (50:13)
And I walked backwards naked through blizzards to get to school every morning. So yeah, it sounds like that, doesn't it? I'm getting a little long in the tooth for this conversation. I had a really fundamental microbiology background. Didn't have a clue. Had really planned on being an academic. Decided just almost on a lark to try applied microbiology and went out and worked in the oil industry. So I was actually enhancing oil production in oil fields using microbiology, which works really well, actually. And then I started doing toll like scale up and fermentation design. None of that prepares you for the business side of what I do now.

Dickson (50:49)
Yeah, exactly.

Alan (50:51)
That didn't lubricate your entry into what you're doing now?

Brad (50:55)
No, basically I had an event drop into my lap. There was a government research company that was owned by the government in Alberta called Cambiomed. And the government had pumped-- I don't know-- maybe $100M or something into it. And they had like a 100 people and 800 research projects. And it was your typical company but not really a company. It was a research institute, and they did some amazing science. But the government was tired of paying for them. So the minister of the department who ran that whatever at the time basically walked into my office where I was and dropped this in my lap and said "Fix this. You measure of success is I don't want to read about it in the newspaper." Oh, really, oops.

Dickson (51:39)
You'd better buy the newspaper. [laughing]

Brad (51:41)
I buy a briefcase, cause I didn't own one. I bought myself a cellphone, cause I didn't own one. And I marched across the field to their headquarters. I marched in the door and they had like a 100 or something people working on them that day. I fired 85 of them that morning. And they each got about 5 minutes to tell me what they were doing. This was all new to me-- I didn't have a clue. And what we were left with was six or seven really really cool projects. Just AMAZING science. And so I said "Well OK, we don't want to pay for them, so we'll partner them." We partnered all of them except for one in three months.

Dickson (52:15)
Wow.

Brad (52:16)
It was like I thought partnering was easy in those days, because it was for that. But that was the quality of the science, it wasn't me, honestly. So I was getting exposure to all this partnering stuff based on that. And there was the dregs, the last project left over was just sitting there, and we decided to form a company around it. So I knew some guys in Calgary who do a lot of oil work here, because I grew up with them. They're my friends. And they threw some seed capital at it and we formed a company. And we went public almost immediately, and so I had to learn all this stuff on the fly. And here we are-- that

was in 1994-- I've raised probably, I don't know, probably half a billion, plus, dollars for Canadian companies and different biotechnology companies now. And four fifths of that was two companies, and the rest as a director on other companies. I'm on boards-- I'm put on boards quite often on companies to take them public-- that's kind of what I seem to be good at. My wife teases me, she goes you know the thing you like least in the world is what you're best at, so you must have offended some minor deity somewhere. Because I am the biggest science nerd on the planet-- I love science, I love research, I love all that stuff. I mean my name is on most of the patents of the company, I'm involved with the research of the company, but my job every morning is to come up and service the public market and raise money so that Matt Coffey can spend it-- That's the way we divide things around here.

Dickson (53:41)
Is the Heritage Foundation at all involved in any of this?

Brad (53:44)
The Heritage Foundation was there on day zero. Or whatever they're calling it now-- They renamed it something that nobody knows. So we all call it the Heritage Foundation still. It's something like Healthtalks or health institute for-- [interrupted]

Dickson (53:56)
Linda Humphreys is a good friend of mine-- [interrupted]

Brad (53:58)
She's the one who phoned me up to talk to the guys at the University of Calgary.

Dickson (54:03)
She's a fantastic woman and a great fly-fisher.

Brad(54:06)
Absolutely, and just a super person-- [interrupted]

Dickson (54:09)
Totally agree. And her husband too, and he was in the oil business, as you know.

Brad (54:12)
Yeah, and a very good pilot too.

Dickson (54:16)
Yeah. He's unfortunately not with us any more.

Vincent (54:22)
Brad, can I ask you-- early on in our conversation you mentioned some other types of tumors aside from head & neck-- So do you have plans to do some trials? I think you mentioned breast cancer and some brain cancers [interrupted]

Brad (54:35)
We have a randomized study going right now with metastatic pancreatic cancer in the first line. That's an interesting study in that we are not using Gemzar. So we're taking patients who have never been treated and saying "Please forgo the standard of care, which is

Gemzar, and go into this randomized study where they'll either get carboplatin and paclitaxol as the control arm, or carbotax[4] and Reolysin in the test arm. And we should have a data readout on that late this year or early next year. We're running a randomized ovarian study, with paclitaxol-- so taxane-failed patients are either getting treated with paclitaxol or paclitaxol-reolysin. And we have good early clinical evidence in humans that would say that those two things should work-- so that's why we're doing them. We have a number of single-arm studies-- so without control arms-- that will be candidates for randomized studies this summer. We're running two lung studies-- we're doing a squamous cell lung study in a phase II and a non-small cell lung that we're pre-screening for RAS status. Both of those will have data readouts this summer so that I'll pick one of those to do a randomized study later this year. And the last randomized study this year is likely to be colorectal. And it's kind of funny that colorectal will be the fifth randomized study: it should be the first-- That's the native habitat and it metastasized to the liver about two-thirds of the time. So that will be a randomized study later this year as well.

Vincent (56:00)
And that's given intravenously for the colorectal?

Brad (56:02)
Everything is intravenous.

Dickson (56:05)
What about cervical cancer? I didn't hear that mentioned.

Brad (56:07)
Ah, well, cervical cancer is interesting in that a subset of cervical is squamous

Dickson (56:12)
--Right--

Brad (56:13)
and the non-HPV cervical cancers are mostly squamous. And if you look at our most aggressive responses in head & neck, they're squamous cell. You look at our squamous cell lung responses that we've disclosed-- very aggressive responses. And so the obvious next one is to look at squamous cell cervical cancer

Dickson (56:33)
--sure--

Brad (56:34)
because there seems to be a sweet spot there for Reo in squamous cell for some reason.

Dickson (56:36)
And bladder cancer?

Brad (56:38)
Uh, we've only treated a few bladder cancer patients and they've all been metastatic bladder cancer patients. Uh, Matt Coffey's father-in-law used to run the Tom Baker Cancer

4 "Carbotax" is an abbreviation for the combination of carboplatin and paclitaxol.

Center here, and he used to say "Stay away from superficial because EVERYTHING works in superficial bladder cancer." I mean you just need to irritate the lining of the bladder. He says if you instill whiskey-- he's Scottish-- you instill whiskey into a bladder

Dickson (56:59)
[laughing] Which is easy for a Scots to do, actually [laughing]

Brad (57:03)
Yeah, they just do it from the other end. I always think a catheter He's like, "No Brian, I don't need a catheter

Dickson (57:09)
No, we do it the old-fashioned way.

Brad (57:13)
I don't drink Whiskey so I was thinking of it medically not medicinally. Yeah, but we've had some really nice responses with metastatic bladder cancer. But again, we're a little company and we don't have the resources to chase everything.

Dickson (57:26)
Well, I was just thinking of an overlap that occurs in Africa between urinary bladder schistosomes, uh *schistosoma haematobium*, because we have this other podcast called "This Week in Parasitism", and there's this squamous cell epithelioma that develops in a lot of these patients,

Brad (57:45)
--yes--

Dickson (57:46)
and there are co-carcinogens associated with it. And then that tends to metastasize and of course the patient dies. But I wondered how this would fit in with that, because you could probably just infuse it right into the bladder itself.

Brad (57:56)
Oh, absolutely, and we've done animal models on that, actually at the U of A, there are a couple of researchers there that are interested in that. You basically give rodents metastatic bladder cancer and infuse it directly into the bladder and it works marvelously well. It's a great delivery system.

Dickson (58:13)
--very interesting--

Vincent (58:14)
So all this was with Reovirus. Do you have plans to do any other viruses, or is that--

Brad (58:19)
Uh, we do. And there are a number of virus projects around that we're looking at. Our corporate strategy is to get phase III data before we spread ourselves out into other areas. So as soon as we get phase III data then I can expect you to see us visibly looking at other viruses.

Dickson (59:41)
So soon Canada will be cancer-free, is what you're trying to say? [chuckling]

Brad (58:42)
Well, right now I'm looking at somebody walking down the street smoking-- There are always new patients.

Dickson (58:51)
That's true. That's true.

Brad (58:53)
Carry on smoking, young man.

Dickson (58:54)
Oh Jesus.

Brad (58:55)
The sad fact is that many of the cancers we are trying to treat are environmental.

Dickson (59:00)
--sure--

Brad (59:01)
Most head and neck are environmentally caused-- well HPV exposure is environmental too. Well if you don't smoke and you don't hang your head over a charcoal fire, which we do voluntarily in North America and not-so-voluntarily in places like India, or chew bettlenut [spelling], which is a hugely aggressive carcinogen [interrupted]

Dickson (59:20)
--Isn't that interesting!--

Brad (59:23)
you don't get head & neck cancer. So we could eliminate head & neck cancer by changing habits. It's like type-2 diabetes,

Dickson (59:29)
--sure--

Brad (59:57)
it's a self-induced disease. I think a lot of cancers in the end-- I mean lung cancer is a classic. Most bladder cancers are due to smoking.

Dickson (59:38)
--sure--

Brad (59:39)
I mean most people don't think about what smoking does to the human body. So we could probably cut the cancer rate in half just by changing people's personal habits-- that's not going to happen. People are not going to change their habits when they're twenty for

something that's going to bother them when they're seventy.

Dickson (1:00:00)
How about mesotheliomas?

Brad (1:00:01)
Uh, we've treated only one mesothelioma, and had a really good response. I mean it's one data point, so it doesn't mean anything but it's better than no response.

Alan (1:00:07)
Well, that's 100%.

Brad (1:00:08)
[collective laughing] So I could file for product approval.

Vincent (1:00:15)
So Brad, I have one email that I'd like you to listen to and perhaps answer, and then we'll let you go. OK. This one is from a listener Ivan, who writes

> Hello TWIV team. I'm an avid listener to this show, TWIP, and now TWIM and this will be the second time I wrote with a question. We all know about the use of lytic viruses in the treatment of cancers, which can be very promising. I was thinking if there could be another way to use viruses in cancer treatment if the tumor cells could be infected with a modified virus that will promote over-expression of MHC class 1 proteins then hypothetically the immune system would be stimulated to get rid of the infected cells by CD-8 cytotoxicity, NK cells, over-expressed MHC class 1, and by the natural proliferation of the virus. I was just wondering if such a treatment is possible. I haven't seen any research paper describing such a methodology, and my knowledge is still not sufficient enough in order to answer this question myself.
>
> Keep up the good work, and I'm looking forward to many future episodes of TWIV.

Ivan is from the UK, part time biomedical student and electrician and hopefully future virologist.
What do you think, Brad?

Brad (1:01:23)
I will go one level up and answer that question. When you look at viruses for the treatment of cancer you really have three categories. The first is as pure vaccines, where you're basically infecting a tumor in some why and causing a pure vaccine-like immune response against the tumor. And that technique has been tried and hasn't worked all that well, candidly. But, I think it's more because, as we all know with autoimmune therapy, it's a little tough measuring. And now that we've got the Dendreon example, we can actually measure things.

The second is the payload delivery vehicle method. The herpes story with Biovex is a good example-- they attract in an immune response but it's not a vaccine-like immune response. It's more of an infection-based immune response, if you want to think about it that way.

And the third is what ours is, which is using an active oncolytic virus that is a cytotoxin itself. And they all have a little bit of overlap, of course. Reo has a secondary vaccine-like effect after the fact, and so on. The approach that the emailer described I haven't heard of people doing, but it is I think perfectly logical and perfectly feasible. So somebody could do

exactly that. And it certainly would fit in more probably with the second category, with the payload delivery. But again, you get a little crossover. I think the immune area is-- once we figure out how to measure things properly, and of course we're stuck with overall survival as really the only effective way because you don't see really see responses as an early indicator in the traditional way. And part of that is because it's kinder and gentler, if you think of it that way. Pancreatic is probably the best example: A pancreatic primary tumor is 80% normal cells. If I get rid of the other 20% and the tumor shrinks 10 or 15%, it's not even called a clinical response. But if you look at the neoplastic tissue it's gone. We're used to cytotoxins that just trash the whole tumor. So if you take these nice gentle immune things then they stabilize the tumor and the tumor might shrink a little bit and it's great and it's stable disease at best, you may very well have gotten rid of all the neoplastic tissue. And where you're only going to see it is when you look at lifespan. And that's Dendreon, I mean there's no early benefit that you see with Dendreon's product, but they get lifespan. That's what counts in our business. So I think the email approach is hugely doable, and I would encourage that person to pursue that thinking.

Alan (1:04:15)
Yeah

Vincent (1:04:19)
Well, Brad I hope you are wildly successful, for the sake of all the cancer patients out there.

Brad (1:04:20)
And that's something that people tend to forget in our business. We get obsessed with my earlier talk, which is shareholder this and shareholder that. I don't know a single person in any one of these companies that if you scratch the surface to different degrees doesn't come to what we're talking about right now, which is-- Any one of these products when they are successful will make a huge *huge* impact on the quality of life of possibly millions of people. That's pretty impressive. And I'm hoping it's us, but if it's not me I hope it's one of my colleague companies.

Dickson (1:04:55)
Here here.

Vincent (1:04:56)
You sound like you're well-positioned.

Brad (1:04:57)
I've got my fingers crossed. We're at the fun stage. We're not talking 10 years down the road, we're talking you-known in the next year or two we're going to know.

Vincent (1:05:07)
Great, looking forward to it. Thanks so much for joining us, Brad, we really appreciate it.

Brad (1:05:08)
I appreciate the time as well.

Vincent (1:05:13)
Bye-Bye

Brad (1:05:14)
Take care.

Vincent (1:05:15)
Brad Thompson, CEO of Oncolytics Biotech. Wow. One year. That would be great.

Dickson (1:05:23)
We'll have him back.

Alan (1:05:24)
Yeah

Vincent (1:05:26)
Well, he'll be too big to talk to us then.

Dickson (1:05:27)
Oh, no no no. He might want to fund us! [collective laughing] Please, don't pass up that opportunity.

Vincent (1:05:32)
He sounds like he's good at raising money, Dickson.

Dickson (1:05:34)
Absolutely.

Vincent (1:05:36)
Alright, let's do a few more emails here. The next one is from John.....

[At this point the transcriber has become exhausted. The show goes on for another 20 minutes.]

Transcriber's Epilogue:

TWIV had three other episodes on oncolytic viruses in 2011:

> TWiV 124: Viruses that make you better
> TWiV 142: Viral Oinkotherapy
> TWiV 156: Armed and Targeted Killer Meta Analysis

The hosts reviewed their thoughts on the field of oncolytic virotherapy on the 2011 year-end show,

> TWiV 164: Six steps forward, four steps back.

As of November 25, 2012 the Oncolytics REO 018 phase 3 trial in head & neck cancer is still double-blinded and ongoing, with 160 patients enrolled. The study design was modified in September 2012 because the study subjects, particularly the distal metastatic

group, were doing much better than anticipated.[5] Whether this surprise is because that the controls took unexpectedly long to progress (given historical expectations) or because Reolysin was unexpectedly efficacious in the treatment arm will remain a mystery until the data is unblinded.[6]

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5 See the press release

6 The article on the "seeking alpha" website claiming that the REO 018 trial has failed is premature.