SPECIAL REPORT: What’s Next in Neuroscience Therapies

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INTRODUCTION

Brain and neurological disorders are among the toughest conditions to diagnose and treat, but new approaches and technologies are on the horizon that could change how researchers and clinicians approach them.

Powered by Xconomy, the What’s Next in Neuroscience Therapies event brought together scientists, entrepreneurs, and biotech executives at the Hyatt Regency San Francisco in November to discuss their work developing next-generation neuroscience therapies and technologies in areas such as spinal-cord injuries, precision mental health, dementia, and Alzheimer's disease.

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Ethan Perlstein, chief scientific officer of the Christopher & Dana Reeve Foundation and Abia Creasey, vice president of therapeutics and strategic infrastructure at the California Institute for Regenerative Medicine (CIRM) took the stage with Xconomy journalist Frank Vinluan to discuss the cutting-edge research that could become new therapies for spinal cord injuries and other traumatic neurological damage.

Both CIRM and the Reeve Foundation have funds to support research into spinal cord injury. Vinluan began by asking what each organization is looking for as they evaluate where to put that money.

Perlstein began by saying the Foundation recently announced a $50 million translational fund focused on spinal cord injury (SCI). No investments have yet been made but Perlstein said that above all else this is not focused on investigator-initiated projects, which were more discovery in orientation, but more academic in flavor.

“This is explicitly about pre-seeding, seeding and even taking companies out of academia, but potentially other feeder labs that have some kind of technology and that could be a device or therapeutic where the go-to-market indication is for spinal cord injury,” he said.

This has been called a “venture philanthropy approach” and is a trend observed in other therapeutic areas. Specifically, Perlstein said, the Cystic Fibrosis Foundation is seen as the benchmark for venture philanthropy and has shown what happens when a foundation makes the first step to this approach by bringing scientific PhD talent on staff. From there, a foundation can step in to fill financing gaps – the so-called valley of death – that keep promising early-stage technologies from advancing further.

“Venture philanthropy is hot right now and I think it’s just a reflection of where a lot of foundations are in their lifecycle where they’ve done a lot of investment in the basic research infrastructure,” Perlstein said. “They know a lot of discoveries, but they keep hitting that valley of death. They don’t know where to commercialize.”
Creasy, meanwhile, said CIRM’s mission is to accelerate stem cell therapies for patients with unmet medical need, and the organization looks at opportunities based on projects that are robust scientifically and the opportunity to work with the teams involved to move the programs forward. CIRM’s biggest portfolio in R&D is in neurologic and represents about 30 percent of its projects, funded all the way from discovery, through the clinical and to advanced trials.

“CIRM was founded in 2004 through a measure on the ballot that was for $3 billion. We have funded both discovery and translation as well as clinical research,” she said. “We have advanced numbers of programs. We have 60 clinical trials currently that have been funded by us with values up to $20 million for Phase 2.”

She added CIRM awards between $4 million and $6 million grantees for preparing to file an investigational new drug application (IND), under a program called CLIN1. Grants are available for clinical development “where it’s important for the investigators to do whatever the FDA requires in order for them to file a biologics license application.”

When asked by Vinluan how much of that work is specifically in spinal cord injury, Creasey said CIRM has funded five grants in the discovery stage, one in translation, and one that has moved into Phase 1 trials.

QUALITY OF LIFE

Perlstein became Reeve’s first ever CSO in September, and so Vinluan asked him to explain his vision for the foundation in the SCI space.

“It’s about developing and getting buy-in from the vast majority of the community on the SCI cure roadmap, because in many ways there are, first of all, nascent companies but also just technologies that are waiting to be translated and they’re stuck at that point,” he said. “A lot of those are addressing the so called quality of life, or secondary consequences of the injury, which, if you pull the folks living with injury, these are the things that they want fixed first.”

He said a lot of the industry focus gets put on mobility and walking, but “fixing” specifics like bladder, bowel, or sexual function is a major focus for patients. “The roadmap I believe has to be comprehensive in the sense that it can both think about and tackle root causes and focus on regeneration in a modality-agnostic way.” Industry must also “think about quality of life wins, and let’s deliver those so that you can get people to believe again in the promise of cures.”

He also said the SCI community has been “burned, quite frankly” by being subjected to charlatans and snake oil treatments entering the space, and sufferers are taking a lot of risks. “For people to believe that there is such a possibility for a cure, I think you have to deliver some quality of life wins. Our thesis is that we need to focus on investments on those kinds of opportunities as much as you focus on the blue sky [opportunities]. Let’s go after long distance axonal regeneration, let’s really go after reintegrating the circuits, that’s what I want to reflect in the roadmap.”

Creasey reaffirmed the importance of quality of life for patients with SCI, using recent positive results from Lineage Cell Therapeutics, a CIRM-funded firm, as an example. Lineage has an oligodendrocyte progenitor cell (OPC) therapy for the treatment of acute SCI currently being tested in a Phase 1/2a clinical trial.

“This company has been able to attain Phase 2 data that looked really encouraging,” she said. “One of our grantee’s patients, Jake, was a kid who went for a swim, or dove into the...
swimming pool before his graduation and ended up being a paraplegic.”

But through being treated by this company with OPCs, Creasey said Jake is now able to be self-reliant. “He has recovered some motor function on the upper part of his body. He’s more independent. He's been able to go to college.”

Therefore, it is the quality of life when it comes to these patients, “just small amounts of independence; the ability to drive; ability to wash; ability to eat on their own, that kind of work is really important,” and that that needs to be the focus for now, she said. “Someday we will be able to get them, maybe better therapies, but in the meantime, we are onto something with either cell therapy or gene-modified cell therapies into the future.”

**APPROACHES TO TREATMENT**

Vinluan moved on to ask the panel about the different approaches to treatments that they are encountering when evaluating companies and projects.

CIRM is agnostic when it comes to the whole area of neuroscience and goes go “wherever the science takes,” according to Creasy.

“We have multiple shots on goal. If two or three companies apply for grants to do either spinal cord injury or let’s say Huntington disease or ALS (amyotrophic lateral sclerosis), they are all awarded as long as the unmet medical need is still there and there’s quality science and feasibility of conducting the trials,” she said. “The important part here is that we are able to learn from spinal cord injury type studies, and also to help out either patients with Lou Gehrig’s disease or patients with Parkinson’s disease, etc.”

Neurobiology is still young, and the industry is learning how to work with the relevant cells. “What triggers them to maintain a function, how do they stay viable?” she added. “The biology is advanced but not advanced enough, so we understand other times when there’s injury in one type of disease versus the other, how are they similar or different?”

Perlstein said the first approach to SCI is the acute phase and the salvation recovery of an accident, finding out what functions have been spared and determining the long-term potential for recovery. “You have a ticking clock in order to stabilize the situation and I'm modality agnostic,” he said. “I don't care if it's a dog, a dog that can sniff humans. I don't care if it's little drone with a camera that can fly into the crevices to find them or whether you just go through with a drill, it doesn’t matter.”

Once the critical period has ended, next are methods around promoting plasticity, “either promoting the intrinsic factors that allow for that to happen or inhibiting the exchange of factors that are preventing that from happening.”

Once again, Perlstein said he is modality agnostic: “I don't care if it’s cells or stem cells, I don't care if it's just neuromodulation. I don't care if it's a pharmacological target. In fact, I think it's going to be a combination of those things.”

The next area of treatment comes in the form of rehab, Perlstein continued. “That may not be as sexy to think about or talk about, but what are going to be the brick and mortar delivery systems... Whether it’s a stem cell or whether it's a small molecule, how are they going to be delivered?”

The question then falls on how the Reeve Foundation and others invest in rehab. “We have to have some standardization so that we can level the playing field and say everyone is going to be able to be in the best position to accept these great therapies we’ve done because we’ve got the standard of care and standard of rehab. I think there is a business model opportunity to invest in the SCI wellness centers of the future and I think they could become laboratories for sports medicine as you get able-bodied people and people with impaired mobility actually working out in the same spaces.”

“I think you can be just as creative there as you are on the science side, whether you're addressing the acute phase, the chronic, whether you’re talking about quadriplegic paraplegics, there's got to be something for everybody.”
**FINAL HURDLE**

Vinluan asked Perlstein what hurdles still need to be overcome in SCI. “It’s the lack of the structures to support entrepreneurship. It’s the lack of SCI incubators and accelerators. It’s the lack of focus group of say, angel investors in that space. There's a lot of things that are missing.”

Creasey agreed, but added the space also needs better data regarding the natural history of spinal cord injury, better tools to understand how to measure response in these patients, and other modalities to build on the science that is already being done.

“Where are these therapies going to come from? More investment in the area is needed,” he said “But at the same time, I think until we really pinpoint what is it that we know and how to enhance it or antagonize it, we’re not going to be able to improve upon the therapies that we know how to do right now.”

**PROMISING APPROACHES**

Finally, Perlstein was asked about the positive signs in the space.

“Recently there was announcement of the merger of two companies in the neuromodulation space. Both were products of investment over years by the Reeve Foundation,” he said “Whether it’s going to be a noninvasive or implanted device, I think their modulatory therapies are going to finally see the light of day... That’s where we get to move these out of the experimental trial, experimental rehab centers and get this a little bit more prolific.”

The two firms that merged were GTX medical BV and NeuroRecovery Technologies in October this year. The entity is developing an implantable spinal cord stimulation system with real-time motion feedback, and a non-invasive product offering to restore upper limb movement and hand function.

“Those devices are being repurposed from using chronic pain conditions,” he said, adding “There is still room for that kind of development and of course there's room for that kind of investment.”

“I’ve got my eye on that. We can go down a list of modalities and talk about we’re most excited about, but again, I think we both agree that it's going to have to be agnostic to that because we're going to have some kind of combination or sequence of curative treatments that approach something we call a cure.”
An Immunotherapy Approach to Alzheimer’s

By Frank Vinulan

In the final session of the What’s Next in Neuroscience Therapies event in San Francisco, Stephanie Yonker, vice president of legal at California-based biotech Alector sat down with Xconomy journalist Frank Vinulan to discuss her firm’s efforts in developing drugs to treat neurodegeneration, and whether the immune system holds the key to understanding and preventing Alzheimer’s disease. What follows is an abridged version of the discussion.

Frank Vinulan (FV): A lot of companies have been pursuing amyloid beta (Abeta) or tau approaches neurodegenerative disease. But what is Alector’s approach?

Stephanie Yonker (SY): Alector went and looked at the over 40 Abeta trials that have failed – except for maybe Biogen’s attempt to recoup a split trial – and the over approximately 20 tau trials. We looked at the genetics and we found that when you look at genes that are associated with Alzheimer’s disease, 22 of the 25 genes were actually on the microglia.

At Alector we kind of think of the microglia as the police force within the brain, and that when the police force isn’t working well, you have things happen: You have Abeta buildup. You have tau tangles occur. But the tau tangles and Abeta are a symptom of a bigger problem that the microglia are not functioning well. Because microglia aren’t functioning, then that’s why you have neurodegeneration processes and if we can restore the normal function of microglia then we can potentially treat these diseases.

FV: What are your drug candidates doing to restore that function?

SY: The drugs right now are activating microglia, restoring the normal state of microglia. So our first three drugs that are in the clinic are: An anti-sortilin antibody, which goes and increases progranulin levels; An anti-TREM2 antibody [AL002], which activates TREM2, and activates TREM2 on microglia to increase proliferation and activity of the microglia; and a CD33 antibody [AL003], which inhibits and down-regulates the CD33 receptor – think of it as removing the brake on microglia.
**FV:** Is the underlying problem the dysfunction of these immune cells genetic?

**SY:** The first molecule, AL001, the anti-sortilin molecule, is a good example of the genetic tie. It targets frontotemporal dementia (FTD), in particular FTD that is caused by a mutation in granulin.

It’s hard to understand exactly what is causing the neurological effect. You have a target, a single mutation causes the disease. With a single mutation in granulin, almost 100 percent of heterozygous people develop FTD. FTD is a devastating dementia; a seven to 10-year lifespan. And it’s not that you lose your memory, you have behavioral and speech changes. It’s very devastating to the people.

So, this disease is very genetically originated. Progranulin is a secreted protein. So, what we realized is that sortilin is involved in the natural maintenance of the levels of progranulin. So, sortilin targets progranulin to decrease the levels that are in the brain. If you inhibit sortilin, you naturally increase the levels of progranulin.

So, in our Phase 1a study in healthy volunteers, we looked at both serum samples as well as CSF [cerebrospinal fluid] samples and we saw that there was an increase approximately twofold in the level of progranulin in healthy volunteers. We went on to do the Phase 1b and in both patients that hadn’t yet experienced the behavioral condition that is associated with FTD and symptomatic patients, and what we saw is that progranulin once again was restored to the normal levels.

So the second question that we’re going to ask, and we have to wait for the results of course, is whether restoring the normal levels of progranulin in this heterozygous patient is enough to treat their disease? For me, as a classically trained geneticist, this is pretty exciting science and a pretty exciting company to be a part of, to see that if you could actually make a difference in people’s lives in such a genetically defined population.

**FV:** Is the progranulin protein you’re trying to support specifically for FTD?

**SY:** The first indication that we’re going into is FTD, but we actually started our Phase 2 a few months ago and expanded into C9orf FTD carriers too. So C9orf is a different genetic genotype associated with FTD and we have a hypothesis that increased amount of progranulin could also be useful in these indications. C9orf has a TDP-43 driven phenotypic profile and we think that progranulin's ability to affect TDP-43 may be shown out in these experiments. From their proof of concept, C9orf would eventually lead to Alzheimer's disease and Parkinson's disease.

**FV:** But the molecule does not address the underlying genetic mutation, right?

**SY:** You can kind of think of AL001 as enzyme replacement. We’re not trying to go in there and fix the DNA where the mutation is occurring, or we’re not trying to put in a new locus to express more of it. What we’re saying is in people with FTD in a progranulin mutation, they’re making half as much progranulin so if you make a way for there to be twice as much progranulin as they normally have, you’re replacing it without actually having to modify any DNA or anything like that. By inhibiting sortilin, you indirectly get the increase in progranulin. They still have the mutation, they still only have one effective copy of the allele there, but by inhibiting sortilin and the degradation of it, you get to have high levels of progranulin in the brain.

**FV:** Your molecules are all antibodies. What are the challenges that arise here?
SY: One of the questions that you always get asked when you're doing large molecules for neuroscience, is are you sure it's actually going to get across the blood-brain-barrier? But what we've seen, at least in the context of our AL001 trial, is it's not only getting across the blood-brain barrier, it's getting across in levels to cause the change that we think is necessary based on the pathology.

For some of the Abetas and taus, if you're trying to clear so much protein then you may actually need to get a lot of it across the blood-brain-barrier. It may be amount of target versus how much antibody you get across the blood-brain barrier transport, and everybody knows it's not 100 percent.

But how much do you actually need to get across to get the efficacy? At least for AL001 I think there's strong support that you don't need any particularly fancy engineering to the FC (functional connectivity) or anything like that to get the therapeutic effect, or at least to see the biomarker engagement that we are looking for.

FV: Is Alzheimer's your main focus, or are you looking to other degenerative indications?

SY: I think Alzheimer's and Parkinson's are the ones that [everyone is] looking at right now. I think Alzheimer's is almost the holy grail, or the nut that can't be cracked that everybody is going after. We have limited resources. For AL002 and AL003 we have a partnership with AbbVie and right now Alzheimer's disease is where we're going.

There's biology coming out every day, more studies that are being done about different diseases and finding subpopulations in different orphan indications in which you're seeing immune cells constantly come up. Every day I have two or three emails, asking “couldn't we possibly treat this patient or that indication.”

It's a constant discussion, and I think as a company you have to kind of balance the focus versus the breadth.

FV: What about Parkinson's disease? What is the biology there, and what is your approach?

SY: For Parkinson's disease, that's more going to the AL001 and the idea is that microglia are responsible for removing misfolded proteins, but they're also responsible for the natural state of normal synapses and the health of neurons that they're pruning and providing other nutrients.

We're trying to go at it as stepwise report approach, focus on things that you have the highest probability of success and then expand out after once you begin to understand the biology more. It's like a refeeding algorithm. Science is a refeeding algorithm, so for every sample, every patient we enroll, we're getting additional biology, we're getting additional biomarker data that we're building up to understand how the protein is working and then can apply that to other disease states as well.

FV: There are many different drugs that are trying to do a lot of different things. Could an Alector drug be part of a combination therapy for treating neurodegenerative disorders?

SY: It's, I think, at the very beginning, even with the spinal cord injury it may not be a single thing that's the silver bullet that cures it all. It may be multiple steps, and once we understand the biology of what is causing the various stages and steps in a disease, it may not be one bullet. It may be multiple bullets, or it may be a bi-specific.

What we saw in the cancer and oncology field is that you do need to think outside the box. That combination may be necessary, and also that there may be adaptation by the body itself. You constantly have to be thinking ahead and not limiting yourself to the potential that there is going to be combination in the future. Neuroscience is just so much younger in its clinical experience, I feel, than if you look at oncology.

FV: What have you learned that surprised you? What has Alector discovered that has broken ground in understanding the immune system's role in brain health?

SY: Our CEO [Arnon Rosenthal] went to a conference a few weeks ago and everybody was talking about neuroimmunology. It's the hot thing. Everybody's doing neuroimmunology. But Alector was doing neuroimmunology in 2013.

"At Alector, we think of the microglia as the police force within the brain; when the police force isn't working well, you have have Abeta buildup, you have tau tangles. But the tau tangles and Abeta are a symptom of a bigger problem that the microglia are not functioning well... If we can restore the normal function of microglia then we can potentially treat these diseases.

– Stephanie Yonker, Vice president of legal, Alector"
That's the thing that Alector did, recognizing a long time back that within the Abeta and the tau hypothesis there was something missing. It wasn't doing exactly what you anticipated and [we realized] there has to be something more here.

We've discovered molecules. At the end of the day it's an experiment. And I don't know if I can say what we learned because we're still in the middle of the experiment. We have these very interesting molecules, we have the preclinical mouse model data, we have all the biomarker data. But whether that translates to the patient, we're really in the middle of the experiment. What really matters is are you going to be able to help the patient at the end of the day? If you can ask me in three years or four years what I have learned, I will have learned if these molecules work or not.

**FV:** Can you say now whether doubling progranulin production will help the patient?

**SY:** For me personally, is neuronal growth reversible? How much neuronal growth is reversible? Do you need to treat them early or not? These are paradigms. Why did we add an asymptomatic arm on our face? We're going to add an asymptomatic arm in our Phase 3 trial because maybe we have to start treatment before they actually show progression and have neuronal growth.

The exciting thing, at least at Alector, is we're prepared by increasing progranulin twofold level. I think if you can show improvement for patients who are showing loss of neurofilament, I think your hopes for treating Alzheimer's and reversing Alzheimer's disease is pretty amazing. Even if you couldn't do that and you can show in asymptomatic patients that you can prevent or stop FTD from developing, that really is informational as well.

How early should you go for Alzheimer's disease treatment? Is prodromal enough or should you go before they're even showing symptoms? Should we all be almost fed this like magical molecule so that we never have Alzheimer's? I mean I think there's a lot of basic biology questions that I think are interesting to talk about here. There are fundamentally some really interesting questions and Alector is distinctly positioned to be able to address them and actually do it in a smart way to have a win-win, no matter what.

**FV:** Finally, what do you mean by a `win-win`?

**SY:** A win-win in that asymptomatic patients could potentially lead to an approvable drug. Symptomatic patients could lead to an approvable drug. The information we know could inform how we think about our TREM2 and CD33 trials. Do we need to go earlier for Alzheimer's disease patients to be able to have maximum effect? How should we think about setting up our Phase 2 trials and stuff like that? I mean it's a win-win because we're getting information that will help us do our work smarter to help the patients in the future.

"If you can show improvement for patients who are showing loss of neurofilament, I think your hopes for treating Alzheimer's and reversing Alzheimer's disease is pretty amazing." - Stephanie Yonker, Vice president of legal, Alector
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