

Interview

Dr Vincent de Groot speaks to James Eslea MacDonald,
Programme Director for *World ADC Summit Europe*,
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Dr Vincent de Groot
Chief Executive Officer
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Dr. de Groot (M.Sc. Organic Chemistry; Radboud University Nijmegen, The Netherlands, University of Bologna, Italy, and University of Perugia, Italy) obtained his Ph.D. degree cum laude from the Radboud University Nijmegen (Department of Organic Chemistry). He published more than a dozen scientific papers and review articles in established journals and is inventor and (co-)author of several patents and patent applications. Dr. de Groot won several awards, among which 'the International Henny C. Dirven Breast Cancer Research Award 2003', 'the International DSM Award for Chemistry and Technology 2003', 'the KNCV - Dr. H.J. Backer Organic Chemistry Award 2002', 'the Dutch Pharmacochimistry Award 2002', and the 'Organon Young Research Talent Award 1997'. He is a member of the American Association for Cancer Research (AACR), the American Chemical Society (ACS) and the Licensing Executives Society (LES). Dr. de Groot has received the Certified Licensing Professional (CLP) credential from LES.

What in your opinion has progressed the field most in the past 5 years?

The clinical data that has been produced over the past 5 years with a number of ADC product candidates, I feel, is responsible for the ever growing momentum in this field. I think that results of T-DM1 and SGN-35, based on Immunogen and Seattle Genetics' technologies, illustrate the progress of the field and moreover emphasize not only the power of antibodies but also the capability of a linker-drug to change the biological profile of the antibody.

It is these clinical data that has emphasized the progress that has been made to make the point that this type of technology has come to maturity. The level of efficacy that is observed in the clinic has certainly boosted interest in the field.

What in your mind is the most exciting project you're currently working on?

As Syntarga is moving towards a business model in which we aim to develop real products, I think one of our challenging current tasks is to determine which linker-drug we will select for GMP manufacturing. At Syntarga we have the luxury of having many different linker-drug structures that perform very well while having significant molecular diversity. In the long run I believe that this gives us an advantage because we can really tailor the best linker-drug for a certain biological setting.

For now, this poses a challenge for us in terms of having to select one of these linker-drugs to progress to GMP level, make that investment decision and being confident at the same time, that it can be part of many different ADC products - which would also include our own first ADC product. Another challenge that we are working at is to choose an antibody to take forward into development. We are sourcing many different antibody

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opportunities for either in-licensing or for co-development.

It's widely acknowledged that ADCs are not easy to develop, why do you think this is?

There are several reasons for this. Every aspect of an ADC is relevant, every component that you put in an ADC is relevant for the profile of that ADC molecule and I think that there is no aspect that one can take for granted.

An ADC brings together so many elements from different fields and all of those fields need to contribute to an effective product that it is also the right product within the competitive landscape. It is these multi-dimensional aspects that need to be understood that drive the complexity to be able to make the best choices. People from each discipline will have to get the best possible understanding of the other disciplines in order to make the best ADC molecules. ADC is a field where there is a level of complexity that creates many opportunities for the industry to get a share of the market. This complexity allows companies to excel. I think that competition will get tougher as the field grows and that's what makes the field exciting to work in.

What new technologies do you think are set to impact on ADC drug development?

One perspective of the ADC field is that it is in its infancy. And that we are only beginning to understand what it takes to develop a top class ADC. Undoubtedly, more activities can be expected in the areas of target discovery and technology development to enable more effective screening of antibody

libraries for ADC.

Importantly, also linker-drug technology is going to continue to drive development in this field. A lot of progress has been made recently, for example, cleavable vs non-cleavable linkers and new toxins with a novel mechanism of action. DNA-interacting ADCs as developed by Pfizer, BMS, and also Syntarga, can yield ADC products that are complimentary to tubulin-interacting ADCs. There will be more cash invested in linker-drug discovery and I think that this will help to yield ADCs that have the right biological performance. If you have two linker-drugs that are only very slightly different in their molecular structure, they can still yield a difference of day and night in terms of the biological profile of the corresponding antibody-drug conjugate.

Linker-drugs can provide applicability to ADCs in a broad fashion. For this reason, modularity of linker-drug technology is, we believe, a highly desirable aspect. There are many properties of the ADC molecule that can really be determined by the choice of the linker-drug and I think that this also goes beyond some obvious aspects such as potency and safety. The structure of the linker-drug can also tune other aspects, such as drug metabolism, multi-drug resistance susceptibility, and the pharmacokinetic properties of the ADC.

Moreover, the exact linker-drug chemistry can determine the kinetics of release of the active species and with that one could tune the extent to which the toxin from the ADC is released in an intracellular environment vs an extracellular environment. This may have an impact on the types

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of target that one can address with an ADC. High sophistication of linker-drug technology does not have to come at the cost of molecular complexity. Molecules can still be structurally as simple as they are nowadays but it's a matter of developing that understanding.

What impact would a market approved ADC have on the sector?

The impact of an ADC on the market will be significant, assuming that the ADC has a high therapeutic window. I think that with ADCs reaching the market with the pronounced clinical trial results that we have seen to date, the entire community will embrace ADCs much more strongly. It will make development of ADCs easier, help the field become more accepted by physicians and for example make patient recruitment easier.

There are multiple ADC candidates close to the market now and reaching the market I suspect will trigger further investments by big pharma and investors. More companies will start working on the approach, not only the bigger companies but also mid-sized companies will jump on the bandwagon and develop ADC products addressing niche targets for smaller patient populations.

How do you see the therapeutic antibody oncology field changing in response to this over the next ten years?

In many therapeutic settings naked antibodies simply cannot do the job. We will see as a consequence fewer naked antibodies reaching the market in the oncology field. The percentage of next generation antibodies will

increase significantly and I think with a very prominent role for ADCs, next to other approaches such as for example sugar-modified antibodies or bispecific antibodies. Target discovery will continue to change with more investment shifted towards the discovery of targets that are not only tumour specific but that can also be functionally addressed.

For ADCs, I expect an ever-continuing race for the best targets, antibodies, linkers and toxins as well as for the best combinations of all these aspects. New antibody formats that allow for site-specific coupling show a great deal of promise, potentially impacting safety and manufacturing in a positive way, although this promise still needs to be realised in the clinic.

Other types of antibody engineering can also help to improve ADC properties such as immunogenicity, aggregation, PK properties, circulation half-life and ADC stability. All ADCs that reach the market can only do so because they also contain an excellent linker-drug and I think it is clear that not only Syntarga, but all payload technology companies have constantly continued to discover next-generation linker-drug molecules. The quest for new technologies will continue, as there will be a growing need in the industry to fill pipelines with ADCs that can compete in the future.

Vincent will be sharing his experiences in the development of ADC technology at the World ADC Summit Europe taking place in Frankfurt, Germany, 21st-23rd February 2011.