

## New insights into how *Akkermansia muciniphila* improves metabolic health, leading to first human safety trial

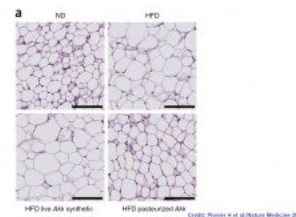
5 DEC 2016 | **Kristina Campbell** (<https://www.gutmicrobiotaforhealth.com/en/author/kristina-campbell/>)

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Previous studies (<http://www.gutmicrobiotaforhealth.com/en/akkermsia-as-a-target-for-obesity-authors-comment/>) have identified *Akkermansia muciniphila* as an important bacterium in metabolic health—able to prevent the development of obesity in animal models. Until now, however, its mechanisms were unclear and its effects had never been tested in humans.

Now, a team led by Patrice D. Cani (<http://www.ingutwetrust.org/>) of Université catholique de Louvain (UCL; Belgium) and Willem de Vos (<http://www.nwo.nl/en/research-and-results/programmes/spinoza+prize/spinoza+laureates/overview+in+alphabetical+order/willem+de+vos>) of Wageningen University (the Netherlands) published a paper in *Nature Medicine* (<http://www.nature.com/nm/journal/vaop/ncurrent/full/nm.4236.html>) showing that a pasteurized version of *A. muciniphila* was able to reduce fat mass development, insulin resistance, and dyslipidemia in mice; moreover, the pasteurized bacterium modulated both the host urinary metabolome and intestinal energy absorption. Researchers attributed these effects largely to a protein (called Amuc\_1100\*) isolated from the outer membrane of *A. muciniphila*, which appeared to interact with Toll-like receptor 2.



In the paper, the researchers also reported the first safety testing of *A. muciniphila* in 20 human subjects with excess body weight and metabolic syndrome; for three months, these individuals received either a placebo treatment, pasteurized *A. muciniphila*, or one of two doses of live *A. muciniphila*.

GMFH editors caught up with Patrice D. Cani to learn more about the significance of this work.

### Several bacterial species or consortia are under investigation for their beneficial effects in obesity and diabetes. Why is *Akkermansia muciniphila* unique?

*A. muciniphila* is unique in the field and potentially interesting as a next-generation bacteria because it resides in the mucus layer, a niche in close vicinity to host cells, but also because it displays beneficial effects on several pathologies. Numerous papers (<http://www.em-consulte.com/article/923265/alertePM>) have shown that the direct administration has proven protective not only against obesity but also against type 2 diabetes, gut barrier disturbances as well as atherosclerosis in various studies. Others have found more *A. muciniphila* in colon cancer ([http://online.reed.es/Revistas/REED\\_2015\\_107\\_11/Contenido/pdf/vol107num11\\_en\\_3.pdf](http://online.reed.es/Revistas/REED_2015_107_11/Contenido/pdf/vol107num11_en_3.pdf)) for instance, but we do believe that this is due to an opportunistic behavior: more mucus produced is more food for *A. muciniphila*.

Here in our paper we show that pasteurized *A. muciniphila* retains all the beneficial effects on metabolic parameters and is even more potent than the live bacteria.

### According to this new work, how was *A. muciniphila* able to exert these beneficial effects?

Unexpectedly, Hubert Plovier (PhD student in Cani's team) found that pasteurisation doubled the effectiveness of *A. muciniphila* which eventually prevented the development of the diseases.

The teams wanted to understand why *A. muciniphila* behaved differently when live and pasteurised, which led them to their second major discovery. Noora Ottman and Judith Klievink from the team of Willem de Vos isolated a protein present on the outer membrane of the bacterium. This protein also remains active (stable) after being heated to 70°C. Pasteurisation therefore likely eliminates anything that is unnecessary in the *A. muciniphila* bacterium and retains the protein, which probably explains its enhanced effectiveness. We produced the protein (Amuc\_1100\*) by genetic engineering and then tested it in mice. The results showed it was as effective on diabetes and obesity as pasteurised *A. muciniphila*.

The discovery of this protein is also really promising as it also has a positive impact on the immune system: it blocks the passage of toxins into the blood, reinforces the immune defences of the intestine, and ameliorates leaky gut syndrome, for instance. Thus, the Amuc\_1100\* protein provides hope for the treatment of other diseases such as inflammation of the intestine that appears, for instance, in cases of stress, alcoholism, liver diseases, and cancer.

Using the pasteurized bacteria or the active protein we have isolated circumvents the putative risk of using live *A. muciniphila* on damaged intestine.



### Short-chain fatty acids (SCFAs) have also been discussed in the context of obesity and diabetes. In this study, did you investigate whether they were affected by *A. muciniphila*?

It has been previously shown (<http://www.sciencedirect.com/science/article/pii/S0882401015301789>) by Willem de Vos that *A. muciniphila* produces SCFAs such as acetate and propionate and probably also contribute to reinforcing the gut barrier. But in this study because *A. muciniphila* was pasteurized we did not investigate this parameter.

### What's the next step in finding out whether these bacteria could improve human metabolic health?

Proof that the positive effects in mice also extend to humans still needs to be confirmed.

The clinical investigation is being carried out in the university clinics of Saint-Luc at UCL study Microbes4U (<http://www.microbes4u.be/>) since December 2015. The study is currently underway and we have just passed the first stage, namely proving that the use of the bacteria is safe and not dangerous for the humans that are obese and diabetic (more than 40 patients have been screened for safety).

### If *A. muciniphila* proves useful for achieving a long-lasting shift in the microbiota of humans, do you think complementary dietary strategies will be required?

We have to be careful and a lot of work still must be done. However, I do believe that body weight loss will be possible only if an adequate equilibrate nutrition is present (rich in prebiotics, polyphenols, omega 3...).

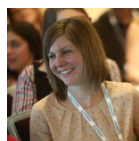
### In the years to come (and pending human trials), do you think this intervention could make a difference in the epidemic of obesity in developed countries?

We think that we have to be careful translating all the mouse results into humans. What we really hope is at least to improve metabolic parameters such as low-grade inflammation, glycemia, and cholesterol. If the administration of the bacteria, alive or pasteurized, may change body weight, that is of course interesting.

It is difficult to say that we will cure obesity by using only *A. muciniphila*; however, reducing cardiovascular risk factors or reducing specific markers will likely be the case.

### Reference:

Plovier H, Everard A, Druart C, et al. A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. ([http://www.nature.com/articles/nm.4236.epdf?shared\\_access\\_token=OV0R6bpDg3fRgy0XN1p9HNRgN0jAjWel9jnR3ZoTv0MNT5qpt\\_nTzfFwL9J5xic3enmGOOSXGKfLAXVC5RCYQlcOz89PD1iyEa4tje3fcRtf7CqZwxX9AyCqvMpiqqQA5jxfsNVnKb7YpCQomvi\\_3s0AccdBiWAb\\_OvH68IDm-k%3D](http://www.nature.com/articles/nm.4236.epdf?shared_access_token=OV0R6bpDg3fRgy0XN1p9HNRgN0jAjWel9jnR3ZoTv0MNT5qpt_nTzfFwL9J5xic3enmGOOSXGKfLAXVC5RCYQlcOz89PD1iyEa4tje3fcRtf7CqZwxX9AyCqvMpiqqQA5jxfsNVnKb7YpCQomvi_3s0AccdBiWAb_OvH68IDm-k%3D)) *Nature Medicine*. 2016. doi:10.1038/nm.4236



#### Kristina Campbell

Science writer Kristina Campbell (M.Sc.), from British Columbia (Canada), specializes in communicating about the gut microbiota, digestive health, and nutrition. Author of the best selling Well-Fed Microbiome Cookbook (<https://www.amazon.com/Well-Fed-Microbiome-Cookbook-Recipes-Repair/dp/1623157366>), her freelance work has appeared in publications around the world. Kristina joined the Gut Microbiota for Health publishing team in 2014. Find her on: Google (<https://plus.google.com/u/0/107897204860617720641/about>) • Twitter (<https://twitter.com/bykriscampbell>)

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