Building Bridges to Restore Function

Dr. Silver: So there are inhibitors in the peripheral nerve, the proteoglycans, especially around in the basal lamina, and often what people have done in the past for nerve transfers is to pre-degenerate to get rid of those inhibitory molecules, but David Muir, University of Florida, Gainesville has shown that if you chondroitinase-treat a fresh nerve, which is what you're working with, that dramatically helps remove any of those inhibitors and allows for much better regeneration in peripheral nerve types of regeneration settings.

Dr. Brown: Now, I've seen that applied to grafting.

Dr. Silver: To grafting.

Dr. Brown: [0:49] and then that's the thing they're degenerating and it's in there.

Dr. Silver: Right, they had to say, but it seems to me that when you cut the nerve and you graft, you're going to get some – there are going to be some inhibitors there. It's a little bit --

Dr. Brown: You end up taking the distal end where those axons are going go into.

Dr. Silver: A shot of chondroitinase on both sides.

Dr. Brown: On both sides.

Dr. Silver: I think it could be remarkably helpful.

Dr. Brown: Okay.

Dr. Silver: So faster, better.

Dr. Brown: That sounds good to me.

Dr. Silver: But I mean, the whole thing you'd present is just remarkable that the brain can figure this stuff out.

Dr. Brown: It is amazing and you do have to take in consideration brain injury. Those patients don't as well. So if you've had a concomitant brain injury with the spinal cord injury, it really is dependent upon somebody who's able to learn, able to develop some sophistication with what they do have before you can go to the next level. If you don't have good fascial control of the muscles that your brain does control, then rewiring them to something else is not going to work, as well. So it's a mixed bag. Well, why don't we field some questions? Yes sir?

Audience: Yeah, incredibly interesting. I'm a c5 6 myself so what about the scenario where you could actually extend or use nerves from your legs and move the you know, essentially bridge from the nerve where it exits the spinal cord below the level of the lesion and plug that back into the stump if you were to create a stump and use chondroitinase there to plug it back in above my lesion?

Dr. Brown: Cord to cord?

Audience: Well, essentially if you were to – let's just say you're to cut the cord and then you're to take the nerves that head off from below the lesion level so that innervate let's say my legs or my intercostals or something like that and bridge them up and plug them into the bottom of the spinal cord and just let the brain figure it out. What would happen?

Dr. Silver: That's kind of Carl – Thomas avulsion. The dorsal root entry zone is another barrier regeneration. So axons regenerating into the spinal cord or towards the spinal cord from the sensory nerves so you know, they can regenerate not only out towards the muscles and skin. They can also regenerate in the roots, back towards the spinal cord, but when they get to the cord, they stop. So when you take a nerve and you put it back into the cord, you have all the same problems that we do after a spinal cord injury. So the axons get stuck but we've published papers that suggest that the same strategies, chondroitinase and increasing the intrinsic growth response can get axons, at least sensory axons back in. There's some work from Thomas Carlstedt. If you stick roots in the vicinity of the motor neurons, those axons can come out. But the scenario that I think you're talking about and like to talk about is more, but it just seems like anatomically that's not going to work.

Dr. Brown: There's a bunch of papers by a gentleman named Giorgio Brunelli, from Italy in and he has been doing this where he plugs it in the corticospinal tract and talks about those axons actually grow into the muscle itself.

Audience: Yeah, I saw him about three years ago and it's profound, the functionality that you can get in terms of just legs are going crazy. Standing and things like those.

Dr. Brown: Well, it's a fascinating concept that it works because it talks about a different neurotransmitter. It's the plasticity of transmitters. It's a different neurotransmitter somehow activating the muscle which we never would have guessed would activate the muscle. But the downside of this is that you are losing all the amplification that you would have within the spinal cord. So you've got a weak cortical signal that usually comes down to the spinal cord and then you have pattern generation, this sort of thing, amplifying it to a signal that would really make those muscles move. Now, you're bypassing that entire system and going directly to the muscle so the amount of energy required to activate that muscle in the useful ways is tremendous, and so I don't think that's going to be a long-term strategy, but it's a very important concept to keep moving forward. Yes, ma'am?

Audience: Dr. Brown, would you discuss the thoughts of taking like an intercostal nerve and then transferring it say for hip faction or even the lower trunk regions?

Dr. Brown: Intercostal to distal nerve or to cord?

Audience: To distal.

Dr. Brown: To distal nerve. I have done one of those cases, and I realized after my first couple of these nerve transfer cases that we were on the wrong path with one's concept and that is, it was so easy to take apart those nerves distally and stimulate them and see what the target is and know that you're sending the right axons to target. That we were doing this without completely denervating the target. That means we were leaving some of the dysfunctional axons, the ones that cause spasticity in there. I'm going to talk while I

have this down. If you imagine if you have five axons that go to a target and you have one left over and the other four have to come from proximal, that one is going to sprout and take over those muscles well before the other ones are going to move their way in there to compete with it. And so the one that I did, I did that sort of a transfer on and the recovery hasn't been great. So what you need to do is number 1, if you're going to go a quadriceps, you need a lot of axons. You need several intercostals. There's always a cost to this. You're going to lose some of your trunk balance, some of your sit-up function and then you need to completely transact that from a nerve and put it in there. So you could get some function, but I've had a lot of patients call me up and say, "You know, I'm a T8 injury. Can you take what I have left over and make my legs move?" And not very well. We could go after a gluteal target. We could after a knee extensor target. How strong is it going to be? Is it going to bear your weight? Probably not. We could probably get it to move, but that's still going to be a tough one to do without making the cord better. Yes sir?

Audience: Both of you, excellent work. Thank you very much for presenting today. Dr. Silver, I don't know if you're familiar with the work of Susan Harkema.

Dr. Silver: I am.

Audience: There are stimulation trials that she's currently doing, and one of the fascinating aspects of that is that the point was to try and get motor function, obviously, but in at least two of the subjects, now three, by her personal report, they're actually seeing spontaneous bladder and bowel improvement, so I wondering if you just want to comment on that based on your observations and your studies and your models?

Dr. Silver: Yes. I think what we're learning is some of these more primitive systems, bladder and perhaps, bowel and maybe even sexual function are intrinsically plastic. That is, the descending nerve fibers that innervate the motor neurons that control these functions either sprout and/or can regenerate to some extent on their own. What we're doing in our lab is to giving that plasticity some help from above. Now, it is conceivable that if – so the spinal cord is really trying to rewire itself, and we think for some of these primitive functions working really hard. We just need to kind of increase the gain, increase the input to some threshold. We're doing it by regeneration of long tract fibers in a rodent. But it's also possible to increase the gain by epidural stimulation, so you increase the excitability of the spinal cord and those rewired circuits that aren't working without epidural stim now all of sudden function. What I also think is a really important concept to ponder about is the possibility that the restored function that is being brought about by the epidural stimulation and training also increases plasticity, just by working the system. I hear anecdotal stories from a guy named Anders at the VA at Case Western, people who are on diaphragm pacemakers. And he tells me anecdotally, that sometimes, there seems to be some kind of plasticity and people go off that pacemaker. So activity itself can enhance plasticity. So I'm looking forward, I hope, to combining epidural stim and/or rehab with our bridge-building techniques and/or these various nerve transfer techniques that we just heard about, try to maximize the output of what the nervous system is trying to do. But what's really cool is that the brain figures this stuff out. You know, all these axons that are regenerating, we're not controlling them. They're going where they may, and yet the output that we see in the animals is just improving. They don't get worse if we do things right. So I'm just really optimistic especially

after hearing his talk that the brain can figure stuff out so maybe we don't have to be so perfect in our regeneration. We just got to get some axons to go. The bladder really is, the animals can pee. They don't walk so well. A little bit but I think these primitive functions are something we can approach.

Audience: I had another question for you, Dr. Silver. I was a little confused with the propriospinal neurons.

Dr. Silver: Yeah.

Audience: Is it simply that after the glial scar is cleaned up a little bit and you use the chondroitinase so they just grow on their own?

Dr. Silver: Yes.

Audience: Like they would just do that anyway so there's nothing else that needs to be done to spur on propriospinal neurons. They will just go if they have the room?

Dr. Silver: They go. It's been shown in a cat model that certain types of propriospinal neurons have the ability to grow past a very small scar that's created with a very thin knife. So they have an intrinsic capacity to regenerate. Also we're finding that certain brain stem neurons the ones I showed you, have a very strong capacity to regenerate if they're given the chance to get past the scar. So that's what we're trying to do, and we're using peripheral nerves as a guide and getting rid of the barrier models. But once they're across, very slowly, they just keep on going. Now, we have focused on bladder function because that's what comes back the best. But I did not point out that the animals do regain some ability to move. But I wouldn't call it walking. They go from a BB score of 2 to B score of 7 which is 5 points but a 7 is not all that specular. That's basically the ability to move three joints without any weight-bearing versus one joint. So I don't triumph in that. So there is probably some activity, some locomotor activity mediated by propriospinal system or the gigantocellular nucleus for very crude kinds of locomotor response but nothing close to walking.

Audience: Would it be worth investigating, then adding some kind of locomotor therapy?

Dr. Silver: Absolutely.

Audience: To see if that spurs on better propriospinal growth and then resulting in --

Dr. Silver: Absolutely. Great point. That's exactly what we want to do. We want to see if we can now maximize this in what we've got that we know can regenerate if given an opportunity and make those even better. We just don't release especially at chronic stages. We don't see evidence, a return of any locomotor function, in the chronic animals, that last slide I presented. So nothing so far, but we do see a return of some bladder function.

Audience: But chronically then, would it not be worth still trying to add some kind of locomotor component?

Dr. Silver: I'm not done yet. I told you. We talked about that one preparation phase. Now, we're going to go – now, I'm inviting everybody I see, everybody I talk to, everybody who hears about this to add their expertise, their ideas, their strategies to try to get other axons

to grow, and I’m a firm believer that once they’re past the scar, they keep going and now I’ve heard, it looks like the brain can really help fix stuff, that’s even malwired, and beautifully. I was shocked and thrilled to see your presentation that that’s just incredible.