

## On the brink of a breakthrough <sup>[1]</sup>

### Discovery <sup>[2]</sup>

The darkest hour came just before the dawn for researchers investigating the potential of a promising new compound in treating a life-threatening muscle-wasting disease.

NIBR's Translational Medicine (TM) team was testing the drug bimagrumab in a small-scale trial with 14 patients suffering from sporadic inclusion body myositis (sIBM). A rare and untreatable disorder, sIBM mostly strikes people who are in their 60s. It weakens their arms and legs to the point where they may be unable to walk or even feed themselves.

Bimagrumab had performed well in animal testing and in human muscle samples, and the 'Proof of Concept' (PoC) trial was the chance to see how patients would respond.

PoCs are carried out in small numbers of patients, typically in a rare disease with a known molecular pathway but for which no effective treatment exists. Choosing well-defined diseases and homogeneous patient populations allows a rapid assessment of the potential impact of a medicine on patients. And at first glance, the data for bimagrumab looked discouraging.

Ronenn Roubenoff, NIBR's Global Translational Medicine Head for Musculoskeletal Diseases, recalls: "We had been so hopeful about bimagrumab at the pre-clinical stage and delivered the PoC in record time. But the analysts were pretty glum when they first saw the data. They had been looking for increased muscle strength and there just wasn't a big enough jump." Despite the initial optimism, it appeared that, as so often happens in development, another project would fall by the wayside after its first use in patients.

Thankfully, though, that wasn't the end of the story. Roubenoff, a physician-scientist who began specializing in muscle disorders in the mid-1980s, continues: "Strength is notoriously difficult to measure clinically. Traditionally, the way neurologists test strength is by having patients push against the doctor for one muscle at a time. This can lead to different results depending not only on how strong the patient is, but also how strong the doctor is! But when we took another look at the results for gait speed – how fast patients can walk four meters – then we saw major gains in every one of our subjects."

For Roubenoff, it was one of those precious moments in the life of any scientist when you've discovered something entirely new. "Gait speed is a huge predictor of survival, and we knew we were onto something very special – and potentially transformative," he says. "There are plenty of very good scientists who spend an entire career in pharmaceutical research and never get to see results as exciting as that."

## **Translating science into medicine**

The episode is a neat illustration of the role TM plays in drug development. Working at the intersection of basic science and clinical application, the group's physician-scientists use their

deep understanding of patients' medical needs – as Roubenoff says “what patients have to deal with day to day, what makes them feel ill and what makes them feel better” – to shape early clinical research so NIBR can evaluate drug candidates as fast as possible.

The success of this study would not have come unless NIBR had broken new ground by being the first pharmaceutical research organization to go beyond traditional tests of muscle strength in evaluating muscle-wasting treatments to look at function and performance. Says Roubenoff: “We introduced tests like the six-minute walk, gait speed and stair climbing, which have more meaning in the real world and are more reliable and more useful in assessing the effects of a muscle anabolic agent.”

This work also utilized an innovative device known as the Actibelt, a high-tech 3D-accelerometer hidden in a belt buckle that can measure accelerations during movement. NIBR used the Actibelt to quantify characteristics of movement and functional outcome in patients while they were going about their daily lives. The use of Actibelt provided further evidence of the real-world impact of the treatment on patients.

## Stepping up development

Following the PoC, the results of which were published in the December 2014 edition of the journal Neurology [3], the US Food and Drug Administration designated bimagrumab a ‘breakthrough therapy’ for sIBM. This designation was created to fast-track the development and regulatory review of new drugs for serious or life-threatening conditions.

Named after Bhima, the Hindu god of strength and stature, bimagrumab is an antibody that works by blocking signals to the drug target – the activin II receptor – which otherwise acts as a brake on muscle development.

In recent months, NIBR has stepped up work on bimagrumab with research in larger groups of sIBM patients. What’s more, trials have begun to explore the drug’s potential for treating a range of more common muscle-wasting conditions, including age-related sarcopenia and chronic obstructive pulmonary disease.

## Rare disease research

“Expansion into other diseases is typical of the Novartis strategy for drug development,” says Roubenoff. “When a PoC is successful, as it was with bimagrumab, we extend development to other diseases that share the same pathway. That’s how the discovery of a treatment for a rare disease can be a gateway to treating more common disorders.”

In fact, if its initial success continues, bimagrumab could be a game-changer. It is estimated that sarcopenia – loss of skeletal muscle mass and strength with aging – may affect 13% of those aged 60–70 and up to 50% of the over-80s [4]. The condition can lead to falls and injuries as well as loss of independence. Diet and exercise interventions can help, but only to a limited degree. If bimagrumab goes on gain approval as a therapy for sarcopenia, it has the potential to benefit many millions of people worldwide – including all those who go undiagnosed simply because there’s currently no viable treatment.

“Helping our ageing population maintain their quality of life for longer is an exhilarating

prospect,” says Roubenoff. “The chance of making an impact on that kind of scale – and in a timeframe of a couple of years rather than decades – is exactly why I first left my clinic and my academic lab for a job in translational medicine.”

## Translational Medicine at NIBR

NIBR’s global Translational Medicine (TM) group builds on basic research advances to develop new therapies that address unmet medical needs. Working at the intersection of basic science and clinical application, TM increases the speed, quality and productivity of drug discovery and development by Novartis and plays a pivotal role in bringing innovative medicines to patients.

NIBR has chosen to consolidate its TM expertise in a single global network of highly qualified scientists and clinicians working across diseases. This is unlike most other large pharmaceutical companies, which put a small group of translational medicine staff into each disease area or franchise. The NIBR model connects hundreds of TM specialists across six sites in Switzerland (Basel), the US (Cambridge, East Hanover and La Jolla) and China (Shanghai and Beijing).

Learn more about careers at NIBR.

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