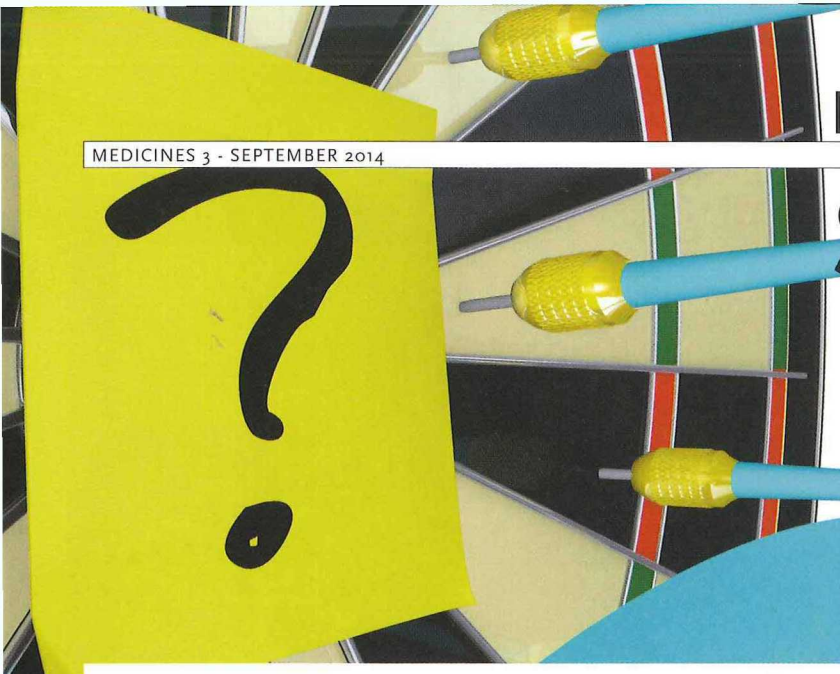

# Success in aiming off-target

**Statins may cause adverse effects such as muscle weakness. Tom Schirris identified a new off-target underlying statin-induced myopathies.**

SHURAILA STOPPEL

Statins are among the most widely prescribed drugs in western countries. By lowering cholesterol, they reduce the risk of major cardiovascular events. But like most pharmaceuticals, statins also have off-target effects causing adverse effects in patients. They are known to trigger muscle toxicity which could lead to myopathies.

"In general, my research, funded by ZonMW, focuses on the effects of pharmaceuticals on mitochondrial functioning to find new off-targets. While we are looking specifically for several classes of medicines I was recently successful in finding a new target for statins", says Tom Schirris. For four years now he has been working as a PhD student at the Centre for Systems Biology and Bioenergetics (CSBB) of the Radboud University Nijmegen. Any new drug target for which the drug was not initially designed, is a serious candidate to explain adverse effects.

## COLLABORATIONS

As part of the Nijmegen Center for Mitochondrial Disorders, the CSBB offered unique possibilities for Schirris's research on mitochondria. "This centre is specialised in working with mitochondria, all the facilities and knowledge for conducting experiments with these organelles are present here", Schirris explains.

The Dutch researcher started his quest for new targets by performing laboratory experiments on muscle toxicity. The effects of several different statins were investigated in C2C12 cells, a mouse myoblast model system. In this system, the PhD student was able to test a large set of different statins, in both their lactone prodrug and active acid form, in a high throughput-like manner.

Furthermore, colleagues from the Centre for Molecular and Biomolecular Informatics of the Radboud University developed a computer program called KRIPO (Key Representation of Interaction in POckets) that is able to describe protein interactions by a pharmacophore fingerprint-based method. "I was therefore able to combine computer-based predictions with laboratory experiments in a systems biology manner."

> 'A great deal of time went into validating the results'

Schirris and his fellow workers started feeding the KRIPO program with information about the binding pocket for statin molecules. The program produced a list of proteins that were expected to interact in the same way as the drug-pocket interaction. Using this as the basis, a detailed lab search for the specific enzyme began.

To demonstrate that specific mitochondrial enzymes were involved, Schirris performed experiments such as cytotoxicity assays and high-resolution respirometry to measure oxygen consumption. He also measured ATP production and enzyme activities of the respiratory complexes and found that statin lactones were more cytotoxic than acid forms.

To confirm the findings on muscle toxicity, Schirris turned to his colleagues from the university hospital. He explains: "A major advantage of working in a university medical centre is collaboration with the clinic." He determined mitochondrial respiratory enzyme activities in muscle biopsy samples from patients with statin-induced myopathies. Because these results were gathered in an additional and clinically relevant model system, the overall conclusions become more reliable.

## MITOCHONDRIA

All the testing eventually led to a new mitochondrial off-target for statins. Inhibition of this complex was experimentally verified in isolated bovine heart mitochondria, yet another model system. "A great deal of time went into validating the results because I wanted to be sure that they were valid." Schirris explains.

Schirris expects to publish this data within the next few months, allowing him to complete his thesis. The results obtained may lead to new therapies for counteracting the adverse effects of statins.

Tom Schirris is participating in the PhD student competition on Monday 6 October, at the FIGON Dutch Medicines Days.