Dave Iverson: Let’s begin first by talking about inosine. This is a drug that boosts urate levels and in epidemiological studies there seems to be a correlation between people with higher urate levels and a lower incidence of Parkinson's. And what was also intriguing was that urate is an antioxidant and so we think that might be also useful in Parkinson's. There's a lot of interest in this. Describe then the nature of the trial which was a very thorough and long standing trial and in the end what the results were.

Todd Sherer: So, there was very compelling evidence and rational for testing inosine as a potential treatment for Parkinson's really based on some biomarker studies from people with Parkinson's disease. And what was most interesting was that there was some evidence that suggested that individuals at the time of their diagnosis who had Parkinson's disease who had higher levels of urate seemed to have a slower progression of the disease compared to those who had a lower level of urate. And inosine as a compound has a great ability to increase the levels of urate in the body. So the hypothesis was really focused on, if we could identify those with Parkinson's who had the lower levels of urate. If we could give them inosine, we could elevate their urate levels to the level of individuals who were showing the slower rates of progression of the clinical symptoms of the disease. So the study was really designed to test that hypothesis, to really target the delivery of the inosine to match and elevate levels of urate in individuals with Parkinson's and then to track those individuals over time to see how the symptoms progressed and how those individuals changed over the period of time that they were being evaluated.

And unfortunately, what was found was that while the study did succeed in using inosine to elevate the levels of urate and this was done very carefully, because there are some potential side effects of having higher levels of urate. So while the trial was able to successfully elevate the levels of urate, we did not really detect a significant change in the symptoms of the disease in those individuals. So very well designed study that tested a very specific hypothesis, and the hypothesis was assessed in these individuals, but as you mentioned, we did not get the outcome we were hoping for.

Dave: And that outcome Todd, was assessed using the standard way in which Parkinson's progression is measured, correct? The UPDRS scale for United Parkinson's, assessing what those scale of progression is, that United Parkinson's disease rating system, so is that ... that's often been a question mark because it's not the most precise of measurement tools. Is there any hesitation, based on that, that maybe a better way of measuring, which we hope of course to someday have, would yield better results, or was the evidence so compelling that the UPDRS, the lack of progress using the UPDRS was really sufficient?

Todd: I think that right now we are limited by the tools that we have to assess the clinical symptoms of Parkinson's. They focus a lot on the motor symptoms of the disease, and of course we know that there are broader aspects of the disease than just the motor symptoms. So I do think given the lack of precision of these tools, we do always run the risk of not being able to uncover more subtle changes that may be happening with treatment. I do think we can be confident unfortunately that if there was something, an effect that was so significant we would've been able to detect it, with the protocols that were used. But as you mentioned there could be not only some subtle changes that
weren't identified but we also know that Parkinson's is quite a heterogeneous disease with a lot of variability and because of the cost of these trials we are limited in the scope of the trials in terms of the number of participants. So we can't really know for sure whether there were subgroups of patients that may benefit versus other groups of patients given the protocols that we have now.

Todd: But I do think, there's a lot of work going on now to try to improve the designs of these trials and the outcome measures that we could use. But based on all the tools we have today, unfortunately this is the result we have, but we will be digging in and analyzing this data in much more detail to make sure we maximize the learning that we have from this trial.

Dave: And we'll talk more about what some of those learnings are with both Inosine and Isradipine in a moment but Walter [inaudible 00:08:37] on Isradipine in some ways a similar story. Large study, 300 participants, multiple sites, carefully designed, placebo controls, all of it. This is a trial designed with facts whether a blood pressure drug might make a difference in Parkinson's. Again, epidemiological evidence suggesting that those who will use this drug had a lesser incidence of Parkinson's. And it was also intriguing because this drug is a calcium channel blocker. And as I understand it, the calcium channel may also play a role in the breakdown of dopamine. So there was a lot of intrigue about this one, as well. Walk us through, if you would then, what was found.

Walter Koroshetz: Sorry I was on mute. Yep, so similar to the urate story, there was epidemiologic evidence that suggested this drug as a potential treatment for Parkinson's disease. And that comes from, kind of big studies looking at people who take calcium channel blockers for their blood pressure, or their heart disease. Some studies showed a 30 percent risk reduction in a new diagnosis of Parkinson's in people who were treated with these calcium channel blockers, and the other attractive feature was there was a number of different types of calcium channel blockers, some of which get into the brain and others that don't. One of the studies showed that the benefit in Parkinson's was really just with the calcium channel blockers that get into the brain. Now that being said, there were a couple of other studies that didn't quite corroborate this hypothesis, but the bundle of evidence was in favor from epidemiological story. On the biological side, the story is that the dopamine neurons have this unusual feature in that they have this kind of, spiking, repetitive spiking pattern in which, during a spike, a firing, there is a large influx of calcium that comes into the cells. Calcium is a modulator of a number of intercellular processes, some of which have been associated with injury to the cell. The idea was that the calcium channel blockers may have been working in this epidemiological data by blocking the flow of calcium into the spiking dopamine neurons and then protecting them from dying in folks who have Parkinson's disease.

Now, the difference with the urate study is that, in the urate study at least you could measure the effect of the inosine on circulating urate levels, if we inspected the calcium channel, there was nothing we could really measure that indicated whether it was changing the firing of the dopamine neuron. So the dose was chosen, a ten-milligram
dose, because it was thought to be in the range from the animal studies that could be therapeutic, and also because there’s a limit to how much Isradipine someone could take without dropping their blood pressure too low, and in many people with Parkinson's, that's a concern, particularly with orthostasis, that some people with Parkinson's, because of the autonomic effect of the disorder have trouble with dropping their blood pressure as they stand up.

So the dose was chosen because of the maximum dose in Parkinson's, and we really didn't have a good way of measuring what the drug was doing at the site we wanted it to be active at. And again, as was mentioned, the trial had a very similar design and again, similar outcomes, and they did not see a significant effect. There was a slight trend toward decrease progression Isradipine, but it was not even close to statistically significant, so the trial again, was what we call futile, and didn't give us the results that we had then hoped for, but again, I would emphasize that the data that comes from this trial and the other trial is incredibly important. So the patients who contributed their data and participated in these trials, we really want to thank them profusely for doing this. I think it will really help us in terms of design of future trials, and clearly help us in kind of rethinking our strategy for developing a more effective treatment to decrease the chances of developing or slowing down the progression of Parkinson's disease.

Dave: Let's talk more then about some of the lessons learned from this, what we can take away from it because, of course, there's enormous disappointment within the patient community, and within the scientific community as well, because both of these seemed like such promising possibilities as you've both described. But as you've also both suggested, there's a lot that can still be gleaned from this that will be helpful going forward.

One thing I wanted to just begin by asking is while it feels disappointing that this didn't work, on the other hand, it's also important to know what doesn't work, because then you can let that one go and move on to something else, that reminds me of something that the noted neurologist Bill Langston said to me once a number of years ago when I was interviewing him and he said something like, "You know, science is the process of going down alleys, to see if they're blind," and I think there's maybe a lot of truth to that. In some ways, you have to go down those alleys.

I'd be curious to hear your thoughts on that, Todd, and why it actually is important to know what doesn't work.

Todd: Well, I think a couple of points to think about, in terms of how to digest this information, I think, one is, just remember that clinical trials are still part of the clinical process, and that we want to test hypotheses in these trials, so it's still very important to take those major steps forward to test these hypotheses to really understand whether we're on track, and what might be impacting the disease, and all experiments have the chance of being successful or unsuccessful. I think what's important is that the design of the experiment should be done in a way that we can really interpret whether we've tested these hypotheses and truly tested whether we've, to use your analogy, walked down those roads. And I think what's very good about these particular trials was how well they were designed and the rigor in which they were conducted. So that,
particularly for the inosine trial, where we really had the biological marker to know that the drug was doing what we hoped it would be doing in the individuals who were treated. We have a lot of information now about understanding whether we tested the hypothesis and, to your point, whether it was correct or incorrect.

I think that's something that is one of the major lessons that's been learned in neuroscience over the last number of years is to make sure that when we do gather the resources, to do these important clinical trials, that they are designed in a way that we can really interpret the outcomes. To know whether we should move on to a different hypothesis and different therapeutic, or whether it's worth to follow up on what we've learned. I think that's a really important aspect, to make sure you really dig in to the data of these trials to learn all you can to make sure that the next steps and the next approaches will be that much more informed.

Dave: Does that also mean, then that while these two trials didn't work, there still may be clues there? In other words, we know something is maybe going on with boosting your right levels and Parkinson's or similar ways that the role of accounting channels may be an important one to continue. Does this suggest that those avenues may still, even though these trials didn't work, are still important clues for us to understand the biologic nature of the disease?

Walter: Well, I think that's the, really, key point is to what's been happening in the area of Parkinson's clinical trials, and that is trying to get at the biology of the disease. So, as you mentioned, in these trials, we were basing it on evidence pretty much that came from epidemiological studies, so people who were taking calcium channel blockers perhaps for 10 or 20 years before they were going to be diagnosed with Parkinson's or people who had high uric acid their whole life which may have affected their chance of Parkinson's. I think that in this and in other areas of neurodegenerative disease, the epidemiology data has not really been a harbinger of success going in to trials. And there's lots of reasons for that, I just mentioned one which is the time span of which these changes may be acting and when you come on with a trial much more short time frame, you're not going see that effect.

But the bigger issue is trying to get at the biology of this disease and developing your drug so that you're hitting the target you want, so in Parkinson's and the inosine trial, the urate was the actor, but the action was potentially on free radical generation. We had no way of measuring that, so we really don't know whether the urate really had the effect on free radical generation. In the calcium channel trial, we don't know whether the drug we used actually effected the calcium influx into the dopamine cells.

So, we're left with those open questions that yes, they could be pursued in the future, but I think also it pushes us to be more clever as we go into our new generation of clinical trials, and I would argue that The Michael J. Fox Foundation and NINDS do the work ahead of time to bring things that can be measured that are very close to the disease, half of physiology, and those become the targets of the therapies, and we don't go on to testing it again, say the UPRS, until we know that we have the dose right, the duration right, the timing of the disease onset correct, and there I think that will really increase our chance at success.
So, I think that's the tact we have to take. These unfortunately are not the only two failed trials in Parkinson's. There have been multiple others that follow the same type of pattern, and I think you can run down a blind alley a couple of times, but eventually I think you have to find another road, and I think that's where we are now is trying to develop biomarkers to open up a highway of therapies that'll increase the chance of success as they go into patients.

Dave: And when we begin to wrap up our conversation, I want to hear more about what some of those promising highways might be. Because there is a lot of excitement, I think, right now about the number, the quantity of both different ways in which that might be achieved, but also just the volume of clinical trials now that there are for disease modifying therapies that was just not the case only a few years ago. But I want to wrap up a couple of more things about the question of the possibility of these repurposed drugs because there has been a lot of hope about that, not only with Isradipine and inosine, but previously with a diabetes drug for that, the dietary supplement Coenzyme Q10, none of which have proved out and, of course, the great attraction of these is that because they're already available, already FDA approved, you can jump the line a little bit and get something to people that much faster, but I'm wondering, Todd, if this isn't the beginning at least or perhaps more than the beginning as a cautionary tale about whether or not there is that much promise in these repurposed opportunities.

I'm thinking now in particular about Nilotinib which has gotten so much attention ... leukemia drug that has shown some promise in early trials. Do you think that this is a cautionary tale at this point as we look at this possibility of repurposed drugs?

Todd: Yeah, I think this is an important giveaway in terms of lessons learned and going into these studies and approaches with your eyes wide open. The great advantages of the repurposed drugs, is that the drug has passed a lot of the hurdles where many potential drugs can fail and not make it to the clinic and that has to do with safety and what we call bioavailability, meaning that if you take the drug, it actually does something ... gets to a place in the body and does something biologically. So, there's some attractiveness to the fact that many drugs as they're developed through the pipeline will fail for various reasons whether it's their toxicity and safety issues or the dosing that required, where their bioavailability or other aspects, you have this great opportunity because the drugs have made it through that whole pipeline, but I think the cautionary part of this is the lesson learned that because by definition these drugs are being repurposed, they weren't necessarily designed with all the characteristics that would be suitable and necessary for Parkinson's disease or a neurological disease.

And that may have to do with its ability to get into the brain or a different population of people that are being tested or exposed to the drug, and this was referred to as it relates to the Isradipine trial where the dosing that we had to use was somewhat limited because every drug even if it's FDA approved still has some window for therapeutics versus safety, and you can be limited to what dosing you could use.

But I think, even more importantly, and where the real cautionary tale is, is that just because we have a good drug and a drug that has passed a lot of these characteristics and has the right profile, we still have a lot of the challenges that we've been discussing,
relating to how do we actually test and assess this drug in the context of Parkinson’s disease? So, we may get a running head start because we have a good drug in hand, but we still have to overcome the challenges of really understanding the biology of Parkinson’s and is this drug designed to really address that biology? Do we have enough information about that? And do we have all the tools we need to do the clinical trial in the most appropriate way to understand the effect of that drug? So, while we may be able to get a head start and part of this maze to solve the disease, we still have many, many other aspects we have to fill in whether the drug being tested is a completely new drug or repurposed drugs.

And I think that is some of the cautionary tale in that there aren’t really any shortcuts here to getting all the way to the end, and we have to, again, go into this with our eyes wide open to know it’s still going to be a very difficult task and we have to be really very diligent and determined to really uncover the best way to do this.

Walter: Yeah, I couldn’t agree more.

Dave: Let me ask you both then about where we go from here. You’re the leaders of two critical organizations in the struggle to find the solution to Parkinson's disease. Walter's the head of the National Institute of Neurological Disorders and Stroke; Todd is the leader of The Michael J. Fox Foundation, and so as you think about this, as you think about harboring your resources in the smartest, shrewdest way as you both alluded to, I'm interested in how you go about making those choices. Your two organizations were critical in the funding of both the Isradipine and inosine trials. The Michael J. Fox Foundation stepped up early and NINDS after that because, in part, there is a lot of pharmaceutical industry interest in repurposed drugs because they can't make as much money. There's not as much return on investment. It's a drug that's already out there. How do you harbor your resources perhaps differently now or in a more shrewd way that will get us to the goal that you've both described.

Dave: Walter Koroshetz, how are you feeling about that now?

Walter: Well, at NINDS, we have multiple, different pathways to take, and similar to The Michael J. Fox Foundation. And I would just throw out that the troubles that we've had in Parkinson's have been repeated in many neurodegenerative diseases. Pretty much all neurodegenerative diseases, so we're not alone in this challenge and trouble with failed trials; trials that’ve failed to show the results we wanted.

So, we invest heavily in trying to come up with new targets and basically interventions that have bigger effect sizes, so I think that's also a critical thing that if you have something in stroke, for instance, where you move a clot out of a brain artery within a couple of hours, you'll see unbelievably dramatic effects. So, there's nothing like a drug or a treatment that has a massive effects ... DBS in Parkinson’s, for example, for the systems. So, I think you always have to search for more powerful targets, but I think we also have to invest heavily in what I call the biomarker space, so here at NINDS, we have now programs to develop biomarkers that look a lot like what a drug company would have for developing drugs. So, going from discovery to validation, generalization to try to get to what we call a much better clinical trial readiness state.
And I think we all would like an answer tomorrow, but I think that the shortcuts have not really led us outside of these blind alleys, so I think we have to really invest in developing a marker in Parkinson's disease that if we changed that marker, we think that we're really effecting the disease progression. So, for instance, alpha-synuclein is certainly the one that The Michael J. Fox Foundation and NINDS have been concentrating on mostly. Can we measure this, say, in the spinal fluid and then that becomes the target if a drug lowers the spinal fluid levels of the alpha-synuclein, then you really got something interesting. And this is, say, for instance what's happening in Huntington's disease now, where you can measure the alcohol protein in Huntington's disease, it's called Huntington, and right now the data coming out of clinical trials is that the gene therapy is really lowering, dramatically lowering the amount of that protein in the spinal fluid, so that's one example.

And Alzheimer's disease, it was amyloid and COW imaging. Those are the targets now to try to make progress in those diseases, so I think we need something equivalent that we can really trust as a mark of the pathology in Parkinson's, so we can measure in patients.

Dave: Along with that pursuit of finding the right biomarker or multiple biomarkers including the ability to scan or image alpha-synuclein in the brain, part of what also you are going to do represented by this project called AMP PD, the Accelerated Medicines Partnership for Parkinson's Disease. Both the Foundation and NINDS are joining forces in some ways to sift through all the data that both organizations have already collected through their biomarker studies, and really finally diced that and figure out what clues are there both about the disease and then about who can be put into which trials so that we're testing the right drugs and the right people. Is that part of what that effort is designed to accomplish?

Todd: Yeah, so I would echo a lot of what was just said about where some of the biggest needs are and biggest role that some of the sort of non profit based funding could go to to really help this field. And, I mean, both government and philanthropy.

There is a lot of excitement around a lot of the new targets in Parkinson's disease. Many have come from genetics. Things like the LRRK2 gene, the GBA gene, Walter just referred to alpha-synuclein. And there's a lot of excitement to develop therapies against various biological targets that we think are linked to the cause and progression of Parkinson's. All of these therapeutic strategies will run into the same sort of common challenge about how are we going to do the trials to optimize the chances of success. And that will involve selecting the right patients, participants in those studies, at the right stage of their disease. But also having the right way to measure the disease in those individuals not only biologically, but also clinically.

And in order to really uncover that information will require large, very significantly costly studies to understand what normally happens in Parkinson's. What's the normal process prior to diagnosis? What is the process at diagnosis? And then as the disease progresses in its early stage and longer stage. And, as we all know, there's great variability in Parkinson's. So, you have to study a large number of individuals at those various stages at both clinically with neuroimaging tools, and a lot of take advantage of a lot new technology to really do high content molecular profiling of individuals
genetically and understanding what's happening in various systems in their body at those stages.

And that's not the kind of project that can be done by one investigator, or even one funding agency. And I think this is really one of the goals of the AMP PD study, which is to bring together not only the foundation, and NINDS, but also some of the pharmaceutical companies to leverage work that was done through a very significant program over the last number of years at NIH to understand Parkinson's disease in a large number of individuals at different stages of the disease, their clinical systems, what's happening biologically. And also the study that the Foundation has been supporting, the Parkinson's Progression Marker Initiative, which has very similar goals.

And I think this collaboration and this type of research is really important because this is a common ground of information that all people could use then to develop their therapeutics. But we have to work together, and collaborate. And one thing that's really exciting is that all the data being shared across these studies so that researchers could really uncover new insights, new opportunities for therapeutics, and also to develop biomarkers.

And I think that's where we're going to see the field going. It's starting to happen now where in some of the therapeutic trials people with only certain genetic mutations are being recruited, or certain biology so that we can be much more precise in how we translate what we think we know about the disease into making real breakthroughs for people.

But I'm very encouraged by the field coming together, the great collaborations that are happening both across the funders but also the academic and industry community because this is a common challenge, as Walter mentions, across not only Parkinson's, but other neurological diseases, and this is the path forward. We really have great impact in advancing our ability to move the field forward.

Dave: So, it sounds in a way then, Walter Koroshetz, that there's a twin challenge. There's a challenge to identify what might slow or stop the progression of Parkinson's disease, hence all the excitement about these genetic trials, alpha-synuclein trials that are designed to modify the progression of the disease. Trials that were not in existence only half a dozen years ago. But at the same time there's the equally, perhaps equally, important challenge of getting the right people into the right trial, being able to assess, and analyze, and measure what the results are so we really know whether or not one of those works.

So, we have to go, going back to that, I guess, earlier analogy we have to go down two alleys at the same time.

Walter: Right. I think you always start off with the hope that it's going to be an easy quick win, but then you have to learn your lessons from prior experience. And often times what that means is narrowing your focus to increase your chance of success, and what you sacrifice there is generalizability, which is sometimes ... Well, in the past that was a real
disincentive for industry if you had a therapy for Parkinson’s but it only worked in people with LRRK2 mutation, they might wonder about what the profit margin may be.

But I think that because there has been so many failed trials from the industry side as well that they’re seeing the wisdom in this approach, which is narrowing down on a particular molecular mechanism that you know is related particularly to genetics, because that’s a human finding in the disease. And then that’s kind of like your beach head. So, you didn’t invade Europe by parachuting all over Europe. You established a beach head, and then you move your forces in. So, I think that’s the analogy I think of that right now if we could get a success in a particular population we would learn so much, and that would allow us to move out from there to see how well things generalize.

And the idea is that your chance of success in that smaller group is higher, because you’re not dealing with a tremendous heterogeneity.

Dave: It reminds me in a way of something that I’d like to ask just a closing thought from each of you. I saw an interview which Andy Singleton, a noted geneticist, participated in, and he said positively he wasn’t just optimistic of the future of Parkinson’s disease research, he was certain about that future. So, while we have all of these unknowns, and all these questions there does seem to be at the same time this great optimism, and, in Andy’s case at least, certitude about getting where we want to go despite all of the obstacles that are still in front of us. Do you share that Todd? And let me ask you to respond first, and then Walter your last thoughts as well.

Todd: Yeah. I mean, I remain very optimistic about the direction we’re going. I think that one of the important points that we’re trying to make, I guess, in this discussion is that we learn so much as we move forward. And there might be a disappointing trial, but we learn so much from it on how to do better, and our ability now to generate data, and the fact that a lot of this data is being made available, and that there’s great collaboration going on across the field. Our knowledge turns are happening so much faster than they used to in the past, and just new information is coming out all the time.

So, I remain extremely optimistic, but I think we have to be realistic that this is going to be very hard work, and we have to remain dedicated, and focused on making sure we are continuing to learn, and design projects and studies in the way that they could be most informative. And I think we’re doing the best that we can on that, and there’s good coordination on working together to do that in the most productive way.

And I’ve now been with the Foundation for 15 years, and this is a very promising time in terms of all the new science that has come out, all the new opportunities that are there. So, I can see the light at the end of the tunnel. But we have to keep pushing through, and make sure that we’re doing this in the most intelligent and focused way to make sure we get the most out of that promise.

Dave: And Walter Koroshetz.
Walter: Yeah. No, I agree with Todd that ... I've been in the area for 35 years, and that the level of sophistication we have now is astronomically improved over, say, the 1980s when I started. And so, yes, I feel very optimistic. I also see, from our point view, and, sort of Todd said as well, that there are multiple shots on gold that are going to be important. There are symptomatic therapies that we may, hopefully, we're going to learn from things like the brain initiative where these tools to examine circuit function in the brain are just exploding, and we have. In the brain initiative now we have projects where we have a closed-loop brain stimulator so that the amount and the direction of the stimulation is actually driven by the brainwave activity in the patient to basically drop down on the incidence of dyskinesia. So, even in the symptomatic area I think there's a point.

I was at a conference last week. Discussions going into regenerative medicine, and trying to transplant dopamine cells again into folks in a much more sophisticated fashion.

So, I think there're lots of activity going. Industry is now interested in Parkinson's, which this is a fairly new development. So, lots of bright spots. But I would say the analogy, again, that I use is that we can see across the river, we can see where we want to go, and we can see that there are stones across the river separated by distances, and we can certainly see that we're going to be able to make the jump from one stone to another close to our shore. But what we don't know is what's the distance in some of these further out stones. And we need to continue to fill in those knowledge gaps so that we can actually make it across the entire divide. And it's hard to predict.

So, certainty I wouldn't go there at this point, certainly in terms of time. I know that other IC directors did about 20 years ago. So, I'm not going to go down that road again. But, again, lots of optimism as the science moves forward. And I would say the NIH is just so grateful for the ability to work so closely with The Michael J. Fox Foundation, and, again, also the patients who take part in these studies. We say, "We did this, or we did that," but really they did it, and hats off to them for helping the science advance.

Dave: Well, Walter Koroshetz, and Todd Sherer thank you both very much for this conversation, and for all of the terrific analogies. I'm especially grateful, Walter, that you managed to get in shots on gold, because no conversation with the Foundation is complete without that particular reference. Thank you both very much.