Opening the door to innovation

Janine Schuurman, Yvo F Graus, Aran F Labrijn, Sigrid R Ruuls, and Paul WHI Parren*
Genmab; Utrecht, The Netherlands

Open innovation is the new buzz, with initiatives popping up left and right. Here, we give a personal perspective on a very successful, knowledge-driven innovation initiated in an academia-industry alliance, which culminated in technology platforms that enable the generation of therapeutic antibodies with novel properties. To start, we provide a general background on open innovation in the drug development field.

"Applied scientist seeks academic partner for an innovative encounter and possibly more. Future drug development not excluded."

Soon Coming to a Pharma Near You...

Drug development requires multi-billion dollar investments in research and development (R&D). Bringing a new drug to the market is estimated to have a $1.8 billion price tag, or multiples thereof when taking drug failures into account.1-3 With costs soaring, the number of US Food and Drug Administration (FDA)-approved drugs per dollar spent steadily declined between the 1950s and 2010s.4,5 Several factors may have contributed to this apparent decrease in productivity, such as an increased regulatory focus on patient safety and cost-benefit, limited potential to develop improved products over existing treatments in increasingly crowded markets, and pressures to reduce internal research efforts as a result of downsizing, mergers and acquisitions.6,8 Large organizations furthermore often suffer from a lack of innovative power due to excessive bureaucracy and hierarchy, as well as slow decision-making combined with a low risk-appetite.

The pharmaceutical industry traditionally was locked into “not-invented-here” thinking, and therefore strongly relied on internal innovation. Yet, it has recently begun to seriously consider external innovation with biotechnology companies and academia. By accepting the notion that revolutionary discoveries were often “invented-there” anyway, the industry cracked the door to open innovation. This concept teaches that both internal and external ideas and resources may be, and should be, exploited to generate new drugs. Open innovation can be applied to all stages of drug discovery and development,7 in which the traditional boundaries between companies and academia are proactively being erased. Interestingly, common approaches to internalize new product opportunities are being integrated with novel innovation strategies leveraging knowledge and competences from academia and biotech in various ways (see BOX 1 and Fig. 1).

It is now clear that new drug development dictates close interaction between large Pharma, biotech and academic research centers. Combining ideas, technologies, capabilities, assets and complementary knowledge is required to enable the successful translation of scientific concepts into products or technologies.8,9 In the past 3 y, new product approvals by the FDA have again been on the increase.4,10 In antibody therapeutics, a novel generation of products is on its way, many of

Keywords: Open innovation, immunotherapy, Fab-arm exchange, bispecific antibodies, DuoBody technology, drug development, technology platform

*Correspondence to: Paul WHI Parren; Email: p.parren@genmab.com
Submitted: 04/23/2014
Accepted: 04/23/2014
Published Online: 04/24/2014
http://dx.doi.org/10.4161/mabs.29004

mAbs 6:4, 812–819; July/August 2014 © 2014 Landes Bioscience
which encompass new therapeutic concepts.9,11 This may provide the first sign of an increased output from the observed shift in R&D approaches and the positive effects of the intensified collaborations between large Pharma, biotech and academia. Exemplary are a number of new therapeutic antibody approaches that recently came to fruition and that created exciting new treatment options for patients. First, there is the success of the antibody-induced activation of cellular immune responses against tumors, which was designated by Science as the breakthrough of the year 2013.12 This advance was the offspring of a close collaboration between academic researchers at the University of California, Berkeley, and the biotech company Medarex13 that led to the approval of the anti-CTLA-4 antibody ipilimumab.14 Second, there have been strong advances with antibody-drug conjugates. A prominent example is the approval of brentuximab vedotin,15 which found its roots in the lifelong search for novel toxins in obscure sea creatures such as the sea hare by Prof. George Pettit,16 and was translated into practice by the biotech company Seattle Genetics.17 Finally, there is much attention for the promise of bispecific antibodies through the spectacular clinical data with bispecific T-cell engaging molecules obtained by Micromet.18

All of these approaches are now being enthusiastically embraced by Pharma. Genmab recently became a player in the field of bispecific antibodies via the development of the DuoBody® platform. The development of the platform, in our view, represents an attractive scientific and commercial success story of an academic-industry collaboration with many lessons learned. We provide the personal perspective below.

**Passion For Innovation: The IgG4 Antibody Challenge**

Continuous innovation is a life-line for biotechnology companies, not only as a necessity, but also to keep the entrepreneurial spirits of workers engaged and at the cutting edge. Without knowing it at the time, we essentially started our first open innovation project within Genmab in 2003. In the course of discovering antibody therapeutics for the treatment of autoimmune and inflammatory diseases, we were considering the characteristics of the optimal antibody isotype to achieve a maximal therapeutic window. Dogma at the time dictated that one should incorporate the human IgG4 subclass as the Fc-backbone of choice to prevent unwanted activation of antibody effector functions by therapeutic antibodies in immune related indications. However, a nagging issue was an unresolved hypothesis regarding instability of IgG4 antibodies in vivo: the Fab-arm exchange hypothesis (see BOX 2). A more detailed understanding of IgG4 biology therefore appeared essential prior to accepting the suitability of IgG4 antibodies for product development. To generate additional knowledge and test the hypothesis, we reintiated IgG4 research in a Genmab-sponsored project with Prof. Rob Aalberse from the Department of Immunopathology at Sanquin Research in Amsterdam. In a parallel effort, in collaboration with the group of Prof. Marc De Baets from the Department of Neuroscience at the University of Maastricht, we started a project to study antibody therapy of the autoimmune disease Myastenia gravis. This work was based on the hypothesis that monovalent, effector-function-deficient antibody (fragments) against acetyl choline receptor (AChR), the relevant autoantigen in Myasthenia gravis, might be able to counteract the activity of pathogenic autoantibodies in vivo.19 A few years later, these two independent lines of research came together. In the collaboration with Sanquin Research, we refuted a long-standing belief in antibody biology by showing that IgG4 antibodies are indeed dynamic molecules that acquire bispecific properties by continuous exchange of half-molecules in vivo. Thereby we confirmed our IgG4 Fab-arm exchange hypothesis,20 Fab-arm exchange in the rhesus monkey Myasthenia gravis model was shown to be at the basis of the anti-inflammatory properties of IgG4.

The new insight in IgG4 biology led to follow-up questions and initiated new lines of research: in collaboration with Joep Killestein and Chris Polman from the Department of Neurology at the VU University Medical Center in Amsterdam, we demonstrated that a non-mutated IgG4 therapeutic antibody, natalizumab, engages in Fab-arm exchange with endogenous IgG4 in humans,21 and we elucidated the key molecular requirements of Fab-arm exchange in collaboration with Theo Rispens from the Department of Pathology at Sanquin Research, Ignace Lasters from Algonomics in Ghent, and
Albert Heck from the Bijvoet Center for Biomolecular Research at Utrecht University.\textsuperscript{22,23} Our collaboration with Albert Heck, in addition, led to an unexpected spin-off into the realm of glycosylation. Here, we identified a novel CH3 mutation that strongly enhances Fc glycan complexity, providing new leads for antibody therapeutics.\textsuperscript{24} This work furthermore supported the development of a novel native high-resolution mass spectrometry method (orbitrap mass spectrometer), which enables facile mapping of whole antibody product microheterogeneity, including glycan profiles as well as antibody-drug conjugate adducts.\textsuperscript{25}

**Translating Science Into Technology Platform Applications**

Although initiated by an apparently simple practical question (i.e., which antibody Fc backbone to use for therapy of immune diseases), we would like to stress that the drive forward was not necessarily motivated by traditional question-and-answer, but instead by scientific curiosity and a passion to solve basic antibody biology questions. Nevertheless, the culture in our company that fosters out-of-the-box thinking within a strong goal-oriented environment led us to eagerly look for potential applications of our new-found knowledge. Three major branches that led to intellectual property and potential applications in the form of novel antibody platforms were initiated to: (1) identify mutations that prevent IgG4 antibodies from engaging in Fab-arm exchange in order to generate IgG4 molecules that are stable in vivo;\textsuperscript{21-23,26} (2) generate stable half antibodies in order to prepare monovalent antibody molecules with extended half-lifes relative to scFv and Fabs (UniBody\textsuperscript{\textregistered} format);\textsuperscript{23,27-35} Notably, the first hint that UniBody molecules could be generated came from a cloning artifact which serendipitously introduced a novel splice site which led to deletion of the genetic hinge region and a researcher determined to understand an apparent mistake; and (3) develop a method to stabilize IgG molecules following Fab-arm exchange in order to allow the generation of therapeutically bispecific antibodies (DuoBody\textsuperscript{\textregistered} platform) (Fig. 2).\textsuperscript{36-41}

The path that led to the development of our DuoBody\textsuperscript{\textregistered} platform turned out to be the most complex enterprise by far. The idea was fantastic, literally, as we initially had no clue as to how to translate the fascinating natural Fab-arm exchange process into a technologically and commercially-viable bispecific antibody platform. Our approach of leaving no stone unturned and having an open mind for the unexpected again provided a solution. In the rhesus monkey Myasthenia gravis model, we concluded that IgG4 anti-AChR provided protection because of in vivo Fab-arm exchange.\textsuperscript{20} This exchange reaction then necessarily involved the human IgG4 anti-AChR mAb and polyclonal rhesus monkey IgG4. The exact sequence of rhesus IgG4, however, was unknown at the time, and it was therefore not possible to perform a control experiment to prove interspecies IgG4 Fab-arm exchange.\textsuperscript{20} This gap remained an irritating loose end, so we set out to clone rhesus monkey IgG4. The “simple” control experiment, which took well over a year to perform, led to a number of surprises. First, rhesus monkeys from Indian and Chinese origin harbor a polymorphism\textsuperscript{42}
in which IgG4 from the former has an allotype (containing an IgG1-type core hinge) that does not allow exchange, in stark contrast to Chinese-origin rhesus monkey IgG4, which does engage in exchange. 22 Second, the CH3 domain of Chinese rhesus monkeys contained a distinct critical amino acid change for Fab-arm exchange compared with human IgG4. Third, the long-sought interspecies control experiment contained a key finding in that it unexpectedly resulted in an extremely high (> 95%) bispecific IgG4 yield. 22 We understood then that matched mutations therefore apparently could drive IgG4 Fab-arm exchange to completion, which was a definite Eureka moment! This work was extended with a library approach to identify the optimal matched mutations at the CH3-CH3 interface allowing directional Fab-arm exchange to occur. We envisioned that the ensuing DuoBody® platform should be built on an IgG1 format, as IgG1 antibodies combine all the desired properties, including in vivo stability, Fc-mediated effector function, long half-life and well-understood manufacturability and developability. To enable this, we sought for appropriate in vitro reducing condition which, combined with the matched mutations identified above, allowed our controlled Fab-arm exchange process to be developed in the versatile DuoBody® platform (Fig. 3). 36,37,40

One final step in building the platform was to demonstrate feasibility of the manufacturing process using standard unit operations for IgG1 and developability of DuoBody® products. We were struck by the robustness of the controlled Fab-arm exchange process as we could scale up from laboratory to manufacturing scale essentially without major adaptations (except for the use of diafiltration for buffer exchange at scale). We found that the DuoBody platform did not add any manufacturability liability on top of those already present in the original homodimeric parental antibody molecules. Indeed the DuoBody® platform generated bispecific IgG1 molecules with identical quality attributes to regular IgG1 products. 36

We strongly believe that the robustness of the process is related to the fact that it was built on a process that comes naturally to antibodies, and which, surprisingly, only required two single matched CH3 interface mutations per antibody molecule.

Now, as of early 2014, the DuoBody® platform has evolved into a successful bispecific antibody platform for the discovery and development of new antibody drugs in internal and external projects. We have successfully executed a number of collaboration and licensing agreement with Pharma, including with Janssen Biotech, Novartis, Kirin-Kyowa Hakko and Eli Lilly and Co.

Getting the Full Picture:
The Academic View

To evaluate the full experience from our journey into open innovation, it was critical to also portray the academic perspective. We were therefore delighted that Prof. Rob Aalberse, Prof. Marc De Baets and Prof. Albert Heck were willing to provide their views.

For these academic researchers, the main motivator for engaging in the collaboration was to generate knowledge, and they felt that they got the most out of the interaction when there was a sole focus on solving important scientific questions. However, once knowledge was gained and the potential for therapeutic or commercial applicability became apparent, this came with restrictions on sharing results with outside parties until intellectual property (IP) was secured. Although it was understood as being part of the deal, some experienced the accompanying change in ‘openness’ as a loss for the collaboration. Nevertheless, all indicated that the delay in being able to present or publish results due to IP issues was very acceptable as the requested periods were reasonable.

All three collaborations resulted in scientific articles in high-impact journals, abstracts, posters and presentation at numerous conferences. Publications were seen as important deliverables by all groups, and it was perceived as remarkable that also for Genmab as a company, publications were an important deliverable. Here, the underlying common aim
to generate knowledge and share this with the scientific community was achieved at its best. Publications helped the academic groups to establish new research interactions within academia, as well as with other companies. The collaborations also resulted in co-inventorships on patents. Whereas in the past, patents were seen as ‘not done’ in academia, patents have become an important deliverable also in universities. In recent years, a specific need to describe ‘valorization’ of proposed research in grant applications has arisen; collaborating with a company helped to put this in perspective. Notably, interactions with Genmab allowed the researchers to become more aware of the enormous efforts required for developing scientific knowledge into products, indeed suggesting that the feasibility of valorization is often overestimated. The knowledge generated not only led to publications, but also paved the way for follow-up research and the development of new or improved techniques. Finally, working with a company provided an incentive to introduce or restructure processes for managing projects or decision-making within the academic laboratories.

All three collaborators indicated that working with a (biotech) company is an excellent experience for academic researchers. However, it’s not for everyone as one should be open to the commercial and result-oriented way of working. The opportunity for PhD students and postdocs to obtain a first-hand view of research in a commercial setting was seen as a valuable extra to their training. Working at the interface between academia and industry provided a steep but valuable learning curve that benefitted both the students, as well as the academic staff.

**Innovation by Collaboration: Lessons Learned**

In summary, we learned that for collaborations aiming at innovation to be successful, the following aspects are key:

- A shared passion for the research topic
  - Focus on generating knowledge and not on potential valorization
  - Shared intention to publish and present at scientific conferences
- Two-way exchange of knowledge with open and frequent communication
- Avoidance of delays in sharing data
- Acknowledgment that intellectual property aspects may be perceived as affecting “openness” and reducing academic freedom
- Respect each other’s expertise and responsibilities
- Acknowledge and reward each other roles and understand responsibilities
- Invest in trust and a respectful and long-term relationship

**Open Innovation: Next Steps**

The development of the DuoBody® platform was initiated with academia and we therefore felt it to be important that, next to its use in drug development, it should also be used to answer important research questions. Basic research employing the platform may lead to new insights, novel uses, or in vitro and in vivo proof-of-concepts in unforeseen applications. To take open innovation to the next level, we announced a challenge to the scientific community at the end of 2013, using crowdsourcing via the commercial site Innocentive.com, as well as by posting on Genmab’s DuoBody.com website and on social media (our social networks on LinkedIn). The incentive given for the most promising ideas and proposals was either a cash reward or grant funding. Interestingly, the response on our first challenge was tremendous, with more than three dozen ideas and proposals received. A scientific advisory board of internal and independent external experts identified a number of top proposals that were recommended for an award. Overall, the quality and innovative power of the

![Figure 2. Science growing into applications. Insight in IgG4 biology and the unraveling of the IgG4 Fab-arm exchange process formed the roots for 3 major branches of research that led to the generation of scientific papers and intellectual property through various industry-academia collaborations. These culminated in 3 novel antibody technology platforms for the generation of stabilized IgG4, stable IgG4 half molecules (UniBody®) and bispecific IgG1 (DuoBody®). Numbers indicate: the number of collaborating parties involved; the number of patent applications filed26,27,29-31,38-41,52; the number of scientific papers published20-25,36,37,53-62; and the number of platform licensees that occurred between 2003 (the beginning of the IgG4 project within Genmab) and April 2014. Design: Joost Bakker (Scicomvisuals).](image-url)
top segment of proposals and ideas was remarkable. Genmab has the intention to continue this effort and future funding opportunities will be forthcoming. Finally, we wish to invite researchers in academia and industry to experience the full power of the DuoBody® platform for bispecific antibody research, as well as development. To further explore DuoBody®, we refer to the opportunities provided on www.douboderm.com.

**Concluding Remarks**

The success story above would not have been possible without the enthusiastic contributions of outstanding researchers from a number of universities and research institutes, as well as from a number of contract research organizations and biotech companies. For the collaborations to be successful, we learned that it is very important to have common goals and be sensitive to each other’s needs and responsibilities. Working at the interface between academia and industry, each with its different goals and purpose, does have its own challenges. Yet, if all involved respect and understand each other’s intentions, there is no reason to hold back: just throw the door wide open to innovation.

**Disclosure of Potential Conflicts of Interest**

JS, YFG, AFL, SRR and PW HIP are Genmab employees and have warrants and/or stock.

**Acknowledgments**

We thank all our partners in research, both at Genmab and in academia, who shared our passion for antibody biology research and innovation. We are especially indebted to Prof. Rob Aalberse, who not only led us into this field, but was also willing to share his insights along the way. Next to Prof. Aalberse, we thank Prof. Marc De Baets and Prof. Albert Heck for their willingness to provide their academic perspective on collaborating with a biotech. From our Genmab colleagues, we need to give special mention to Ewald van de Bremer, Tom Vink, Michael Graemer and Patrick van Berkely who made seminal contributions to forward the IgG4 research and the DuoBody® platform and to Joyce Meesters, Muriel van Kampen, Luus Wiegman, Patrick Priem, Sandra Verploegen, Joost Neijssen, Kristin Strumane, Rob de Jong and Amitava Kundu for their enthusiasm and outstanding input. We thank Joost Bakker for graphics design. Finally, we are very grateful to Jan van de Winkel for his generous support and trusting us for creating and profiting from technology. Boston Harvard Business School Press, 2003.

**References**

1. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munoz BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry’s grand challenge. Nat Rev Drug Discov 2010; 9:203-14; PMID:20168317
2. Herper M. The truly staggering cost of inventing new drugs. Forbes, 2012; http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/.
3. Stohl WR, Stohl LM. Therapeutic Antibody Engineering: Current and Future Advances Driving the Strongest Growth Area in the Pharmaceutical Industry. Woodhead Publishing, 2012.
4. Mullard A. 2012 FDA drug approvals. Nat Rev Drug Discov 2013; 12:87-90; PMID:2370234; http://dx.doi.org/10.1038/nrd3946
5. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov 2012; 11:191-200; PMID:22378269; http://dx.doi.org/10.1038/nrd35681
6. Kessel M. The problems with today’s pharmaceutical business—an outsider’s view. Nat Biotechnol 2011; 29:27-33; PMID:21221096; http://dx.doi.org/10.1038/nbt.1748
7. Chesbrough H. Open Innovation: The New Imperative for creating and profiting from technology. Boston Harvard Business School Press, 2003.
8. Mullard A. New checkpoint inhibitors ride the immunotherapy tsunami. Nat Rev Drug Discov 2013; 12:489-92; PMID:23812256; http://dx.doi.org/10.1038/nrd4066
9. Mullard A. European lead factory opens for business. Nat Rev Drug Discov 2013; 12:173-5; PMID:23449292; http://dx.doi.org/10.1038/nrd3956
10. Mullard A. 2013 FDA drug approvals. Nat Rev Drug Discov 2014; 13:85-9; PMID:24481294; http://dx.doi.org/10.1038/nrd4239
11. Reichert JM. Antibodies to watch in 2014. MAbs 2014; 6:5-14; PMID:24284914; http://dx.doi.org/10.4161/mabs.27333
12. Cousin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science 2013; 342:1432-3; PMID:24357284; http://dx.doi.org/10.1126/science.342.6165.1432
13. Hodi FS, Mihm MC, Soffier RJ, Haluska FG, Burler M, Seiden MV, Davis T, Henry-Spires R, MacRae S, Willman A, et al. Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. Proc Natl Acad Sci U.S.A. 2003; 100:4712-7; PMID:126282289; http://dx.doi.org/10.1073/pnas.0830997100

**Figure 3.** From nature to a bispecific technology platform. The left panel shows the major characteristics of the naturally occurring, bidirectional process of Fab-arm exchange as was discovered during the research described in this Perspective. This knowledge was applied to develop a platform of controlled, unidirectional Fab-arm exchange, of which the major characteristics are shown in the right panel. Design: Joost Bakker (Scicomvisuals).
57. Rispens T, den Bleker TH, Aalberse RC. Hybrid IgG4/IgG4 Fc antibodies form upon ‘Fab-arm’ exchange as demonstrated by SDS-PAGE or size-exclusion chromatography. Mol Immunol 2010; 47:1592-4; PMID:20299101; http://dx.doi.org/10.1016/j.molimm.2010.02.021

58. Rispens T, Davies AM, Ooijevaar-de Heer P, Absalah S, Bende O, Sutton BJ, Vidarsson G, Aalberse RC. Dynamics of inter-heavy chain interactions in human immunoglobulin G (IgG) subclasses studied by kinetic Fab arm exchange. J Biol Chem 2014; 289:6998-109; PMID:24425871; http://dx.doi.org/10.1074/jbc.M113.541813

59. Rosati S, Yang Y, Barendregt A, Heck AJ. Detailed mass analysis of structural heterogeneity in monoclonal antibodies using native mass spectrometry. Nat Protoc 2014; 9:967-76; PMID:24675736; http://dx.doi.org/10.1038/nprot.2014.057

60. Labrijn AF, Aalberse RC, Schuurman J. When binding is enough: nonactivating antibody formats. Curr Opin Immunol 2008; 20:479-85; PMID:18577454; http://dx.doi.org/10.1016/j.coi.2008.05.010

61. Rispens T, Meesters J, den Bleker TH, Ooijevaar-De Heer P, Schuurman J, Parten PW, Labrijn A, Aalberse RC. Fc-Fc interactions of human IgG4 require dissociation of heavy chains and are formed predominantly by the intra-chain hinge isomer. Mol Immunol 2013; 53:35-42; PMID:22784992; http://dx.doi.org/10.1016/j.molimm.2012.06.012

62. Rispens T, Ooijevaar-De Heer P, Vermeulen E, Schuurman J, van der Neut Kolfschoten M, Aalberse RC. Human IgG4 binds to IgG4 and conformationally altered IgG1 via Fc-Fc interactions. J Immunol 2009; 182:4275-81; PMID:19299726; http://dx.doi.org/10.4049/jimmunol.0804338