



# Research Highlight #304

David Alsteens, Ph.D.

Université Catholique de Louvain

## The Past, Present, and Future of Virology Research

Bioengineering is an interdisciplinary field focused on the development of tools that can be applied to different biological systems. David Alsteens, Ph.D., is a bioengineer whose work has a strong focus on nanotechnology. He uses his experience to quantify interactions at the single-molecule level and perform unprecedented high-resolution imaging of proteins, receptors, viruses, and cells.

### Interactions Between Viruses and Cell Surface Membranes

David did his master's and doctoral work at the Université catholique de Louvain (UCLouvain) in Belgium, where he was introduced to atomic force microscopy (AFM), which has been a prominent tool in his research to date. At the beginning, David used AFM to study the surface properties of bacterial cell walls and see how they were modified after incubation with different antimycobacterial drugs. He expanded on his use of AFM during his Ph.D., where he worked on the functionalization of probes to allow the detection of single molecules on the cell surface. These *in vivo* studies from 2007-2011 provided strong evidence that Wsc1, a major cell surface receptor protein, is capable of feeling mechanical forces acting either on the cell wall or on the plasma membrane. Following his schooling, he was offered jobs in both academia and industry, and decided he loved the freedom of research that academia provided. He elaborates on some of his more recent work in this sector that excites him;

"Human viruses can attach to cells. If we want to prevent infections in the future, one way is to block the virus directly during the attachment process. If you look at the drugs that are available against these interactions, there are not many options, but they always try to fight the replication of the virus. We at first tried to inhibit the replication of the virus after it had already infected the cell. But, I was thinking, can we try to block the virus and prevent the infection? I found that an atomic force microscope can be very nice because it allows you to attach an individual virus to a cantilever tip and then check directly how a virus binds to a cell surface membrane."

This work originated during a long-term EMBO fellowship at ETH Zurich, where he established both the experimental and theoretical framework required to map and probe virus-host interactions directly on living mammalian cells. This methodological platform enabled the quantitative characterization of molecular recognition events at the cell surface with unprecedented resolution.



### ABOUT THE RESEARCHER

David Alsteens, Ph.D., is the principal investigator for the NanoBiophysics Lab at the Université catholique de Louvain (UCLouvain) in Belgium within the Louvain Institute of Biomolecular Science and Technology (LIBST). He is a bioengineer who focuses on industrial applications using nanotechnology. His master's thesis at UCLouvain was "Organization of the mycobacterial cell wall: a nanoscale view." He completed his Ph.D. at UCLouvain as well, where his thesis was "Nanomechanics of the yeast cell wall," focusing on using AFM combined with genetic and cellular techniques to probe individual constituents of microbial cell walls. He has received multiple prestigious awards, including the Heinrich Emanuel Merck Award for Analytical Science and the BAEF Alumni Award in Biomedical Sciences.

### NanoBioPhysics Lab website:

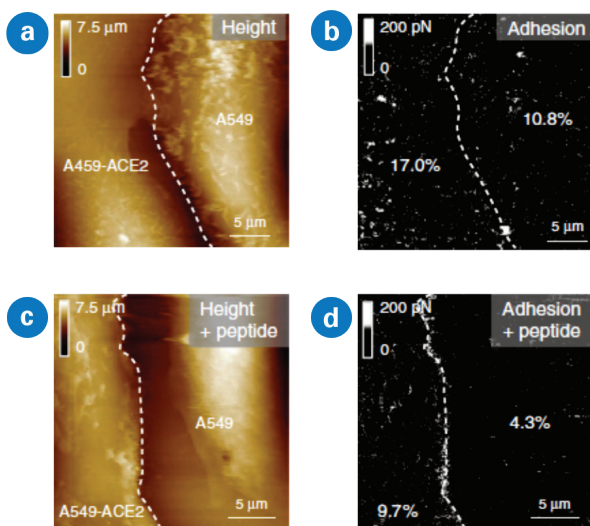
<https://www.nanobiophysicslab.be/>

Upon returning to Belgium in 2015 as a Research Associate of the Fonds National de la Recherche Scientifique (FNRS), David applied this approach to investigate the specific roles of viral attachment factors, with a particular focus on glycan-mediated interactions. His team demonstrated that glycol-clusters decorated with sialic acid can effectively inhibit infection by preventing viral engagement with the cell membrane. These findings challenge the previous assumption that early virus-cell interactions are largely nonspecific. Instead, their results reveal that these interactions are highly specific and can even trigger conformational changes in viral glycoproteins that facilitate host-cell entry.<sup>1</sup> This work provides new mechanistic insight into the earliest stages of infection and opens important perspectives for antiviral intervention.

### Pivoting Tools to COVID-19 Research

The last 10 years of research for David have strongly focused on viruses, and he found that his microscopy tools, imaging techniques, and research experience had him ready to study the coronavirus 2019 (COVID-19) as thousands of cases of infection swept the world:

“Two weeks before they decided to shut down everything, I started to launch research on COVID-19 and the interaction between the different receptors. We pushed forward with working on the virus during lockdown to achieve a fast comparison of ACE2 interactions and the different attachment factors. There are many things that are very interesting to see. For example, the virus envelope can mutate so fast and is even involved in the mechanism of the binding with host cell receptors. Our work has also shown that new attachment factors were able to block viral entry.”



Blocking of S1-subunit binding using ACE2-derived peptide on living cells. Force-distance (fd)-based AFM topography images (a, b) and the corresponding adhesion map (c, d). Repurposed from figure 5 in [2].



The inside of Bruker's NanoTracker 2 head, and a pipette adding one drop of buffer.

Atomic force microscopy and steered molecular dynamics simulation let the group explore SARS-CoV-2 receptor binding domain variants and the angiotensin-converting enzyme 2 (ACE2). His research using the single-molecule force spectroscopy technique suggested that vaccination before infection may provide stronger protection across variants.<sup>3</sup> Understanding the binding interface between the virus and human cell receptors has been the main focus of his research over the last year.

### Integration of Different Microscopy Techniques

David has countless publications and scientific insights that demonstrate his prowess in using different imaging and tracking techniques. These include cryo-electron microscopy (cryo-EM), fluorescence-based techniques, and biophysical approaches, such as optical tweezers and AFM.<sup>1</sup> When asked about what he wanted to work on in his lab next, he highlighted the potential of combining different microscopy techniques and improved replication of cells' native environments;

“We continuously develop and integrate new technologies in our lab and with our collaborators. This includes advanced hybrid approaches, such as combining microscopy with optical tweezers. A central objective of my research is to perform measurements as close as possible to physiological conditions. Rather than relying solely on simplified or artificial model systems, we prioritize experiments in living cells and biologically relevant contexts to ensure that the mechanisms we observe accurately reflect native cellular behavior.”

As a natural extension of this effort to work in more physiologically relevant systems, David and his team increasingly turn to organoids and tissue-like models, which better recapitulate the structural and functional complexity of native tissues. Studying organoids is a tricky task since it requires understanding the intricacies of cell cultures, but tools like Bruker's CellWizard stage offer automated large-scale mapping, high-resolution imaging, and nanomechanical analysis in each chamber.

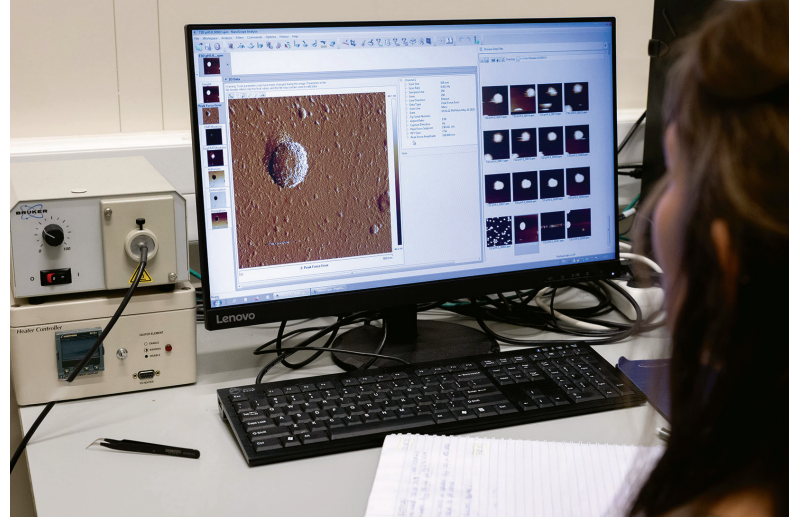
David and his team have recently started using this tool to probe tissues and organoids, holding great promise for their research and new projects.

### Securing Funding for Future Discoveries

David's position offers him the flexibility to launch his own research projects in virology or biophysics without having to worry about whether his work will be funded. However, this is one aspect of scientific research he would like to see change for others who are just getting started in their careers and also want to make meaningful contributions to the field. He mentions that researchers need to balance the risk between asking *easy* and *challenging* questions when applying for grants to demonstrate a likelihood of success, while also exploring new and exciting topics. He details what he would like to see changed for these younger scientists;

"I think as a researcher you should be able to automatically receive some money to do your research every year. I think this is something that we should trust a bit more in the future. A minimum amount of money every year to do research would be beneficial because competing for money creates an unhelpful cycle. Researchers need to provide proof of concept for their experiments, but to get this proof, you need money to do the experiments. It is very frustrating, and I would say that if we trust the researcher, we should give them the resources to work."

Scientific data is created through collaboration, hard work, and attention to detail, among many other factors. David believes that it can and should be more accessible for passionate and trustworthy scientists to more easily do the research they're interested in. This enthusiasm around research, specifically the use of nanotechnologies to explore the molecular and cellular biophysical properties driving different biological processes, continues to drive David's important and innovative work.



BioAFM is an important tool in Dr. Alsteens's lab for imaging and analyzing proteins, receptors, viruses, and cells at the single-molecule level.



David Alsteens and his lab members playing bubble soccer during a team-building activity.

## Learn More

Visit [bruker.com/bioafm](https://bruker.com/bioafm) to learn more about BioAFM, Bruker's NanoWizard AFMs, and the NanoTracker 2 Optical Tweezers system.

## Photo Credits

Images taken at UCLouvain courtesy of Yvan Flamant.

## References

1. Alsteens, D., et al. "Initial Step of Virus Entry: Virion Binding to Cell-Surface Glycans." *Annual Review of Virology* 7, no. Volume 7, 2020 (2020): 143–65. <https://doi.org/10.1146/annurev-virology-122019-070025>.
2. Alsteens, D., et al. "Molecular Interaction and Inhibition of SARS-CoV-2 Binding to the ACE2 Receptor." *Nature Communications* 11, no. 1 (2020): 4541. <https://doi.org/10.1038/s41467-020-18319-6>.
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