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Module 3 – Addressing Historical Challenges in SCI Research

Lost in Translation

In the previous module on Understanding Research and Development, we discussed how basic research in SCI reveals fundamental biological facts about spinal cord injury, while translational research includes all the work needed to advance from that fundamental understanding toward clinical trials of drugs or devices.

Translating basic research into new treatments is challenging in any health condition because while cell and animal models can mimic or simulate human biology, they aren't perfect.

In SCI, there are additional factors that make it hard to translate animal studies into successful treatments for people. For instance, the animal models that are used to study the biology of spinal cord injury are often not the same as those that would be used to test new treatments.

Models that are more similar to humans may give more insight into how well a treatment or other intervention might work in clinical trials. But those models are not necessarily best for studying more fundamental aspects of the biology of the spinal cord.

As a result, a lot of basic research tells us important things about the biology of SCI but does not necessarily translate into the clinic.

Andrew Stewart – How we choose to model spinal cord injury largely depends on the types of questions that we're seeking to answer. A lot of these animal models are designed to answer questions about the basic pathophysiology or the basic biology of spinal cord injury. And they're not necessarily being performed with the intent on being a translatable or a preclinical research model. We do have many different ways that we can model spinal cord injury. Some of them are what we would consider to be more clinically relevant or more clinically translatable. We can model different injury severities, different locations. These tend to be more clinically relevant because they manifest in pathologies that are a little bit more similar to what we see on average in human condition. But some of these models are not necessarily the, the best models to use to answer other biological questions.

In addition, animal models of SCI have to be studied differently than spinal cord injured people. Clinical studies in people often use a measurement called the ASIA Impairment Scale, or AIS, to assess how much motor and/or sensory function a person has at the beginning and end of a study.

To complete the AIS, an examiner asks a person with an SCI to try five different movements in their arms and legs. They also test whether the injured person can feel a light touch or pin prick

at specific points throughout their body. The examiner also tests whether the person has sensation around and, in the anus, and whether they can squeeze their anal muscles.

Naturally, animals cannot tell us what they can or cannot feel, and also cannot be made to move on command. Animals that walk on all fours also use their limbs differently. So the endpoints that are used to measure changes in function in animals are different from the endpoints used in clinical trials.

Andrew Stewart – I think the very nature of testing things in humans is quite different because we can ask a person to try their hardest to move a muscle. We can ask a person if they can feel, you know, something poking their skin. You can't, you can't ask that of a mouse or a rat.

John Chernesky – When you're looking in a, in a small animal model, you know, people living with spinal cord injuries are, are heavily interested in that translatability, right? Making sure that the outcome measures that you're choosing in those early studies is translatable to a large animal and, again, translatable to a human, um, is important because if you start down the wrong path in terms of outcomes from the beginning, uh, by the time you start to move towards human trials, you may not be able to select outcome measures that are meaningful.

The differences between animals and people, and the differences in the ways that animals must be studied, leave us with many unanswered translational research questions about how to predict or calculate the effects we might see in humans based on what we observe in animal studies.

For example, we don’t know how a subtle improvement in an animal’s coordination, or a small difference in paw rotation might translate to improved function in a person.

Measures like the AIS and its motor and sensory components evaluate a limited number of movements and sensations with a scale that can detect whether there is full function, impaired function, or no function.

But they do not differentiate between degrees of impairment, and because of this they are not sensitive enough to detect small changes that might have a big impact on daily life.

Other tests that are commonly used in animal modeling studies are difficult to translate to commonly used measures in human SCI studies, such as the NINDS Common Data Elements.

Another unanswered question is, if we treat an animal within minutes or even an hour or two after an SCI, what is the equivalent time point in a person, and would treating a person that quickly even be possible?

It’s also not clear how results from studies that are conducted on animals, usually young adult female rodents, might translate to people of different ages or sexes.

One challenge of studying chronic spinal cord injury is that longer-term animal studies are also more expensive. Long-term care of animals with spinal cord injuries can be very difficult.

Andrew Stewart – When we're thinking about, you know, taking animals out beyond more than a few weeks it can really be very challenging from a technical standpoint. In the context of, of spinal cord injury, even in animals, it's just like in humans, they lose control of their bladders. So what that means is that for us, as you know, technicians or scientists or animal care staff or whoever's, whoever's performing the duties, they have to go into the lab multiple times a day, sometimes up to four, sometimes as little as two, to manually express these bladders.

Even with daily care, over longer periods of time, animal models of SCI may begin to suffer painful complications that require them to be terminated, which may jeopardize the study.

Andrew Stewart – It's enormously time consuming and challenging to do these chronic studies. And it's also enormously expensive. You know, you are keeping animals alive for longer. And so all of these expenses and resources and time-consuming things and incentives add up to, to really not provide an environment or a culture that's conducive to doing like super long-term chronic spinal cord injury work.

Research advocates can help address many of these challenges by helping researchers consider whether their experiments could better reflect the lived experience of people who have SCI, and by asking questions about how the work might be translated at the next step. Advocates also can insist on funding for studies that would help address unanswered translational questions so that clinical trials have a better chance of success.

In the next video, we'll examine other challenges that make it hard to run clinical trials in SCI.