

# Translational Stroke Research: Where Have We Been and Where are We Going? Interviewing Dr. Marc Fisher (editor of *Stroke*)

Gustavo Saposnik, Marc Fisher, Tom A. Schweizer

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Dr. Marc Fisher obtained a bachelor of science degree in biology and medicine from Cornell University and his medical degree from the State University of New York at Syracuse. He was on the faculty of the University of Massachusetts Medical School in Worcester, Massachusetts, where he served as a full professor and vice chairman of the Department of Neurology. Recently, Dr. Fisher has made the move to Beth Israel Deaconess Medical Center and has been appointed a full professor at Harvard Medical School. He is the current editor-in-chief at *Stroke*, a position he has held since July 2010. Dr. Fisher recently visited Toronto; what follows is an interview that covers various topics ranging from his career as a clinician-scientist, his role as editor-in-chief at *Stroke*, and the past and future of stroke research.

## What led you to become a clinician-researcher?

Curiosity, I guess, is the best answer for this. Because I started as a clinician, I was not trained as a researcher. I was self-trained and was with people that I could work with and trying to answer questions that were related to clinical scenarios that I was seeing as a doctor taking care of patients. Then, luckily, I was exposed to people who were doing research like Justin Zivin, who was at University of Massachusetts when I started. He was the more basic research person. But I think the major reason was just being curious about things around me and trying to answer questions.

## When did you become interested in *Stroke*?

I think it was when I was a resident that I realized that I wanted to try to have an academic career in neurology, and stroke was the most common and (I thought) important disease. I did not want to work on an area that was really esoteric. Basically, the way it started was that I decided I wanted to become an academic person and would try for a couple of years to see if it worked. Stroke was appealing to me because it was so common. Early on, I also could see that doing stroke neurology was similar to cardiology as there were a lot of overlaps between the two areas. If you paid attention

to what was going on in cardiology, it could also be relevant to stroke.

## What was a regular day for you while being at the University of Massachusetts?

Things changed a lot for me in 2010, when I became the editor of *Stroke*. I cut back on my clinical work. After 2010, I basically gave up in-patient service and two clinics a week; some with fellows and some by myself. So, roughly, half of them were general neurology and half were stroke. Before 2010, when I was doing in-patient service two months of the year, four half days of outpatient service, and I ran a basic science laboratory for many years. So I would meet with people in the laboratory at least once or twice a week and we would go over the projects. Obviously, when they had a paper that they were putting together, I would spend more time. I ran the laboratory up until I retired from the University of Massachusetts a couple of months ago. My main focus really was the journal and to try to make it as successful as possible.

## What would be the top three rewards for you? How can Marc Fisher feel rewarded?

As a researcher, [it is] having an idea that was driven by some hopefully clinically relevant and important topic. Formulating an experiment and seeing the results through. I am sure you have experienced the same thing; it is an incredible, nice feeling.

Another rewarding thing is to have people who are working with you. I had, I guess, about 25 postdoctoral fellows over the years. To see their careers grow and take off is also a nice reward. I have met some really accomplished people. Kazuo Minematsu was my first fellow and is now one of the leaders of the stroke field in Japan. Wolf Schäbitz, who went back to Germany, and was quite successful as he became one of the associate editors of *Stroke*. Turgut Tatlisumak, who went back to Finland, and is vice chair of neurology at Helsinki. I think it is really rewarding seeing

From the Stroke Outcomes Research Center, St. Michael's Hospital (GS), University of Toronto, Toronto, Ontario, Canada; Neuroscience Research, St. Michael's Hospital (GS, TAS), Toronto, Ontario, Canada; Department of Neurology, Beth Israel Deaconess Medical Center (MF), Harvard University, Cambridge, Massachusetts; Department of Surgery, Neurosurgery Division (TAS), University of Toronto, Toronto, Ontario, Canada; Institute of Biomaterials and Biomedical Engineering (TAS), University of Toronto, Toronto, Ontario, Canada.

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Correspondence to: Gustavo Saposnik, Associate Professor of Medicine (Neurology), Director, Stroke Outcomes Research Program, Department of Medicine, St. Michael's Hospital, University of Toronto, 55 Queen St E, Toronto, Ontario, M5C 1R6. Email: saposnikg@smh.ca

people that you have been involved with mentoring becoming successful.

The third thing is affecting patients. It was so bittersweet actually, leaving my practice at the University of Massachusetts. Some of these patients I was following for more than 30 years. We had this very personal relationship over time. It was interesting to follow people for so long and feel like you had an impact on their lives.

### **So what do you like and dislike about being a researcher?**

What I really like the most is to be able to take a clinical problem or issue and try to translate that into some kind of modeling and to understand it better. And I would think the focus of the research that I was involved in for many years was to develop better treatment for acute stroke and to understand the pathophysiology of the disease and how it developed and progressed. It was really all driven by clinical observation. I am sure that you have experienced this. You see things and then, luckily, if you are in a position to be able to model it, try to develop treatment. That is what we are trying to do.

As far as the things I dislike; the pace of getting things done is not as fast as I would like it to be. I have been involved in acute stroke therapy development for 30 years or more. If somebody told me 20 years ago that we would only have one approved therapy in 2014, I would say that that would be hard to imagine!<sup>1</sup> But, on the other hand, I also feel like we have really learned a lot over the past 20 years and we are on the cusp of some really great things. The field is going to be dramatically changed five or ten years from now. We need to prepare ourselves for that occurrence; build on that and figure out how we are going to go forward and organize care so that the maximum number of patients can be benefitted by whatever advances that we will have by then.

### **Where do you get inspired?**

I guess the[re are] two places that I have noticed that I am able to find new ideas. One is when you wake up in the middle of the night, having been thinking about stuff and you let it sit there for a while. A lot of times I would wake up in the middle of the night and I would have a good idea of what made sense!

The other place for me would be when I had been jogging (I have been doing so pretty steadily for 40 years). It is a great time to be thinking...It is somewhat boring as it is “out there”—away from the office, but if you want to think about something, it is a time when I am not distracted. I have had some good insights during my “jogs.”

There was some question about a “place” as well. We have a summer house on Cape Cod. My favorite place is going to the beach. If I am not trying to really get away and not think about professional stuff; sitting on the beach, watching the surf...I can have some pretty good insights! And that is where I am going tomorrow!

### **What do you consider to be your major accomplishments as a clinician/researcher?**

The most important one was organizing the STAIR (Stroke Treatment and Academic Roundtable) meetings.<sup>2,3</sup> Before I did that, nobody had actually sat down and put down on paper the recommendations for what preclinical modeling practices in

ischemic stroke should look like. I had the idea coming back from a meeting that Boehringer had held. I was flying back to Boston from Frankfurt, and I was on the plane and I said to myself that this would be a good thing to do... that was the genesis. I ran it by some people and they said it would be a good idea. Out of that, we organized the first STAIR conference,<sup>3</sup> which worked to their criteria for what preclinical practices should look like. Others have built on that. We went from there to clinical trial recommendations.<sup>2</sup> That has been the most impactful thing that I ever did.

The other big accomplishment for me was the idea I had in the late 1980s for an in vivo assessment tool for evaluating therapies in stroke models. So, luckily, The University of Massachusetts was the second place in the United States or probably in the world that got an experimental MRI scan. They hired a magnetic resonance physicist, Chris Sotak, to run the scanner. At that point, the only thing I knew about MRI was spectroscopy. So Chris told me about diffusion, because he had come from General Electric and had helped write the software for giving diffusion imaging. I'll never forget the conversation; he said that radiologists are not used to looking at statistics but they are used to looking at images, and he said that is what we should do. That is how this all started! We could actually show the effect in vivo on diffusion-weighted imaging lesion growth.<sup>4-6</sup> It all started from the idea of needing an in vivo assessment.

### **Moving toward the advancements in stroke, what do you think are five hot topics in stroke?**

Honestly, I am prejudiced because “stroke” is a generic term. At least for me, it is ischemic stroke, because that is where I have always been studying. So I have to limit myself to that because when we are talking about subarachnoid hemorrhage or intracerebral hemorrhage, I don't know enough about those areas to say. I would say for acute stroke, or for ischemic stroke, we are on the cusp of developing and proving clinical benefit for additional therapies and I think one or more of these current endovascular trials will be positive for showing clinical benefit and that is going to be a major advance.<sup>7-9</sup>

The second thing would be the development of advanced imaging technology to assess the extent of the penumbra and core.<sup>10-12</sup> I think we are there pretty much there for magnetic resonance, but the problem is the availability. Hopefully, we will get somewhere with CT perfusion, which is going to be more available. I think having the ability to identify the target of acute stroke therapy is extremely important. It is going to revolutionize therapy because it will allow us to deliver effective interventions.

The third point of advancement is developing additional prevention therapies. I think that the novel oral anticoagulants for atrial fibrillation are quite important.<sup>13</sup> I suspect that with the new trial being organized like Bob Hart's on cryptogenic stroke trial, and there are others that oral anticoagulants, will be extended to other indications besides atrial fibrillation.<sup>14</sup>

A fourth big area of advancement will be recovery-enhancing therapy. I know that is just beginning to be evaluated. I think that there will be both robotics and devices [that] will show benefit for recovery.<sup>15-17</sup>

The fifth advancement will be pulling this all together to maximize outcome after ischemic stroke therapy, which is going to require many different things to show how outcomes can be maximally improved and, most importantly, organizing systems

of care so we can actually deliver these therapies over the next 5, 10, or 20 years to as many patients as possible.<sup>18,19</sup> So I think that is the vision that we will try to implement. What we need to do is train people who are going to become the future academic stars to do this development and implement it! In the United States, we are trying to figure out ways to actually train people. I think in Canada, you need to do the same thing.

#### **What were the major discoveries in ischemic stroke in the past decade?**

As mentioned, I am prejudiced because I worked in this field; I think imaging has been extremely important.<sup>20-22</sup> Another discovery would be better understanding of the pathophysiology of ischemic injury. We understand that targeted only one pathway doesn't make a whole lot of sense. We really need to be looking at multiple targets. Another one, in the United States, would be organizing the stroke network. Naturally, not having to re-organize for funding for every National Institutes of Health trial and for getting those trials up and running quickly and hopefully in a manner that will lead to success. I guess another one would be recognizing that recovery enhancement is another important way to go forward. I am sure there are more!

#### **You highlighted the importance of imaging. How do you think imaging will actually affect the way we treat patients with stroke?**

It goes back to the basic issue that the target of acute stroke therapy is to salvage some of that ischemic brain that is at risk of going on to infarction. To identify that is less important very early after stroke because certainly most people with arterial occlusions have a substantial amount of ischemic penumbra so identification is less important in the 3-hour window. But I think beyond the 3-hour window, it is very important. Because, for example, in the 3- to 4.5-hour window, the benefit of tissue plasminogen activator is modest, so the number needed to treat to get one beneficial outcome as defined by the magnetic resonance spectroscopy is 14.<sup>23-25</sup> So, my own personal perspective is that there are likely to be imaging and clinical parameters that will identify those responders and nonresponders. We have no idea who and what those are at the moment, but I think that we can gather that information. Certainly, beyond 4.5 hours, I can't see how we can extend the window without identifying imaging-based parameters that are predictors.<sup>26,27</sup>

Another really important thing about imaging that I think a lot of people ignore is what has come out of imaging trials. For example, Gregg Albers has been able to identify a pattern called a lumen mismatch that identifies people who are going to be harmed by treatment.<sup>28</sup> A lot of our colleagues in the field say we don't need the imaging, we will just use CT angiography or magnetic resonance angiography with an occlusion with clinical parameters. However, imaging can help identify those patients who not only benefit, but [in whom] there is a real risk of bleeding and mortality.<sup>29-31</sup>

This is an interesting analogy. I have not written this, but I think advanced imaging for ischemic stroke is like doing microbiology for infection. If you go back and look at what happened when penicillin was first developed; there was no microbiology. People said at the time, we are just treating everybody with penicillin because if you don't, they are going to die! This is what

a lot of people say about ischemic stroke; we will just treat patients because we don't have any alternatives. However, if you can identify the target tissue for predicting responders, it is somewhat analogous to doing microbiological evaluation for treating infection.

#### **You mentioned some interesting paradigms: Responders versus nonresponders. There are other paradigms (e.g. recanalization vs nonrecanalization) that are commonly used in acute stroke care. The controversy about recanalization versus nonrecanalization is after the fact. It does not help to predict outcomes a priori, does it?**

I think you have to go back. The first thing would be when there are data that suggest that if you don't have an occlusion, you are less likely to benefit from recanalization therapy.<sup>2,32,33</sup> You would have to take it back to a more basic level; is there a perfusion deficit? You might not pick up the occluded vessel because it is difficult to see a more distal occlusion. If there is no large-vessel occlusion, then the interventional radiologist has nothing to go after.

#### **What is the role of risk stratification for selecting specific therapies?**

The risk scale that you have come up with as well as others I think it is going to move us in the direction of making treatment decisions.<sup>34-37</sup> I think it is going to require larger sample sizes of patients so the prediction scores are further validated. I have not really spent a lot of time thinking about this, because I am more focused on the imaging, which has to be proven. My guess is that we will end up with some kind of prediction modeling which is a combination of clinical parameters, comorbidities, clinical scoring, *and* imaging. And what is happening with atrial fibrillation predictions for recurrent stroke is getting more sophisticated.<sup>38</sup>

One problem with these prediction models is that there are so many papers submitted and it is getting a little overwhelming. I think the field needs to get focused on a few scales: get them validated and combine them with imaging as well as clinical parameters. We can't have 20 scales, where everyone is trying to come up with their own scale. Unfortunately, this is what I see happening.

#### **As the editor of *Stroke*, how many hours per week do you dedicate to doing journal work?**

It has changed over the four years because I have gotten more efficient over the time I have worked here. The people I work with have gotten more efficient. We have a fine assistant.

I would say I spend about 12–14 hours a week directly on it, but there are other things that I can't say directly impact on what I do for the journal. I can tell you that Vladimir Hachinski, before I started at *Stroke*, told me that it will not take as much time as you think. He also told me that he spent a lot of time thinking about stuff related to the journal that he didn't include in his "dedicated" time; and that is true for me! So I would say the direct work is not as much as people would imagine, but I spend a lot of mental energy at times.

**What have you learned from being the editor of the *Stroke*?**

“It is a village.” A lot of people contribute and it is very important to see that the “village” is inclusive. The stroke field is a big field and it is an increasingly important field not only in the developed countries but in the developing world as well. The most valuable and important lesson I have learned is that you need to make an effort to involve the many parts of the field; the different constituencies and the different geographical components. Personally, I have spent a lot of time communicating and traveling to China. I go there a couple of times a year because it is such an important disease in China; it is the number one cause of death. I feel like it is important to make them feel like they are part of the community. It is a big village; everyone has to get involved, [and] that is what I am trying to do.

**What is the most satisfying aspect of your job as editor?**

The most satisfying aspect of being the editor of *Stroke* is the ability to influence the field by inviting reviews and editorials that educate the stroke community and get it to think about important clinical and research issues.

**How much does the editor-in-chief influence the type of articles published in *Stroke* (i.e. basic science versus clinical vs drug trials). Some idea if there is a balance that is desired for the journal.**

The editor does not have much influence as to what type of articles is submitted in regard to original research. We try to not have bias in our evaluation of original research articles. Invited content is where we can exert influence over content.<sup>39</sup>

**How does *Stroke* handle academic and economic conflicts of interest?**

We ask authors to disclose economic conflicts related to their paper such as stock ownership. Academically, we ask handling editors and reviewers to recuse themselves if they have obvious conflicts with the authors of papers assigned to them.

**What do you consider to be your major accomplishment as the editor of *Stroke*?**

I think my major accomplishment has been to be as inclusive as I can concerning the nature of the content we publish in *Stroke* and the composition of the editorial board and other head groups. The cerebrovascular field has many diverse components and in my opinion *Stroke* as the leading journal in the field needs to acknowledge the importance and contributions of all of those components of the field.<sup>39</sup>

**Can you tell us examples of “the good” and “the bad” of stroke research?**

I would say good research is highly innovative and novel that expands our knowledge base and inspires others to move the field forward. Bad research would be research that does not comply with the high standards of research as exemplified by the preclinical checklist I initiated in 2010.

**How does being a scientist allow you to explore other interests in life?**

The opportunity to interact with friends and colleagues around the world over the past 30 years has had a profound influence on me as a person and my world view. With such people, I initially have stroke as a common denominator and then we get to know each other personally, which gives me great insight about them, their country, and their culture.

**Could you name three important qualities to be a respected scientist?**

Integrity, insight, and ability.

**How would you define “success”?**

I can only speak for myself, but to me success is self-recognition that you have tried the best as you can to move the field that you work in forward, done research in an ethical and innovative manner, helped to train your successors, and contributed to your local institution as well as national and international organizations.

**How would you define “being an expert”? How much do you trust/rely on expert opinions?**

An expert is someone who truly knows the field he or she works in and recognizes both the positive and negative aspects of work done by themselves and others. Some so-called experts are not really experts, and how much I trust experts is an individual decision based upon their accomplishments and integrity/intellectual honesty.

**What advice would you give to a young student considering a career in science?**

You need to pick an area to work in that is truly interesting to you and hopefully one that will allow you to make meaningful contributions to society. Once you have chosen a field, you should be trained and mentored by talented productive mentors. You can then try to figure out how best to launch your career, which can be difficult with the current funding environment.

**Closing Remarks**

Several major advances have occurred in stroke in the past two decades. Most relevant areas include acute stroke (e.g. new thrombolytic agents, new devices for endovascular therapy), stroke prevention (e.g. new antiplatelet agents, benefits of antihypertensive and lipid-lowering agents), and rehabilitation (e.g. robotics, virtual reality technology). Risk stratification can help tailor specific interventions aimed at improving stroke outcomes. Finally, Dr. Fisher highlighted that curiosity, teamwork, and mentorship are key elements when pursuing an academic career in stroke.

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