Feature Article

An Afternoon With Dr. Mitchell Brin...

At this year's FACE Conference, I had the privilege of spending some time with Dr. Mitchell Brin from Allergan to 'pick his brains' about the long history of Botox®, the many surprises along the way and its future journey, for both aesthetic and therapeutic uses. I hope you will enjoy this interview as much as I did...

Lorna: Tell me a little about your history and your role at Allergan.

Mitchell: I was one of the early researchers to use botulinum toxin when I was at Columbia University. I was very fortunate that when we started to use the toxin we had a protocol with the FDA that was for treating involuntary movement disorders.

One thing is that we had no recipes, we had no guidelines; there was limited understanding of how to use it.

So my early work was in exploring potential uses. I was at Columbia until 1994, and then I went over to Mount Sinai School of Medicine where I was an endowed Professor. Then in 2001 I joined Allergan as the Therapeutic Area Head of Botox and Neurology.

I oversaw Botox development and our oral neurology molecule programmes; and as everything expanded it was clear that they needed someone who would be able to look at and support the research and development activities and regulatory activities across all the different therapeutic areas. So, in 2007, I became the Chief Scientific Office for Botox.

So with botulinum toxin, as you know we treat blepharospasm which is ophthalmological, hyperhidrosis which is medical dermatology, aesthetic, neurological and urological disease areas, so there are a lot of interactions among the scientific bodies and the regulatory agencies.

Whereas when I joined the company everything was under one silo, now we have different therapeutic areas, so to make sure that strategically and from a knowledge base there's continuity, that's my primary role.

L: You touched just now on all the therapeutic uses of Botox. We're celebrating 20 years since the licensing of the drug in the US. Did you sense in those early days that there would be such a broad scope of uses for it, and has that surprised you in any way?

M: So going back to the early days in 1984, we saw that there were many 'potential' uses, but uses going in the directions they did; to me this was quite remarkable.

The aesthetic observation we made, that the Carruthers made, that other people made, was really one of those departures from anticipation.

The potential for use in chronic migraine, which came out of the experiences of aesthetic use, was another departure from anticipation

Senior Vice President, Global Drug Development & Chief Scientific Officer Allergan

Dr. Mitchell Brin is a physician neurologist with extensive clinical development experience with 29 years of pharmacology, experimental therapeutics, small molecule and neurotoxin research on a background of extensive patient care. This research & development experience includes 17 years academic experimental therapeutic (drug / biologics / device) and genetic clinical trials with studies supported by competitive U.S. FDA grants and awards, the National Institutes of Health, private philanthropy and 12 years in the biopharmaceutical industry.

In 2001, Dr. Brin joined Allergan. In 2007, he assumed the responsibilities of Senior Vice President Global Drug Development, and Chief Scientific Officer for BOTOX. In this capacity, he provides strategic cross-functional support of the neurotoxin and next generation biologics program. This includes global scientific support and clinical expertise across the continuum of all toxin therapy (cosmetic and therapeutic) product research, development, regulatory, drug safety, safety pharmacology, formulation, medical affairs and corporate strategy. He continues to publish actively and is a Professor of Neurology at the University of California Irvine (UCI), where he evaluates and treats patients.

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because I think all of us were thinking motor disease, muscle contraction and did not immediately appreciate the potential in the treatment of sensory disorders.

So branching into the aesthetic area was not the medical direction that we had been thinking, and then going into the sensory pain area of chronic migraine was another new direction.

The other thing which has just been outstanding is that when I started using toxin the full understanding of how it worked wasn't available; we didn't know cellular SNARE complexes and many other cellular pathways and mechanisms that we now appreciate.

There are continuous advances in our understanding of cellular function – there was just a big article that came out of Italy just two days ago where they were expanding on what's happening in the cell.

L: In terms of developments in your most recent understanding, are you still learning other things that you can now discuss that you've only recently found out, in terms of the mode of action, particularly in relation to aesthetic indications and the way that the toxin is actually functioning or even new things that you're now finding?

M: So, on the motor side, which is relevant to aesthetic, I think we're getting a better appreciation of the speed of the effect and how long the toxin lasts in a cell. For some of those things our understanding is getting deeper.

On the sensory side with pain mechanisms, that whole area is beginning to become clearer, but every time you get clarity there are more questions.

The interesting thing is that we use toxin to treat patients, those observations we then take back into the laboratory to figure out "why did that happen to that patient". Then you say, "well there must be a scientific reason". So the toxin is now teaching us about physiology as much as it's teaching us how to treat patients.

L: Let's talk about future research. You mentioned in the presentation that you gave to the delegates at FACE the mass of data now available, namely 65 trials for a variety of indications you have studied at Allergan. There are now licences across the globe for the aesthetic treatment of the glabellar area. Are Allergan currently undertaking more trials, particularly to gain more aesthetic licences?

M: We invest very heavily into R&D and development - almost $1 billion in 2012 - so future research is a key area for us. I guess the most that I can reveal is that we're looking at other things but I just can't go into detail. Part of that is that we are a conservative company; we tend to not go public on things until we've got very solid Phase II data. So the things that we're exploring we tend not to discuss.

We do sometimes say that Botox is a 'pipeline in a vial'. That goes back to your earlier question about did we anticipate how much would come out of that vial and that answer's probably no.

"We do sometimes say that Botox is a 'pipeline in a vial'."

L: I'd like to move on to toxin resistance. Does it happen; is it a myth? Should clinicians be advising the kind of 'needy' patient that wants repeated and regular treatments that actually they're going to build up immunity to the toxin; to their detriment? Where do you stand on that, what's your clinical understanding of it?

M: So in terms of resistance, if you take a look at it carefully, the most common cause of people saying that they're resistant is technical.

Did you put enough injection in the muscle you wanted to target? So there is an art to targeting a muscle where you want to target it, where you want to inject it.

Now on the other hand, there will be patients who get antibodies. We had that develop when I was early in my training and my experience. What we found is that when people were injected frequently at higher doses for therapeutic indications this happened. In our aesthetic clinical trials, regarding getting true antibody resistance to Botox, it is very rare.

I have no doubt, since it's a foreign protein, that very occasionally someone may get antibodies but its very uncommon and that's just the observation. If you talk to doctors who have been doing this for years and years at the low doses used in aesthetic practice they will say 'very occasionally or rarely', which is not necessarily surprising because it is a foreign protein. Nevertheless, it is reported very rarely.

L: In the UK, Botox was given a licence for the chronic migraine indication and NICE have now recommended it as a treatment for patients matching certain criteria on the National Health System (NHS). Where do you see the future in terms of treatment for Chronic Migraine?

M: I do support the concept that people should work with their routine doctor and that's what happens in healthcare; you do try medications first and if things work well, great, that's terrific for the patient. For the person who's developed really chronic disease, and I call it a disease because these people have serious health implications. They've tried a prophylactic medication and they still suffer so severely. Botox is another tool that the doctor has and whether it's the first, second, third or later option, it's certainly risen to the point of significant consideration in the treatment paradigm.

We do believe that we've demonstrated that among the choices a doctor has it's certainly in the top group to be considered. The ultimate customisation of treatment for a patient, what's best for the patient, that's made in the doctor's office.

L: Allergan recently moved away from an animal assay test to a cell based assay for batch release, an option which you mentioned incurred considerable costs to achieve. Why did Allergan chose to do that? Was this a business benefit lead decision or an ethical decision?

M: It wasn't business lead; it was the right thing to do.

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Quite frankly, what it came down to was it was the right thing to do, the reason I give the cost is to send the message that even though it cost a lot of money, we felt it was the right thing to do, and it's really the sign of a company that's willing to invest for something important.

As a matter of fact it is no cheaper to do the cell based assay for us because it's very advanced technology. The equipment is expensive, the training of the operators is expensive and performance of the testing is expensive. So it wasn't for business financial reasons.

Because we have this assay, we don't use mice for the drug release in those countries that the test is licensed. The assay took many years to develop, and is very specific and optimized to the Allergan Botox product and we are very proud of our breakthrough test.

L: We're now seeing a problem with counterfeit or copycat products, primarily from China. In the USA, you have the FDA who make a great effort to stop the unlicensed products actually coming in to the country. Some of your competitors have introduced new security measures in terms of their packaging to try and stop the counterfeiting. Is this a headache that Allergan is having to deal with too?

M: We're very committed to dealing with counterfeits and we spend a lot of energy on this.

We're engineering things into our packaging. We've got a hologram built into the vial. We train doctors to look for the hologram. On the crimp you're going to see the lot number. Look at the box carefully. If you pick up a box and something's different; did the company change it? If we were to change our box we would tell you. But if something doesn't look right or the vial just doesn't sit right, the colour of the caps is a little bit different etc, then the one thing we want the doctors to do is immediately call the company, whether it's in the USA or Europe or anywhere, we have interactions with the governments and as soon as we see something that isn't right we immediately report it. The governments are also very responsive because they see counterfeits as a major health concern.

L: Is there anything else that you'd like to share with UK clinicians?

M: I think one thing that we're very proud of is the quality attributes that are in our manufacturing, they're in our production and actually most importantly, in our people.

For example, looking back on our discussion about the cell based assay. We, as a company want to do the right thing and the right thing is asserted with purity of thought, we figure out where you get the most quality, the most positive impact and that's why we did the cell based assay.

"We, as a company want to do the right thing."

But that's also what we think about with our entire program, whether it's researching a drug, or our whole manufacturing process.

We have an excellent history with the regulatory agencies in terms of our manufacturing so that when people get the product they know there's a lot behind it. That's the sort of thing that when a doctor gets a drug they assume everything's okay and they don't think about all those checks and balances, all the work to ensure that the quality is of the highest level but that is so fundamental to the treatment of patients. You want to know that you're getting a quality product to treat your patients.

I'd like to thank Allergan and Dr. Brin for the opportunity to hold this interview. Anyone with specific questions about the content of this article should contact the Allergan Corporate Affairs & Public Relations Department on 01628 494444.

Lorna Jackson

Lorna has been Editor of The Consulting Room™, the UK's largest aesthetic information website, for a decade, since 2003.

She has become an industry commentator on a number of different areas related to the aesthetic industry, collating and evaluating statistics and writing feature articles, blogs, newsletters and reports for The Consulting Room™ and various consumer and trade publications, including *Aesthetic Medicine*, *Cosmetic News, Journal of Aesthetic Nursing* and *Aesthetic Dentistry Today.*

Lorna has also been asked to present at various industry events, including Smart Ideas, BACN and Merz Aesthetics Business Workshops and the FACE Conference.
