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**Announcer:** The *BioWorld Insider Podcast.*

**Lynn Yoffee:** This is the *BioWorld Insider Podcast* and I'm Lynn Yoffee, BioWorld's publisher. The FDA's June approval of Aduhelm, the first plaque-targeting therapy for Alzheimer's disease brought some rough waters to the company, Biogen, and the biopharma market. There are many lessons to be learned from that approval and the ensuing fallout. We've brought together two experts to get their thoughts on what lessons Aduhelm's regulatory approval brought to the market.

Today, BioWorld staff writer Lee Landenberger is talking with Michael Agadjanyan, who is the president of the startup Nuravax, which is developing antibodies to prevent Alzheimer's and Parkinson's disease. He's the Vice President and Head of the Immunology Department at the Institute for Molecular Medicine, which incubated Nuravax.

We also have Robert Glanzman, who is the Chief Medical Officer of Clene Nanomedicine. That company is developing a nanotherapeutic for Parkinson's disease. Previously, he's with GeNeuro, Roche, and Novartis. Welcome to our podcast. Lee, over to you.

**Lee Landenberger:** Thanks, Lynn. I'm lucky to be sitting with two gentlemen who are deeply involved in running companies and the clinical development of vaccines and therapies for dementias. We are looking ahead to 2022 and trying to sort our way through the wake of Aduhelm, which has presented certain problems and maybe even some opportunities for those who are developers such as you two.

Michael, I wanted to start with you. I want to ask about regulatory approval and approaching the FDA and the EMA. Some say the trust in the FDA has been damaged in the process of approving Aduhelm. I wonder if there's a certain way you're approaching your development to avoid some of the problems that Aduhelm encountered.

**Michael Agadjanyan:** Yes, that's a very important question. I would like to respond to that slightly differently. First of all, we need to understand that, still, the amyloid theory is the major idea of the initiation of Alzheimer's disease. Obviously oligomerization of beta-amyloid is a key element of starting the process of pathology, which is followed by tau aggregation and accumulation as well as other processes including inflammation and severe degeneration. Saying that, Abeta is probably the early event of a starting cascade of processes, and when it's started, so it's very difficult to stop.

Basically, work which is done with immunotherapy, including AN-1792 trial, which the pioneer was Dr. Schenk from Elan, which showed that immunotherapy may reduce the pathology in mice first, and then 14-year study showed that even they stopped the trial because of **[unintelligible 00:03:26]** they still can see clearance of pathology. We know for sure that antibody are clearing of pathology. We do not know exactly mechanisms of that, but removal of amyloid from the brain antibody specific to Abeta and even tau, it is definitely shown. We need to come up with that.

Secondly, the Abeta theory is supported by many genetic mechanisms. For example, it's well known that people with Down Syndrome, people with Trisomy 21st chromosome which has APP gene, actually more APP gene, they get 75% of adults with Down Syndrome. This time I feel that Abeta theory is kind of still the major theory which you'll hear for Alzheimer's disease. Yes, we have other processes which are extremely important, but that's coming next. Therefore aducanumab which was developed against fully human antibody, which is develop against **[unintelligible 00:04:51]** is very important that it was in the clinic and it shows clearance of amyloid in the brain of treated people.

That part is, for me, clear. Pathology, we came clear. The problem which they have actually was aducanumab is two. First of all, there's no clinical effect of them, therefore it's not clear for me why they approve it. The second problem which I do have is that the extremely high dose of antibody which they are using. They are very high, 10 milligram per kilogram. That dose is inducing still **[unintelligible 00:05:35]** and that's another side effect problem, which may actually stop to do that, stop to treat the people with aducanumab.

Also cost of this is incredibly high. It's like $56,000 I guess. That's also the big obstacle for the using of monoclonal antibody. Basically, taking all these together, I would say that monoclonal antibody may work in late stages, but we need to learn to deliver the monoclonal antibody directly into the brain. Because going with very high dose of specifically tau, we're talking about gram now, to put it into the people at every month or every three months, it's impractical and unlikely even feasible. I don't know how we can do that.

However, from all this monoclonal antibody, both in the anti-beta and anti-tau, we learn a lot. We learned, as I mentioned, that we can clear the pathology in the brain. We learn that we should start as prevention instead of treatment therapy. Prevention could not be done by monoclonal antibody simply because it will be extremely expensive, dangerous because side effects, and impractical because everyone wants to go to doctor's office and infuse monoclonal antibody. It's not practical, definitely for me at least.

At the same time, a vaccine which we're using for hundred years, so it's working very well. If vaccine is immunogenic and inducing good immune response in people, maybe that's alternative of monoclonal antibody therapy. That's what I think we're doing. We are moving. Instead of working with monoclonal antibody, we're making immunogenic vaccine which can induce strong immune responses, produce enough antibody daily. Because it's a long lasting process, it will produce antibody long period of time, and then booster injection can always keep it steady.

This way, you can protect people from aggregation of amyloid and tau, and at least delays the disease startup, at least delays Alzheimer's disease. That is I think our point. That's what we're trying to do for last 20 years.

**Lee:** Thank you. Robert Glanzman, at Clene, are you doing the same thing to avoid troubles that Aduhelm or aducanumab had by doing the science differently, and I assume you think it's better?

**Robert:** Yes. Look the amyloid hypothesis has been beat to death. 15 years ago, I think Michael you were probably involved in this, Elan had a vaccine to amyloid-beta. The trial stopped because of the 1% risk of encephalitis. When we looked at the pathology in those patients, post, there was no amyloid-beta in those brains at all, in the brains of those patients who died. It was completely cleared, and if you look at the cognitive scores of those patients, they were just as demented as everybody else. We've known for 20 years that the amyloid hypothesis is simply incorrect.

That maybe because amyloid is actually a result of Alzheimer's disease and not a cause of Alzheimer's disease. Companies have spent billions of dollars and have very successfully developed antibodies and other immunotherapies to clear amyloid from the brain, and none of those therapies have ever been shown to have any significant effect on cognition. When I was at Roche, I can tell you we spent a lot of money doing PET studies with gantenerumab. Gantenerumab was highly effective in clearing amyloid-beta in the brain, and based on the PET studies, we looked for any correlation to clinical effect in those PET studies and couldn't find any.

This is a bit of incorrect theory. It's time we put it to bed. Here at Clene, we're not working an amyloid-beta at all. We're trying to allow cells that are compromised to make more ATP. ATP is the monetary exchange of energy within cells. If you allow cells to make ATP, they can do their own housekeeping and they can clear amyloid-beta just fine by themselves. We've shown in multiple preclinical models that just by giving neurons the ability to generate ATP in a setting of stress, they can do their own protein clearing. Aduhelm is a tragedy, I think, for the community. I think the neuro division is going to go down in infamy for the approval of this drug.

I think the problem is, of course, it's not a benign therapy. 40% risk of ARIA. ARIA is simply a euphemism for just cerebral hemorrhage. We're looking at micro hemorrhage because, of course, amyloid doesn't just build up in the brain. It builds up in the blood vessels. Any immunotherapy that you attempt for clearance of amyloid in the brain is going to impact blood vessels and cause either hemorrhage or encephalitis or both.

This is not a benign therapy. There's already been one death in the post-marketing database and that's the only the beginning. You're looking at literally billions of dollars being wasted from our healthcare system. The last thing you want for an 80-year-old person who's demented is to give them micro hemorrhage. It's a tragedy I think, and it's going to go down as such. I think it's something we're just going to have to live with for a while.

**Michael:** Robert, what is your alternative?

**Robert:** The alternative is to find out what the actual pathology, instigating pathology, of Alzheimer's is.

**Michael:** You don't know, right?

**Robert:** Nobody knows, my friend.

**Michael:** That's very fine. No, nobody knows, but we do know that amyloid theory is a fact by genetic data. Scientifically, today, amyloid theory is the only one which is showing that Alzheimer's disease is related with aggregation Abeta and tau. I am not saying only, but I am saying it's only theory which is approved by the genetic markers. We're making mice with APP mutation, and this mice has exactly the same thing which you have.

We have biogenic animals with Abeta and tau, they lost their memory, they have Abeta, they have tau, and this is all-human. It is working very well. In San Salvador, there is a village in the rural area. In that area, old people who has a mutation in APP, they have Alzheimer's disease. You cannot fight that. This is science. There are some other ideas and you are welcome to discuss these ideas and I will be glad to hear that.

**Robert:** Look, you're right. Let's get to the science. The science is that there've been billions of dollars spent on clinical trials with amyloid clearing mechanisms, all of which were highly successful. Aducanumab is not the first monoclonal antibody to clear Abeta in the brain. It's not even the best monoclonal antibody to clear Abeta in the brain. None of these studies have ever shown any relationship between clearing Abeta in the brain and clinical effect. That's the problem, my friend. It's science. The science shows that it simply doesn't work.

**Michael:** Well, of course, of course, you are right. That what I said at the beginning. It is the problem. The problem is if we would like to come to the bottom of this problem, we need to start to immunize people decades before they will start the amyloid aggregation. That will prove is that working or not, because then you at least can delay the disease. By the way, Robert, I never heard that any monoclonal antibody or even a vaccine can cure the people if used as therapeutic model. Only vaccines, which are preventive-- Are you vaccinated with COVID or you don't believe in vaccine, Robert?

**Robert:** No, no, no. COVID is not Alzheimer's disease. Let's not confuse them.

**Michael:** No, that's the whole story. It's the same story. Vaccine is a prevention. It's not therapy. That's the whole problem. You would like to use the monoclonal antibody as therapy. It doesn't work. Of course, it will not work. It may help in case of, for example, cancer, but that's a different story because you are basically-- What are you doing with checkpoint inhibitor? You're using monoclonal antibody against checkpoint inhibitor and activate the immune system. Your own immune system is taking care of your cancer. The same thing here.

I am absolutely sure that our own immune system is putting some people in situation once they get Alzheimer's disease, and they put other people when they have impaired immune system to Alzheimer's disease. Antibody are working, but they are not for treatment. They are for prevention, Robert. If you can give me other idea about Alzheimer's disease and we can target something else, I will be glad to discuss that.

**Robert:** Yes, certainly. I can tell you we have preclinical data, certainly, showing that simply allowing cortical neurons under stress to make ATP, they can clear their own misfolded proteins. That's true in multiple models, not just Alzheimer's disease. Look, if you're right and you can vaccinate people at the age of 20 and that will prevent Alzheimer's disease, great. Do the experiment and show the data because, right now, your hypothesis is just like everybody else's hypothesis, it's a hypothesis. If you want to do the experiment-- [crosstalk]

**Michael:** It is not hypothesis. That hypothesis is tested in five animal models. If we got just a grant from NIH for $14 million to try that hypothesis. We are working with dual vaccines. We will start with preclinical AD. It's true we are not going to get data in the next four, five years, or even maybe seven years because you need to wait because we are going to immunize people at preclinical stage, and that is why obviously you are right, it's not a simple thing. That hypothesis I came with 2007. If we will start that time, we'll probably will be doing a lot.

Unfortunately, we didn't, but I do understand why because majority of big pharma, which you worked with, I didn't, they were saying we need 25 years to understand if your hypothesis is right or not. Thankfully, today, the situation has changed. Thankfully, today, we have a biomarker. We have really interesting biomarkers and saying that Alzheimer's and Abeta and tau doesn't make sense, you cannot say simply because biomarkers showed what. We have biomarkers now for brain, which is PET Scan. We have biomarkers for CSF, which is ELISA.

We have biomarkers in blood, which is much more interesting, which is ELISA combined with immunoprecipitation and LC-MS/MS analytical technology. All these is for last five years. These biomarkers is changing whole fields. Now, we can go ahead and do what you said, immunize 20-- maybe not 20, but 40 years old people with APOE4 positive, for example. That's a genetic biomarker. Then look back to that, look to gallbladder and see what's happened with biomarkers.

Again, obviously, you're right, this is all experiment, but saying that it's spent hundreds of million dollars or billions of dollars without a reason, it's not entirely correct. I think that money is spent because Alzheimer's disease is very difficult disease, because it's very difficult to cure that, because we do not know much, but because of immunotherapy and an excellent work of Dr. Schenk, which was published in Nature in 1999, we are now learn much, much more about Alzheimer's. We know about TREM2 now, we know about microphages, we know about inflammation more.

These is all because his work and immunotherapy. I kind of agree that we need to open our eye and find other indicators, other molecules, other changes in the body which is bringing to Alzheimer's. I am completely 100% agree with you, but please do not say that amyloid theory is completely wrong. It is not. It is supported by solid science.

**Lee:** Robert, let me ask you a question. The full clinical trial data for Aduhelm hasn't been published yet. I'm curious, does that affect anything with what you're doing? I'm also curious about how important getting peer-reviewed data is in getting your story out to everyone else.

**Robert:** Those are two questions. I'll take the second first. Certainly, having peer-reviewed publications is important because that means that presumably independent knowledgeable people have reviewed your experiments and they've shown that they've looked for compounds and that you've done a good job looking for compounds and have appropriately done the experiment and appropriately analyzed the data. I think peer review is important. Peer review isn't always perfect. It does fail at times. It's not perfect, but it's the best mechanism we have I think for independent review.

Like I always say, if your data aren't replicated, it's not science, it's art. Until your data are replicated, it's not science. In terms of the Aduhelm full data set, honestly, I think the most positive spin possible on these data have already been published. I think the data are what they are. Of course, the problem is that the subgroup that they found that had some benefit-- Of course, when you look at subgroups in studies, the history of actually taking positive subgroups and then planning phase three programs based on those subgroups is not good. Generally, those studies fail. Biogen now has 10 years to do another pivotal trial to try and prove that their high dose subgroup actually has an effect.

In the meantime, a lot of people going to be harmed. I think the data are what they are. The studies were actually stopped by the DSMB for futility. I think that tells you something, that independent people did not think that there was any potential for benefit in this program. Again, you're basing the approval on a biomarker that has never been shown to have any relevance to clinical benefit and that's a problem.

**Host:** Michael, let me ask you a question. This is a follow-up on something you mentioned earlier. We're talking about cost, and I'm curious about cost abatement for these kind of therapies and vaccines in the coming year, so do you see any rolling back of costs?

**Michael:** With monoclonal antibody, it will be difficult to expect anything. Lynn, I mentioned that I do not believe on therapy with monoclonal antibody at all. That I'm 100% with Robert. What is a point every month or every three months, inject 10 milligram per kilogram? This is for aducanumab. In tau, for example, again, they're using grams, so it's extremely high concentration on immunoglobulin.

They put in intravenously into the people every month or every three months. That's impractical and it will be extremely, extremely expensive. They came before with $80,000. They reduced to $53,000. Even you will go down for $30,000 it's still extremely expensive, and vaccine is actually very cheap. You're talking about small fraction of that. You probably talk about $1,000 or $500, $1200.

Then you need a vaccine only two times, three times. One injection, one booster, and then maybe hopefully yearly or every six months another boost, so that's not expensive at all. Seems that's it very affordable, but of course, we are far away from that because there are only-- Actually they are not a good vaccine now in market because they are not immunogenic. The problem is that elderly people has immunosenescence.

The T-cell response of elderly people is going down, specifically naïve T-cells, and memory T-cells is going up. If you take self-antigen, you have also problem with not recognizing self, which is **[unintelligible 00:23:27]** which he got Nobel prize. That self has a tolerance and non-self you can generate immune response. That is why people should do the trick to generate good response in elderly people with immunosenescence. In general, vaccine cost should be extremely low. It's not compared to monoclonal antibody.

Monoclonal antibody, even I know one person from Iran, he was a senior vice president. He was recently calculated amount of plant manufacturing which you can prepare monoclonal antibody. Even that, it's a big problem, so you cannot produce so much GMP great product monoclonal antibody in CHO-cells to cover entire population every month or every two months or every three months, injecting so much monoclonal intravenously.

**Lee:** Robert, you have similar discussions over Clene about final costs for everyone and keeping them down?

**Robert:** No, absolutely. Like Clene, it's a little bit of a unique situation. The manufacturing is the secret. That's the secret sauce. Being able to manufacture clean-surfaced pure nanocrystals or transition metals, which makes stable **[unintelligible 00:24:56]** be suspension without the addition of any excipients, or anything on their surfaces, really the trick.

With the way we put our cost of goods, it's somewhere north of a small molecule and south of a monoclonal antibody, and where that lands exactly, we'll have to wait until we adapt the scale to find out. I totally agree with my colleague here that monoclonal antibodies versus vaccine, the vaccine approach, it's a much more elegant approach. It's a much better approach. I think if this approach is going to be positive at all, it's going to be exactly as my colleague suggests, you would immunize people with a vaccine while they're young.

That should be safer because there's less amyloid build-up in blood vessels, so you should have less micro hemorrhage, encephalitis; and presumably, it should be more effective. Because whatever those processes are, you're catching them earlier on in the course. Again, I don't want really debate the amyloid hypothesis. There's a lot of animal data to support it. There's multiple negative trials in human beings to refute it, so it's not something we're going to solve here today.

**Lee:** Okay, well, let me ask you both the one last question. When you're looking ahead, giving everything that's happened to Aduhelm in the last year, at the very least, what are the implications for other Alzheimer's drugs in the pipeline? Robert, why don't you go first?

**Robert:** If the FDA is now ready to approve drugs for severe diseases based on biomarkers, that is a huge change from where they've been in the past, in my experience, and I've been around a while. In my experience, you always needed to show substantial evidence of efficacy on a clinically-relevant endpoint. That's always been the bar, that seem to have changed. If it's going to change for Alzheimer's disease, you would think it would certainly change for ALS, which is a universally fatal disease.

If you could convince FDA that you have a biomarker that is predictive of disease progression, and you can show a benefit, you should be able to get an approval based on that. Now, I don't think that ALS has an imaging biomarker yet, a PET like yet, but there may be electrophysiology measures that you could use, things like motor unit estimation that are predictive in the proper hands. From a practical standpoint, I think the only real impact it would make in Alzheimer's research would be if you had to do studies with aducanumab as a standard of care.

Then you would have to obviously beat aducanumab, which I don't think would be difficult if you have a drug that's effective, but it would be rather costly and rather challenging to actually implement a large Alzheimer's trial. You have to have an active comparator, it's much more difficult than placebo. To me, that's the real practical application.

**Lee:** Michael, your thoughts about looking ahead given everything that's happened with aducanumab, the implications for other drugs in the pipeline?

**Michael:** I didn't work with FDA. I mean, I work with FDA when they approve our clinical trials, but I didn't work inside the FDA. I don't know how it's work, and as I said, I am not MD. Obviously, it's very sad that even a pretty high clearance of amyloid, for example, I think, donanemab clear so much that they stop injection of people with this anti **[unintelligible 00:28:42]** automated Abeta humanized monoclonal antibodies.

I think we're learning a lot, as I mentioned, starting from 1999 when immunotherapy started. We learning a lot about Alzheimer's disease. That's very very important. We know now about very important factors, inflammation, we know about macrophages, microglia more. We know about TREM2, which is very important molecule. We know about APOE4, guys. We know that APOE4 is all because of immunotherapy. We know that APOE4 positive, having two genes APOE4, you have a big chance to get Alzheimer's disease.

That's making our life with prevention easier because we can choose APOE4 people and test the vaccines there. I would say immunotherapy and monoclonal antibody are very important to understanding and learning something. I agree with Robert, this is expensive. I agree with Robert, it take a lot of time, and sometimes we're getting sad results. There's no clinical effect on any people who're getting this monoclonal antibody, but at the same time, it's opening new avenue. Even Robert who is against amyloid therapy agrees with me that the vaccine can be used at prevention and it has more sense. I agree with him that too.

I think we should try and hopefully in the next 7 to 10 years, we will understand, are we right or you have this right and we should completely stop thinking about amyloid and tau, which I guess it will not happen. Then we will move to completely other direction. Again, but everything is possible, of course, this is very complex disease. This is very difficult disease. It's multifactorial disease. Unfortunately, not simple, but when you see these people with this disease, and God forbid, if you will have a family with this disease, you will see how difficult is that, how much we need to work and how much money we should spend to try to do that specifically in population when aging is becoming normal.

**Lee:** Robert and Michael, great discussion on an incredibly-complex issue. I want to thank you both for your time and for your insights.

**Michael:** Thank you.

**Robert:** Thanks guys.

**Lee:** Lynn, back to you.

**Lynn:** This has been a fascinating discussion. Thank you, Michael and Robert, we really appreciate your perspectives and your very passionate, intelligent conversation on the topic. As always, BioWorld will continue to keep you informed of all the most important scientific, clinical, and business updates in the field. That's our show for today. If you need to track the development of drugs, turn to BioWorld.com, follow us on Twitter, or email us at newsdesk@bioworld.com. Also, if you're enjoying the podcast, don't forget to subscribe. Thanks for joining us.

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**Announcer:** BioWorld, published by Clarivate, is a subscription-based news service, but all of our COVID-19 content, over 6,000 articles and data entries since the start of the pandemic, are freely accessible.

**[00:32:25] [END OF AUDIO]**