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Letter from the Editor

A new look on nutrition

In the January 2013 issue of *MedNous* we featured an article about a new joint venture between Hutchison China MediTech Ltd of Hong Kong and Nestlé Health Science which is taking a botanical drug product for inflammatory bowel disease into clinical development. Nestlé Health Science was set up in January 2011 to explore the research area between nutrition and pharmaceuticals. The concept is to find out whether the chemistry behind food production can play a role in the prevention and treatment of disease. On page 23 of this issue, we explore the nutrition theme further with a profile of a small company in the Netherlands which is developing a combination anabolic steroid-vitamin D product to help elderly patients recover from a hip fracture. The company, OrgaNext Research BV, was founded by Marjanne Prins, a nutritionist by training, who spent more than two decades marketing fertility and contraception products at NV Organon. Organon was acquired by Schering-Plough Corp. in 2007, and two years later, the entire group was taken over by Merck & Co. Inc. Ms Prins left Organon to set up her company in 2009.

The OrgaNext compound, nandrolone decanoate and vitamin D3, is a fixed-combination medicinal product which is thought to have regenerative potential. Studies in human skeletal muscle cells taken from a young and an elderly donor have demonstrated that the combination stimulates the expression of cell receptors and causes a proliferation of satellite cells in the muscle, according to the company. The effect of the combination is greater than that for nandrolone decanoate alone, which has a history as a muscle enhancer. As a former marketing executive, Ms Prins can see the impact of an ageing population on government healthcare budgets. She therefore has targeted her candidate product for elderly patients who want to regain a modicum of independence after suffering from a hip fracture. The company has completed a Phase 2a study in healthy volunteers and is preparing for a second study. It will then move on to patients. If everything goes according to plan, it will seek to register the product in the US with the goal of launching it in 2017.

T-DM1

The FDA's approval of trastuzumab emtansine (T-DM1) for HER2-positive breast cancer in February is a milestone in drug development. T-DM1, now known by its commercial name Kadcyla, is the third antibody-drug conjugate to be approved by the agency, but only one of two currently on the market. Pfizer's Mylotarg was withdrawn in 2010. Seattle Genetics's Adcetris, approved in 2011, is the other authorised product. T-DM1 is the culmination of years of research by ImmunoGen Inc which developed the toxin-linker technology which underpins the new compound. In 2000, this technology was licensed to Genentech/Roche whose trastuzumab (Herceptin) antibody completes the compound. For a brief history of the T-DM1 development, please read our interview with ImmunoGen's John Lambert on page 11.

– By Victoria English, 7 April 2013

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Dutch start-up looks to stimulate muscle growth

The anabolic steroid nandrolone decanoate has had a colourful history. One of its early uses was to help bodybuilders grow muscles but it soon became a banned substance in sport. It has also been used, off-label, by people with HIV to counter muscle deterioration. Now a small company in the Netherlands is seeking to position nandrolone in the care of the elderly.

The company, OrgaNext Research BV, is developing a combination of the well-known anabolic steroid with vitamin D in order to help treat elderly patients with hip fractures. The expectation is that the treatment will stimulate muscle cell growth and help these patients recover some independence of function.

OrgaNext was founded in 2009 by Marjanne Prins, a former marketing executive at NV Organon, the Dutch contraception and fertility specialist. When Organon was acquired by Schering Plough Corp in 2007, and then the combined group was bought two years later by Merck & Co Inc, Ms Prins decided to set up on her own.

A nutritionist by training, she was particularly interested in how people lose muscle mass as they get older. People who are 75 years or more need twice as much protein as a healthy 25-year-old, she said in an interview with *MedNous*. If these same people are sick, they need almost four times as much. Ms Prins's initial idea was to create a company to make breakfast products for the elderly. This soon gave way to a more ambitious plan: to explore nandrolone decanoate as a regenerative medicine product for elderly patients suffering from a hip fracture.

Nandrolone decanoate (Deca Durabolin) was developed by Organon and first approved by the US Food and Drug Administration in 1962 for the management of the anaemia of renal insufficiency. Clinical studies in HIV patients in the 1990s gave convincing evidence that the steroid was effective in treating a type of muscle loss known as AIDS wasting^{1,2}. During this time, the drug was widely prescribed off-label to this HIV patient group. But for reasons not disclosed by the company, the drug was withdrawn from the market in 2002. The FDA subsequently issued a notice in the *Federal Register* stating that the withdrawal was not related to any safety or effectiveness issues. This paved the way for generic manufacturers to get approval to market the drug.

"Because nandrolone has a very high specificity and binds strongly to the androgen receptor in the muscle, but only very lightly to the androgen receptor in other tissues...we believed that it had a very good safety profile for the elderly," Ms Prins said in the interview. The big question was whether it should be investigated alone or in combination with another agent. Drawing on her nutritional background, Ms Prins knew that elderly people, particularly those who have been hospitalised, have very low levels of vitamin D, an essential element for bone health. Insufficient quantities of vitamin D have been associated with falls and bone fractures in the elderly.

Ms Prins and her collaborators therefore decided to test both nandrolone decanoate and vitamin D first separately and then together in commercially available human, skeletal

muscle cell lines from an elderly and a younger donor. The results of the tests were unexpected. They showed that not only did the nandrolone decanoate and vitamin D bind to the androgen and vitamin D receptors respectively, but they also stimulated expression in each other's receptors as well. Moreover the response in cells derived from the older donor was stronger than that from the younger one. Finally, the two agents had a synergistic effect on the proliferation of satellite cells in the muscle. These findings were presented to the annual meeting of the Endocrine Society in Boston, Massachusetts US in June 2011 and were also published in the society's journal *Endocrine Reviews* that same year. "We were so excited because it is a problem for the elderly to activate satellite cells in the muscle," Ms Prins commented.

Needless to say, OrgaNext is patenting its technology, and has been discussing its findings with regulators in both Europe and the US. The product will be evaluated as a fixed combination medicinal product, rather than as an advanced therapy medicinal product because there is no manipulation of cellular material.

The company has conducted one Phase 2a single-dose study in healthy volunteers and is preparing for a second multiple-dose study also in volunteers before moving on to patients. If approved, the OrgaNext product would probably be administered for a period of not more than six months. Assuming all goes according to plan the company will seek to register its product first in the US with the expectation of launching it in 2017.

The outcome that OrgaNext will be looking for is both growth of muscle and an improvement in the lives of the elderly. In this regard, it is working with the US National Institute on Aging on tests that would define clinically meaningful improvements. This would likely be a combination of tests, such as being able to get up from a chair or gain speed walking. The overall objective is to help the elderly gain some measure of independence.

The OrgaNext approach is one of many that seek to stimulate cell proliferation without actually using human cells as therapy. In the UK a small company called Progenitor Labs Ltd is seeking to discover small molecule drugs that could instruct human progenitor cells to generate cells to restore organ function. In March, the company received seed funding of £4 million from SR One, the venture capital arm of GlaxoSmithKline Plc. (Please see page 25).

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1. J. Gold et al, 'Safety and efficacy of nandrolone decanoate for treatment of wasting in patients with HIV infection', *AIDS*, 1996 Jun;10(7):745-52.
2. P. Sardar et al, 'Therapeutic effects of nandrolone and testosterone in adult male HIV patients with AIDS wasting syndrome: a randomized, double-blind, placebo-controlled trial', *HIV Clin Trials*, 2010 Jul-Aug;11(4):220-9.

MedNous interviewed Marjanne Prins by telephone on 27 March 2013.