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► **To cite this version:**

Jean-luc Pellequer, Eric Westhof. Marc van Regenmortel, personal recollections on a forward-thinking editor. *Journal of Molecular Recognition*, 2024, pp.e3080. 10.1002/jmr.3080 . hal-04489583

HAL Id: hal-04489583

<https://hal.science/hal-04489583>

Submitted on 5 Mar 2024

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REVIEW

Marc van Regenmortel, personal recollections on a forward-thinking editor

Jean-Luc Pellequer¹  | Eric Westhof² 

¹Univ. Grenoble Alpes, CEA, CNRS, IBS, Grenoble, France

²Architecture et Réactivité de l'ARN, Université de Strasbourg, Institut de biologie moléculaire et cellulaire du CNRS, Strasbourg, France

Correspondence

Eric Westhof, Architecture et Réactivité de l'ARN, Université de Strasbourg, Institut de biologie moléculaire et cellulaire du CNRS, F-67084 Strasbourg, France.

Email: e.westhof@ibmc-cnrs.unistra.fr

Abstract

Marc van Regenmortel was the Editor-in-Chief of the Journal of Molecular Recognition for the last 25 years. Without attempting to summarize Marc's exceptional career and achievements, we would like to tell the story of the tortuous and contingent path to the unravelling of a key molecular recognition process in antigenicity. Life is indeed full of contingencies and scientific life, full of meetings and random encounters, is prone to contingencies, a key element in discovery and innovation.

KEYWORDS

antigenicity, B-factor, epitope, mobility

Marc van Regenmortel's career in virology started in Schaarbeek, a neighborhood of Brussels, where he was born. It just happens that one of the authors (EW) was born in Uccle, another neighborhood of Brussels. Marc went to school in the nearby "Athénée Robert Catteau" where an impressive curriculum was taught (6 languages besides mathematics and sciences, history, and geography), a feat that would be difficult to achieve nowadays ... Then, the choice for the next step, the University, had to be made. Marc wanted to study microbiology and virology.

In 1946, Marc was infected by the polio virus (a strain imported to Belgium by the American soldiers...) without much consequence except that it allowed him to skip military service and, most importantly, Marc had been intellectually inoculated by the science of Virology. He was fascinated by antiviral immune responses that had saved him from paralysis. This also led him to choose a *Master in Agriculture* where both microbiology and virology were taught.

After hesitating between Canada, the Belgian Congo, and South Africa, Marc picked South Africa, considering that Afrikaans are close enough to Flemish to manage there and study. Marc did his PhD at the University of Cape Town with Alfred Polson, a renowned biophysicist, who had worked with The Svedberg and Arne Tiselius in Uppsala before the war. Alfred Polson was working on polio for which the possibility of obtaining 1 mg of virus was a major challenge. He was therefore extremely happy when Marc brought to the

laboratory tens of grams of plant viruses! Biophysical methods have always been very demanding on the amount of material (until recent years).

Marc then moved for almost 2 years to the Mecca of American virology in Berkeley, as an International Fellow in the US Public Health Service, within the laboratory of Wendell Stanley who had crystallized Tobacco Mosaic virus (TMV).¹ This started a 20 year-long love story with TMV and immunology. Quickly afterwards, Marc obtained professorships in Stellenbosch first, then at Cape Town, and, after a sabbatical stay in Strasbourg, in 1978 he joined the Centre National de la Recherche Scientifique (CNRS) and the Institute of Molecular and Cellular Biology (IBMC) in Strasbourg to succeed Léon Hirth and run the Immunochemistry laboratory. In Strasbourg, Marc started working on peptides and cyclosporine. In 2001 he became an Emeritus CNRS Research Director in Strasbourg.

In 1981, one of us (EW) left a post-doctoral stay in the United States to join the same Institute with an EMBO fellowship to work on x-ray crystallography of transfer RNAs with Dino Moras and Jean-Pierre Ebel. The laboratory had managed to obtain computers and graphic stations to work on the structures of tRNAs and their complexes using x-ray crystallography.

Marc had sent to the lab a bright young scientist Danièle Altschuh to analyze the structural characteristics of the main epitopes she had identified using synthetic peptides able to displace the whole antigen

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from the antibodies. For this, they had selected some available crystallized and refined proteins including, naturally, the TMV monomer.² In those times, the set of solved and refined protein structures was very restricted (less than a dozen). One of us (EW) helped her to color the epitope residues on the graphic screen and look at the results. Soon, it became clear that she was losing her time. A plot of the B-factors or thermal factors as a function of residue numbers gives the regions with high mobility or disorder (high B-factors). Surprisingly, all the epitope residue numbers that Danièle had identified fell on peaks of high B-factors. This meant that the main epitopes of those proteins were all in regions with high mobility and poor structural characterizations. With the plots, she left to see Marc. In a couple of weeks, Marc had written a paper with Aaron Klug, whom he knew well because he had completed his PhD in Physics in Cape Town University, and from which he had received the refined TMV coordinates.³

That manuscript was later accepted by *Nature*⁴ and became a source of many controversies and heated discussions at meetings. Very often those in favor were arguing with those opposed because they stuck to a rigid lock-and-key concept forgetting the dynamical pathways prior to the formation of the final complex. Marc explained to me at length, first, that it was a correlation and not causality and, secondly, the differences between antigenicity and immunogenicity. But the phenomenon is a fascinating aspect of the molecular dynamics in the recognition processes. On this point, I noted back then a quote that Marc quipped during a dinner: “*Structure–function, infernal couple, dissociates every microsecond.*”

These experimental results that led to the correlation between segmental mobility and antigenic sites would not have been possible without key scientific technological developments. First, the structure refinement and visualization programs of large macromolecules linked to computer technology. But also, the chemical synthesis of peptides that Marc and his team at the IBMC had developed very early for the study of antigenicity and the production of monoclonal antibodies. In the team, Jean Neimark and Jean-Paul Briand invented and built in 1985 an automatic multisynthesizer of peptides in solid phase⁵ and in 1986 created a company Neosystem to sell peptides around the world. In recognition of these achievements, the team received a French Team Research Grand Prize in 1993. The company renamed *Polypeptide Laboratories France SAS*, is now world leader in the production of peptides for medicine. As Jean Neimark wrote to one of us (EW) recently, “*without the openness of mind, the trust, and the constant support of Marc, we would not have achieved this.*” A sentence from S. Brenner⁶ comes to mind: “*Progress in science depends on new techniques, new discoveries and new ideas, probably in that order.*”

Marc regularly stresses the use of the proper words for describing without mental bias scientific observations, points to misleading perceptions and reasoning (correlation vs. causality) and loves telling stories about scientific discoveries and the tortuous pathways leading to them, sometimes based on false premises. As mentioned above, the 1984 *Nature* article was not readily accepted. A similar study on another protein, myohaemerythrin, reached the same conclusion a couple of months later⁷: “*Mobility is a major factor in the recognition of the native protein by anti-peptide antibodies.*” The year after its

publication, Marc published an article⁸ with warning cautions: “*Attempts to elucidate the so-called ‘complete’ antigenic structure of a protein are bound to fail if only one experimental approach is followed. (...) Antigenicity therefore depends on the criteria used to define it. Our results clearly illustrate the operational nature of any definition of antigenicity and caution against the use of any single criterion for differentiating between antigenic and non-antigenic regions in a protein.*” In 1985 an extensive analysis of the various intrinsic and extrinsic factors contributing to antigenicity appeared.⁹ One of these was the correlation between mobility and antigenicity which was incorporated into several programs aiming at predicting epitopes of a protein on the sole basis of its three-dimensional structure.¹⁰

Contingencies or serendipity led one of us (JLP) to meet Marc Van Regenmortel during the last year of his master's degree in 1989. Without a clear strategic career plan, but clearly attracted by computational work in biology, I was directed to talk to EW. Fate decided that I could pursue my interest by sitting in the office of the Immunology laboratory headed by Marc at the IBMC. As mentioned above, in the 1980s the production of synthetic peptides led immunology to enter into the “rational design” of peptide-based vaccines. The strategy was luminous, it would not be necessary to prepare a vaccine from live biological material, but instead by some short synthetic version of proteins to elicit an immune response and protect the organism against an infection of the cognate live and infectious target molecule.

Marc Van Regenmortel's pioneering work on the characterization of epitopes led to a relational concept that describes the surface of a protein target capable of binding antibody paratopes. Such a fundamental endeavor was performed on the well-known model system, TMV. The laboratory produced monoclonal and polyclonal antibodies raised against TMV, and a phenomenological classification of epitopes (metatope, cryptotope, neotope) was very insightful in both immunology and structural biology. A peptide-based vaccine required a different definition of epitopes, that is, the distinction between continuous and discontinuous (also known as conformational) epitopes. Although some research focused on the topic of “discontinuous” synthetic peptides, the combination of several small continuous epitopes linked by amino acid spacers, most synthetic-based vaccine strategies in the 1980s and 1990s relied on continuous epitopes. The Holy Grail was simply to find these continuous epitopes in proteins of interest.

It was the scientific initiation of one of us (JLP) to enter the realm of epitope prediction. The first task in Marc's laboratory was a fundamental scientific practice that still guides my current research: standardization. In the 1980s several authors published numerous strategies for predicting the location of continuous epitopes in proteins. As with novel advances in the research field, a lack of uniformity was evident and made the practice of epitope prediction very unreliable. As a starting activity, I was instructed to wander through the library and collect experimental data on the epitopes discovered. Again, the insight of Marc's tutoring was crucial, enforcing the quality rather than the quantity of data. Functional cross-reactivity was the key parameter for epitope selection, a direct consequence of the peptide-based vaccine strategy.

By current standards, the continuous epitope database was meager with 11 proteins and 66 epitopes¹⁰ and was marginally extended to 14 proteins and 82 epitopes by the end of the analysis.¹¹ Nevertheless, this small database was the starting point for the PhD work of one of us (JLP). The first PhD project was to write a new computer program that would be able to test existing epitope prediction methods against a validated epitope database. The guidelines from the second thesis director (EW) were very clear: the program should be extremely user-friendly and robust. So PREDITOP was created¹² and was in demand for several years beyond PhD graduation. Both researchers and industry, especially suppliers of synthetic peptides, used the program. A rejuvenated version, BEPITOPE, was made almost 10 years later to include modern options such as printing capabilities and searching for motifs in proteins.¹³

Commitments of one of us (JLP) to my new employer sent me on another scientific challenge where epitope prediction became a source of personal satisfaction, a rare feeling in modern research. However, the revival of BEPITOPE triggered an unexpected contact from the National Institute of Allergy and Infectious Diseases (NIAID) to participate in the “*IEDB Tool Analysis Workshop*” on November 4, 2005, in Bethesda, Maryland, USA, for a project hosted by the La Jolla Institute for Allergy and Immunology. It was another opportunity to meet Marc at Baltimore/Washington International airport. The peculiarity of this jamboree was the emphasis on standardization of prediction methods as described by the NIAID: to agree on a set of metrics that can be used to validate tools and as test sets for the Immune Epitope Database (IEDB). The adventure continued for a full year until the final “*Antibody Epitope Prediction Tool Evaluation Workshop*,” which was held on September 7–8 (2006) at Washington, D.C.; another opportunity to meet with Marc, this time on the tarmac at Dulles airport. The *Journal of Molecular Recognition* was instrumental in publishing a highly cited collective review¹⁴ describing the requested metrics to be used in testing novel B-cell epitope prediction methods.

Serendipity struck again when the career of one of us (JLP) turned to biophysics and atomic force microscopy. With absolutely no experience or knowledge in the field of Atomic Force Microscopy (AFM), I remembered the story of my second PhD project under Marc's supervision, which involved measuring the binding affinity between antibodies and antigens using what was a completely novel technology: the Surface Plasmon Resonance BIAcore. One of Marc's long-term career activities was to be able to precisely measure the binding affinity between antigens and antibodies. This goal was partially achieved with the help of a brilliant PhD student: Agnès Azimzadeh¹⁵ who tutored me in this technique. The knowledge developed in Marc's laboratory attracted the Swedish company Pharmacia, which used its historical expertise with dextran molecules, to serve as beta testers of its automated instrument for measuring not only equilibrium binding constants but also more importantly, kinetic binding constants. It has been one of my very short attempts in experiments in my career for which I am grateful for the help of Danièle Altschuh and Gabrielle Zeder.

From this experience, one of us (JLP) tried to reproduce the protocol and in 2006 contacts were made with an AFM manufacturer, named Veeco (now Bruker). However, the need was different. Rather

than a need to test a novel instrument, we were more limited in the knowledge of all their potential capabilities. Physicists mostly trusted the field of AFM and there is no offense in saying that we often spoke a different language. To bridge the gap between physicists and biologists, one of us (JLP) with the help of Pierre Parot founded AFM-BioMed, a non-profit organization dedicated to organizing conferences and summer schools for students and researchers in the life sciences. A full account of this story can be found here.¹⁶ This personal digression into AFM simply introduces another interaction with Marc Van Regenmortel as Editor-in-Chief of the *Journal of Molecular Recognition*. At the first international AFMBioMed conference held in Barcelona in 2007, the proceedings were published in the *Journal of Molecular Recognition*^{17,18} with enthusiastic support from Martin Rothlisberger, Executive Commissioning Editor, and Marc. Since 2007, every AFMBioMed conference has published its proceedings in the *Journal of Molecular Recognition*. In addition, Martin suggested that Wiley support young scientists with some bursaries, a practice that continues today.

One of Marc Van Regenmortel's most impressive gifts was his ability to memorize scientific literature. Even experienced researchers and collaborators in the laboratory were constantly referring to this gift, a tantalizing model for a young researcher. Such a powerful background made philosophical discussions with Marc a particular delight, even for a “grasshopper.” His eloquence and perfect writing style led to the production of numerous books and book chapters, including productions with his long-term involvement in the International Committee on Taxonomy of Viruses. It is therefore not surprising that Marc was Editor-in-Chief for such a long time. Marc was a strong proponent of publishing data in a relevant journal of the field, a traditional practice of an “old age” in complete divergence with modern quantitative-driven publication strategies. Retrospectively, reading and writing were one of the most important lessons of my time in Marc's laboratory. Although writing will be done better than our wildest dreams with “Artificial Intelligence,” reading will remain a peculiarity of *Homo sapiens*, but for how long?

AUTHOR CONTRIBUTIONS

Both EW and JLP contributed to the writing of this article.

ACKNOWLEDGMENTS

We thank Rebecca C. Wade for helpful suggestions. IBS acknowledges integration into the Interdisciplinary Research Institute of Grenoble (IRIG, CEA).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The manuscript does not contain new data.

ORCID

Jean-Luc Pellequer  <https://orcid.org/0000-0002-8944-2715>

Eric Westhof  <https://orcid.org/0000-0002-6172-5422>

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How to cite this article: Pellequer J-L, Westhof E. Marc van Regenmortel, personal recollections on a forward-thinking editor. *J Mol Recognit*. 2024;e3080. doi:[10.1002/jmr.3080](https://doi.org/10.1002/jmr.3080)