Obituary Huib Ovaa (1973-2020)

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Huib Ovaa (1973–2020)

With the untimely death of Huib Ovaa on May 19, 2020, we lost a bright star in chemical biology. Huib was an exceptionally creative investigator who inspired many and was a driving force in the field of chemical biology of the ubiquitin system. A synthetic organic chemist by training, boundaries between chemistry and biology ceased to exist for Huib, who flourished in environments (Harvard Medical School, the Netherlands Cancer Institute, and Leiden University Medical Center) dominated by biochemists, molecular biologists, cell biologists, and immunologists. Huib's accomplishments were recognized by his appointment to the Editorial Board of *Cell Chemical Biology* as well as by a number of international awards and are documented in more than 200 publications. This past summer Huib fell ill. While it first appeared as if he had contracted a relatively harmless infectious disease, it soon became apparent that he suffered from something far more serious. Huib faced his diagnosis with his characteristic optimism and courage, shielding those around him as much as possible from the burden of dealing with his cancer.

Huib got his start in chemistry as an undergraduate and subsequently as a graduate student at Leiden University. He obtained his doctorate in 2001 and graduated cum laude with his thesis entitled "Olefin metathesis in carbohydrate chemistry: synthetic applications." It was at this point that Huib made the bold decision to immerse himself in a biology-centered environment, through postdoctoral work at Harvard Medical School, where he fell in love with the ubiquitin system.

Protein ubiquitylation is an aspect of cell biology and human (patho)physiology that is of immense importance yet is incompletely understood because of its daunting complexity. Ubiquitin monomers are not only linked to a bewildering array of other proteins but also often assembled into "chains," typically with a specific lysine on one ubiquitin isopeptide-bonded to the C terminus of the next ubiquitin in the chain. The regulatory capacity depends on vast enzymatic systems of "writers" linking ubiquitin to other proteins or ubiquitins to each other, "readers" that bind specific ubiquitin moieties and thereby exert control over the functioning of ubiquitylated proteins, and "erasers" that deconjugate these modifiers. Adding to the complexity, there are numerous ubiquitin-like modifiers, with their associated writers-readers-erasers, adding to the richness of protein post-translational modifications. In the ~15 years that spanned his independent career, Huib established himself at the center of the ubiquitin field, and gave decisive impetus to new directions. His chemical toolkit to study the proteins that regulate ubiquitin and its close cousins has been instrumental to the research of many scientists and remains so today. It is a chemical toolkit that would not have seen the light without Huib's mastery of sophisticated organic chemistry.

When Huib began his postdoc at Harvard Medical School, the first steps toward the construction of probes that target ubiquitin-specific proteases had been made. Noncovalent interactions with ubiquitin could direct an electrophilic warhead at ubiquitin's C terminus to capture the catalytic cysteine of deubiquitylating enzymes. Huib immediately recognized the need for improvement in the production of these tools. Without facile access to various ubiquitin electrophiles, identification of modified targets by mass spectroscopy would be an uphill climb. Huib quickly eliminated preparative roadblocks, designed elegant and efficient new chemistries, and by doing so expanded the series to ubiquitin-like proteins including SUMO and NEDD8. These "activity-based deubiquitinase probes" enabled the de-orphaning of many deconjugating "eraser" enzymes predicted to act on ubiquitin and ubiquitin-like protein adducts. It also led to discovery of new ones, including ubiquitin-specific proteases of a completely new family, found in herpesviruses. His postdoc period exposed Huib to many aspects of molecular immunology, a topic that fascinated him because from a chemical perspective—with the possible exception of the deployment of proteasome inhibitors (which block production of antigenic peptides)—this field was almost virgin territory. He not only made important additional discoveries of the proteasome itself, but he learned enough about the properties of the major histocompatibility antigen (MHC) products to contribute to this field throughout his independent career. Among his early accomplishments after becoming an independent Group Leader at the Netherlands Cancer Institute (NKI-AVL) in 2004, Huib's lab devised a strategy that yielded a much more straightforward route to the production of MHC tetramers, which are essential tools to immunologists worldwide. By introducing UV-cleavable groups in the MHC-bound peptides to create conditional MHC ligands, the number of peptide-loaded MHC tetramers could now be easily expanded to test many MHC-bound peptides for corresponding T cell reactivities.

Huib Ovaa

As an independent investigator, Huib made contributions to a variety of topics in organic chemistry, medicinal chemistry, and chemical biology, but he will be best remembered for his preoccupation with ubiquitin. Huib's vision was that a "ubiquitin toolkit" as he called it, capable of chemically modulating every potential facet of this fascinating protein, would be a driver for unearthing a treasure trove of crucial cellular regulatory pathways and

mechanisms. Over the last decade, Huib's lab designed and synthesized an enormous array of differently linked polymers of two or three ubiquitins and essentially the entire ubiquitin family. As a chemist, Huib derived great satisfaction from synthesizing such large molecules. The true creative genius of the Ovaa lab ubiquitin chemistry is in the seemingly infinite ways that synthetic ubiquitin-based probes can be designed. Huib's lab has opened the door to interrogating ubiquitin chains that are known to exist but are largely intractable because their readers, writers, and erasers are unknown. True to Huib's original vision—and to the ubiquitin field's great delight—the lab's collaborative studies revealed and continue to reveal surprising new aspects of the ubiquitin system.

The Ovaa ubiquitin toolkit also served as a starting point for new scientific quests. In this vein, Huib discovered a reaction that was not supposed to occur. In an attempt to generate triazole-linked ubiquitin conjugates, he found that the catalytic cysteine thiol in the active site of a ubiquitin-specific protease could react with a C-terminal alkyne installed at ubiquitin's C terminus. Just as remarkable as the chemistry, from the perspective of the ubiquitin field, the particular ubiquitin probe synthesized—ubiquitin with the C-terminal carboxylate replaced with an alkyne—proves to act as the most active and most broadly reactive ubiquitin-based probe so far. It will be exciting to see (and first studies from the Ovaa lab point in this direction) whether probes equipped with an alkyne that target other cysteine proteases (cathepsins, caspases) will be equally effective and whether such molecules may actually, as Huib hoped they would, become the basis for new therapeutic agents.

Having established a comprehensive toolkit to study ubiquitin "erasers," Huib's lab in recent years took on the challenge to design probes for ubiquitin "readers" and "writers." His innovative chemical tracking of ubiquitin through E1-E2-E3 cascades in living cells—analogous to lineage tracing using genetic markers—has enormous potential. The elegant chemistries designed for this purpose once again show Huib's ingenuity. Huib passed away knowing that his lab was on target for groundbreaking work, putting the discovery and further development of E3 ligase probes within reach.

We knew Huib in different capacities—mentor, colleague, competitor, collaborator—and each of us came to know different facets of his multidimensional personality. Huib was a brilliant scientist, but above all else he was a friend. Huib lived for his work and enjoyed his life to the fullest. He radiated passion and enthusiasm, and those who were the beneficiaries of these traits were enlivened by it. He loved research and was wholly dedicated to the people he worked with. He selected his scientific partners with care and devoted himself and his research group to them unconditionally. He maintained high standards for his students and postdoctoral researchers, for whom he would walk through fire to support. Huib took pride in his achievements, but perhaps his greatest source of pride was the people in his group. He was a wonderful, inspiring, genuine, open-minded, and loyal colleague whom we will miss dearly.

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