“The Neuro Funding Rollercoaster” with Harry M. Tracy

Transcript of Cerebrum Podcast

Guest: Harry M. Tracy, Ph.D., is the founder and president of NI Research in Cardiff, CA. NIR’s bimonthly publication, *NeuroPerspective*, is utilized by pharmaceutical companies and venture capital professionals. NIR has also published *NeuroLicensing* and the *Private CNS Company Review*. NIR provides consulting services to pharmaceutical companies and to venture capital/private equity groups. Tracy also practiced for thirty years as a clinician and consultant in a variety of psychiatric and neurological settings. He received his Ph.D. from the University of Miami, and completed his clinical training at Massachusetts General Hospital/Harvard Medical School. He has been a research associate in the Department of Neurology at the University of California, Davis

Host: Bill Glovin serves as editor of *Cerebrum* and the *Cerebrum Anthology: Emerging Issues in Brain Science*. He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Welcome to the Cerebrum podcast. I'm editor Bill Glovin. Today our guest is Harry Tracy, founder and president of NI Research in Cardiff, California, and author of this month's *Cerebrum* article: “The Neuro Funding Rollercoaster.”

You can read the article, and more about Dr. Tracy by linking to Dana.org. Let's get right to it. Let's begin with, where does most of the funding for neuroscience come from?

Harry Tracy: The fact is most of it comes from institutional investors, VCs, funds, mutual funds, depending on whether companies are public or private. It comes from the investor community. That considerably outweighs the amount that comes from the pharma industry itself.

Now, I'm talking about support for small or midsize companies. Obviously, large companies are generating their funds and their science research internally. I suppose, to some degree, that would dwarf competitively the amounts that come for support for small companies, but that amount has been decreasing over time.

It's very hard to break down exactly how much big pharma puts into neuroscience because they don't break out their R&D investments by

therapeutic area. That's in some ways inferential. That's the more difficult to quantify amount.

So, it's the pharma industry, either internally or via partnerships, and then the investor community in terms of IPOs and venture capital.

Bill Glovin: How about in comparison to government funding? NIH, for example?

Harry Tracy: NIH has certainly stepped up. I haven't tracked the exact amount but we're still talking ... There has certainly been some major investments in Alzheimer's. I think it tends to be more area specific. Alzheimer's certainly a large area of support. Addiction research, I think, has primarily been supported by NIDA and various NIH subcomponents. That industry is actually put very low on the substance abuse and addiction research.

The other area that I think has relied on governmental support has been traumatic brain injury (TBI). It's been the military that has provided the bulk of the funding for TBI research for the last decade or two. Department of Defense, U.S. Army, and such.

Bill Glovin: Would you say it's about a 50/50 split between what the government provides, and what bio pharma and other avenues, venture capital and this, provide?

Harry Tracy: No. I think that ... Again I haven't quantified this, but as I said in the article, I think the government has not come up anywhere near the 5 percent of the total funding. It's more supplemental. In certain areas, it's dominant. But if you look at the overall year versus support, the fact is the government does not pay for the most expensive components of drug development, which are the late stage clinical trials. Government does support early stage research, discovery research, pre-clinical research, and they have started to support some small phase one and phase two studies. But generally, they are just pilot sized studies with figures of $10 to $20-million cost. When you talk about major trials, for Alzheimer's for example, where you're talking $300, $400, $500 million for a trial, the government does not get involved in that at all.

Though it actually is the pharma industry itself that pays for it internally or collaboratively. When it comes to the major expenses, the government does not address that at all. They cover some of the earlier stage investment.

Bill Glovin: Traditionally, neuroscience has lagged far behind cancer and heart research. Is that still the case?

Harry Tracy: That is still the case. Again, you'd have to talk about the industry but frankly I haven't broken it down because I don't look that closely at other areas. But I'm sure cancer has continued to be the dominant recipient of funding, both from industry, VCs, and the government. That's been the major area for investment.

Bill Glovin: Your article titled, "The Neuro Funding Rollercoaster," focuses on funding from venture capitalists and private and corporate lenders.

Why is there so much fluctuation? Why the rollercoaster?

Harry Tracy: I think to some degree everything is cyclical. The components that play to the cyclicality of investments in neuroscience ... One is the macroeconomic environment. When the economy hit it's down point in the 2007-2010 timeframe, investment in a whole lot of areas went down. I think the beta, if you will, the vulnerability of neuroscience, is greater than some other areas because of its unpredictability.

That's the micro element, in that neuroscience has, for a number of reasons that I talked about, been seen as more risky. And it has been. The tools that we've had have made it inherently more of what you would have to call a crap shoot in many ways. So, when you see a change in overall investor sentiment and a retraction of providing funding, neuroscience gets hit a little bit harder.

But when you talk about unmet need, neuroscience is near the top of the list. So, when money came back into the economy in general, and the pharma industry more particular, neuroscience benefited greatly by comparison.

I think the rollercoaster is more pronounced for neuroscience because of that factor.

Bill Glovin: With more people living longer, and quality of life tied to development of drugs for cognitive decline, you'd think that the holy grail for drug development would be a pill to slow Alzheimer's or other forms of dementia.

Is that not the case?

Harry Tracy: What I have written is that Alzheimer's is the single biggest prize in the pharma world. When you look at the scale of the aging population, and the consequences, social and financial and personal, from Alzheimer's, there is nothing bigger I believe than to find something that would slow Alzheimer's significantly. By slow it, I'm referring to the fact that you have to cure Alzheimer's.

If you can delay it so that people remain independent and functional until the likely end of their lifespan, it doesn't actually matter whether it was cured. It's the idea of being able to maintain individual function a decade or two longer. That for many people would be sufficient. That would be a huge gain all around.

Bill Glovin: We recently published an article titled "Failure to Replicate: Sound the Alarm," which detailed the problems with neuroscience studies.

Are replication issues tied to funding?

Harry Tracy: Replication issues are true across the board in all fields, not just neuroscience, from my understanding. When various entities have gone back and tried to achieve replication, it's surprisingly difficult across the board.

So, it's not just neuroscience. I think one of the issues in neuroscience is ... I'm not sure that replication is the issue specifically to neuroscience funding. Certainly, we have had a number of high profile programs that seem to show promise early on, and then fail. So, I suppose one could say that's a replication issue. Although I think that tends to be a replication failure of going from a small phase two trial, where one thinks one has seen a signal of effect from something, and namely you expand it into a large phase three trial, and you don't see that signal anymore. It's not necessarily large scale trial that then doesn't replicate properly at phase three.

The fact is, you can go back and find some of the big approved drugs, antidepressants of the 1990s, where it took many trials, eight or nine large trials, to find two that provided the basis for an FDA approval.

It's not just a neuroscience issue, but certainly replication has been one of the areas of unpredictability that makes neuroscience perhaps a little bit more risky.

Part of that is because the endpoints in neuroscience tend to be, what they call, squishy, which makes application much more difficult. If you've got an endpoint that is that objective, that relies upon a patient report or an assessor's evaluation, that throws some noise into the system, and makes it more difficult to have reliable repetition of a pattern.

Bill Glovin: With funding for psychiatric drug development at a practical standstill, I'd like to get your thoughts about funding for alternative therapies for psychiatric and learning and memory disorders.

Digital apps and games have gotten a lot of attention. Peer Therapeutics and Alkali Interactive are examples of companies developing these types of therapies. They're even being tested in clinical trials now.

Is this a direction you see investment in neuroscience going?

Harry Tracy: There is always to appeal to novelty. Peer Therapeutics and Alkali both have obtained some funding. And I think there is some value to be gained, because neuroplasticity is not only a product of drug interventions. There are a number of avenues to reach neuroplasticity.

The digital apps, or digital approaches, haven't proven themselves yet. Cognitive training via computer apps is something where there is still a lot of uncertainty as to how, for as generalizable as it is, if you develop a skill in a very specific modality, does that extend to other cognitive domains? So far, the evidence is mixed at best.

Secondly, how durable is it? Does it last? Until they show that what they achieved is generalized to a broader range of functions and lasts for a certain amount of time, I think that investment is still going to be more exploratory than substantive.

I will say that ultimately most therapies, in psychiatry and neurology, too, are better off being multimodal. Combining drug therapy with a digital app, just as combining drug therapy with psychotherapy, the combination tends to be better. You're basically approaching the problem via more than one avenue towards achieving change.

Bill Glovin: How about the Sync Project, which focuses on music for mental health and the treatment of mental disorders, such as anxiety, along with pain, fatigue, and insomnia?

It appears to me that some of these treatments and interventions have the potential to be as potent and effective as traditional drug therapies, and they seem to have limited side effects.

Are you tracking these types of companies' treatments? Is it just hype, or is there real scientific and clinical rational for these types of therapies?

Harry Tracy: The use of music as an intervention ... There have been specific areas where utilizing that kind of approach has been shown to have some benefit. I'm thinking of stroke therapy, where melodic intonation therapy basically accesses a different part of the brain that has impacted in a stroke that leaves a patient aphasic. It basically permits the reorganization of brain structure. There is a direction that the plasticity will follow, and basic use of a musical stimulus substantiates that.

I'm not yet convinced that, for a generally intact brain, that music therapy, per say, is going to have some predictable or generalizable effect. I'm not dismissing music. Obviously, it's a very powerful force in human culture. But, in terms of data suggesting that in critical situations a musical intervention has a predictable effect across a range of patients ... I just don't think that data exists yet.

I think it's an interesting approach. Again, I think it's one of these things that, as part of a multimodal combination, might have some value. I do not foresee a time that intervention, via say musical stimulus, is going to replace more standard pharma therapy, but I'd be happy to be shown otherwise.

Bill Glovin: Do you track these types of therapies? Digital and music-wise?

Harry Tracy: I track digital apps. I think you have to pay attention to the whole universe of what's out there. I don't see them as, right now, the major leading edge of the next generation of treatments, but again I think they have a place to play.

Bill Glovin: Your article mentions a form of MS where new drugs have been developed, and suggests it could be a model for neurotherapeutics for other drugs in the future.

Is there anything new on the horizon?

Harry Tracy: I think actually the next area that may start having some of the same success as we've had with Relapse-Remitting MS ... There are two areas. One is migraine, where there are now programs in late stage development that they'd be very effective at preventing migraines. That would be a different model for treating migraines than we've had in the past where we tried to interrupt a migraine once it had already started. Some of the CGRP antagonist programs might actually provide migraine prevention, and that would be your truth in paradigm.

The other place I'm looking at something more near term, is the rapid treatment of depression. Where, instead of waiting two, three, four weeks to see if an antidepressant has an effect, the so-called ketamine model does indicate that one can have a substantial effect on depression within hours. Hours to days. That would be a new paradox treatment of depression.

Bill Glovin: It seems as if genetics is the new frontier for solving the mysteries of psychiatric disorders.

Is that the direction you see investment for neuroscience going in? Or is it still too new? And, do you also track investment in genetic modification?

Harry Tracy: The problem with psychiatric disorders is that for the most part genetic contributions tend to be based on what is probably a very multi-genetic plethora of features, including epigenetic factors. It's not as simple as saying this mutation leads to this disorder. It's very wound up and complicated. It's not as if you could intervene in a single gene or two and achieve change. I think that we're starting to have big data approaches to showing patterns of genetic alterations and variation that may parse up populations, subpopulations within larger categories, that may be responsive to specific treatments.

It's pretty early on though. That is one of the reasons that companies that have genetically framed treatments for orphan disorders, things like spinal muscular atrophy, take a lot of support from investors lately because there is a population that's clearly genetically defined, in where invention addresses that basic flaw in the system, if you will. But that's a relatively rare case within the overall universe of neurological and psychiatric disorders.

Bill Glovin: Addiction seems to be a big problem in both obesity, opioids, and all kinds of other areas. Heroin? Is that an area where there's any movement on investment?

Harry Tracy: It's lagged. The scale of the problem is immense, but our ability to address it has been extremely limited. I think they are starting to have a better understanding

of the brain changes that go along with addiction. In terms of not only reward characteristics of addiction, be it associated with opiates or stimulants or food or whatever, but also the characteristics of what happens when the system has been deprived. The negative valence of the public brain experience, if you will.

It's not just how good it felt when one had it, but maybe more to the point is the aversive quality of this withdrawal. That may be a more fruitful area for intervention. There is, I think, some work being done in that area that has been promising but it has not gotten much support from the industry. Addiction therapies have received very little support from pharma, and that's one of the areas where the NIH has had to step in very actively for many years now.

Someone's probably going to have to show success. This is true for a number of disorders, but addiction is one of them. They will have to show success for the industry to get on board and show that this is a viable area for intervention.

Bill Glovin: Are there any areas, or any issues that I've left out that you think are important and worth mentioning?

Harry Tracy: I would say this. It's relevant to the Alzheimer's issue that you mentioned before. There is, if you think of an aging population, the issue of mild cognitive decline that I think starts to be salient for all of us at a certain point. The FDA I think has been extremely reluctant to see that as a valid target for intervention, in and of itself. I think there is some antipathy on their part, fearing that anything that might be used to treat the memory decline that aging adults tend to encounter might then be used for the purpose of cognitive enhancement in younger, healthy adults.

They've really never embraced the concept of a drug that is used just for enhancing memory, if you somehow can't tie it to another larger scale disorder, be it schizophrenia or pre-Alzheimer's, if you will. I think that's one thing that I hope will see a regulatory change in sentiment.

Defining MCI as a worthy and valid target, in and of itself.

Bill Glovin: Thank you, Dr. Tracy.

To read “The Rollercoaster of Neuro Funding,” log on to www.dana.org. Join us next time when we talk about Astrocytes with Philip Haydon, Professor and Chair in the Department of Neuroscience at Tufts University.

Bye-bye for now.