Corrected: Author Correction

‘Stealth’ corporate innovation: an emerging threat for therapeutic drug development

Therapeutic innovations of potentially great clinical impact should embrace the overarching values of research accountability, data transparency and validation through the scientific peer-review process.

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“It is terrible to become rich and to know nothing else.”—Euripides

Academic research and industrial innovation are both integral drivers of the discovery process that eventually culminates in innovative therapies and new medicines[1]. Academic research is conducted on university, hospital or research-center campuses furnished with several degrees of freedom but also hampered by funding constraints. Industrial research in large companies tends to resonate more with the rigid organizational blueprint and internal regulatory control that spans the entire spectrum of corporate structure. Start-up companies (start-ups) are somewhere in the middle: they may have components of both academic and industrial origin, but in theory their major advantage is that they can avoid both the funding constraints of academia and the rigid organizational constraints of large companies.

Academically led innovation typically thrives on competitive funding from public agencies and charities, and this makes the investment of a comparatively large portion of such funding on high-risk ideas difficult. Large companies are also increasingly risk-averse in trying to invest in innovation and leave much of this early, high-failure-rate step to start-ups or academic laboratories.

The reliance of academic research on public funding mandates a strong sense of accountability, mainly toward the contributing taxpayers or charity donors (i.e., the broader public). In turn, this research accountability should be reflected in a high level of data integrity and transparency, which is achieved mainly through several rounds of review by expert scientists before the described research product (e.g., drug target or candidate) can reach the public domain in peer-reviewed publications. Taxpayers and donors should know that their hard-earned contributions are being invested in work that gets validated by rigorous peer review and also may eventually help patients. Such opportunities can be nourished only by robust scientific evidence and peer-validated technologies in the development of innovative patient treatments[2]. Naturally, similar requirements for transparency and data integrity should also apply when such research is partially or fully conducted by start-ups, regardless of which investigators are involved (e.g., from academic institutions, hospitals and/or companies).

Rigorous scientific scrutiny at all steps of the discovery process is essential regardless of whether this innovation is generated in university laboratories or in cubicles at biotechnology (biotech) companies. The introduction of therapeutic innovations of potentially great clinical impact carries even greater responsibility for communicating and engaging with the scientific community through clear and demonstrably consistent underpinning data. Data validation by means of peer-reviewed publications should also apply to medicinal products discovered and clinically developed entirely within industrial venues. The investor-driven funding that enables start-up and biopharmaceutical (biopharma) research to advance its pipeline of products through clinical development should not create impediments to the maintenance of data transparency and open access to research. Industry-based research should not be communicated only among company executives, investors, stockbrokers or venture capitalists through vaguely formulated press releases with no primary data or independently validated conclusions. Instead, its underpinning data should be made publicly available to allow evaluation of its validity and the long-term consequences of its conclusions.

The exposure of some types of industrial research results to rigorous peer review is lagging behind that of their academic counterparts. This insufficient peer validation may be a more prominent issue for research covering the early stages of the discovery–to–clinical validation pipeline, which is usually conducted by smaller companies (including start-ups) than for larger biopharma companies working further down the pipeline. The lack of peer-reviewed publications from small companies and start-ups has been attributed to many factors, among which the protection of corporate intellectual property from competition holds a prominent place, especially for early-stage research[3]. Most major pharmaceutical companies engage in peer review of their technologies or products at critical checkpoints of technology development. However, it is the aspiring start-ups and small- or medium-sized biotech enterprises that tend to rely more on media exposure than on actual scientific evidence, in an effort to direct investor funding toward their products, as early as possible[4]. This evolving and increasingly accepted practice of shielding scientifically important corporate data is at odds with the standards of research accountability through peer evaluation, data transparency, research integrity and data openness[5].

Placing such general considerations into perspective, Cristea and colleagues evaluated the lack of peer-reviewed evidence from healthcare ‘unicorns’[6] — that is, biotech start-ups with promising technologies and market valuations that exceed the US$1 billion threshold. Many start-ups had secured exceedingly high market valuations despite a lack of peer-reviewed publications to support their

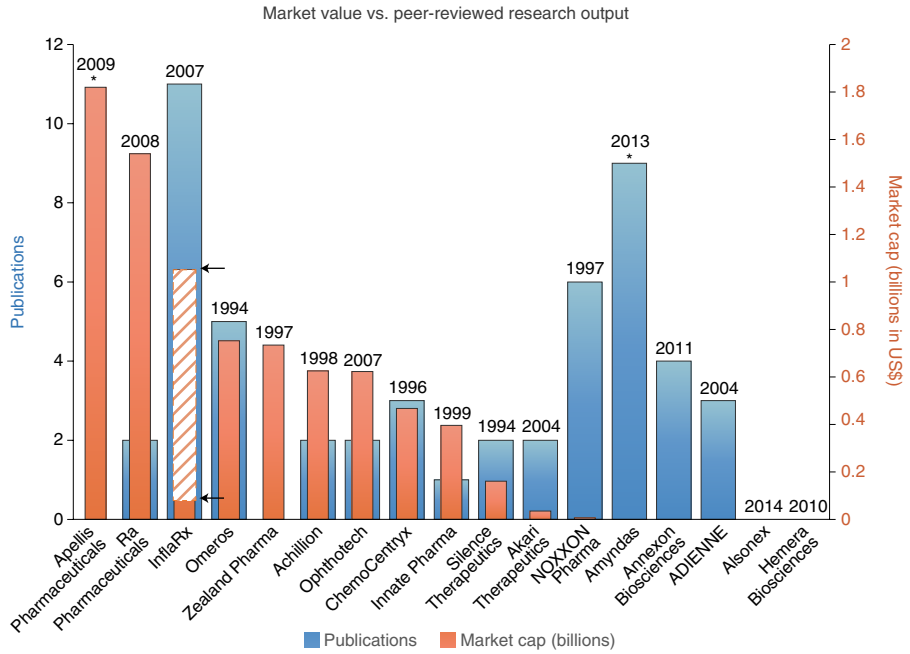

Fig. 1 | Market valuation of complement-related drug–development companies versus research output (peer-reviewed publications of company-sponsored research) that validates their complement-related technology or drug candidate. All market caps were retrieved through Yahoo's finance search engine (https://finance.yahoo.com/) and were converted for uniformity into US currency (right vertical axis) on the basis of currency exchange rates as of 30 July 2019. Our analysis included five privately held companies (not listed on the stock exchange): ADIENNE, Alsonex, Amyndas, Annexon Biosciences and Hemera Biosciences. For reasons of conformity, market values for these companies are shown as US$0 here. 'Publications' (left vertical axis) refers to peer-reviewed papers (original research articles, reviews and editorials) retrieved through Elsevier's Scopus search engine (https://www.elsevier.com/solutions/scopus). Conference presentations, conference proceedings or corporate presentations and investor- and/or shareholder-oriented releases have been excluded from this analysis. All the primary data used for this analysis, with details on each company's publication record and related citations, are provided in Supplementary Datasets 1 and 2. Numbers above bars indicate the year in which each company was founded; asterisks indicate companies that are clinically developing different versions of the same C3-inhibitory peptide compstatin; hashed bar indicates the market cap of InflaRx before the announcement of the failure of IFX-1 in the phase II trials for hidradenitis suppurativa.

market-directed innovations. To further probe the extent of this stealth mode of research and its potential adverse repercussions in the healthcare industry[4], we decided to apply their analysis to the 'complement system drug space' and investigate whether similarly obscure corporate practices fuel 'stealth' innovation among start-ups active in the clinical development of complement therapeutics.

We should emphasize that most of the clinical indications currently targeted in the complement drug space are designated as 'rare' or 'orphan' diseases[7]. The small numbers of treatable patients and the projected low financial return of orphan medicines impose commercial risks, and special policies (such as the US Orphan Drug Act) have therefore been put in place to help companies counterbalance such risks. These policies offer several incentives to companies that are developing orphan medicinal products, such as market exclusivity rights and expedited regulatory approval and oversight during clinical development[8]. Today, complement drug discovery has been thrust into the limelight of the healthcare industry, with more than 20 candidate drugs advancing through clinical development (i.e., phase II and/or phase III) for a wide spectrum of complement-mediated diseases[9–11]. A growing number of start-ups have engaged in the development of complement-targeting drug candidates, alongside established pharmaceutical companies that have also initiated complement drug programs as part of their highly diversified portfolios[9]. In exploiting the rekindled interest of the biopharma industry in targeting this innate immune system, several start-ups have managed to acquire exceedingly high market valuations that probably reflect mounting investor interest in what appears to be a rapidly evolving field of not only clinical opportunity but also commercial opportunity. But is this interest of the capital market firmly rooted in scientific facts or is it driven instead by media hype?

To gain insight into the extent to which complement-dedicated start-ups with high market valuations have engaged in peer-review validation of their products, we conducted a literature search for publications co-authored by these companies. Scopus (Elsevier) was selected as our literature search engine, and our retrievals included original research articles, editorials and reviews. The 'affiliation name' of the company was combined in a search for documents that included the term 'complement' in the title, abstract and/or keywords and also in extracted metadata (all fields) associated with the document in question. All publications were cross-validated manually for the true association of their content (abstract) to complement research or complement-targeting therapeutics, with exclusion of use of the term 'complement' in its grammatical sense. We chose to include in our analysis 17 companies with clinical-stage complement drug leads disclosed through their official websites, focusing on programs whose documentation in the literature commenced since 2003 and on complement innovators with consistent commitment to this drug space[9]. We focused only on start-ups; thus, large global healthcare companies with recently initiated complement drug programs were not included in this analysis. Our search yielded quite striking results for a group of start-ups and medium-sized enterprises that are either publicly listed on a major stock exchange or privately held (Fig. 1)

The data demonstrate that companies with the highest market valuation tend to make fewer of their research results accessible to the scientific community through peer-reviewed publications. For publicly listed companies with known market valuation, with few exceptions (such as Omeros and InflaRx, which both have a notable publication record), there is an inverse relationship between market valuation and peer-validated research output (Fig. 1). This observation should be considered with some caution given the relatively small number of companies assessed. However, it not only resonates with the main message conveyed by the perspective article of Cristea et al.[6] but also raises awareness about a 'stealth' research culture that may have infiltrated the complement-drug-discovery space,

disengaging valuation of the for-profit entity from evidence-based scientific documentation.

It should be noted that InflaRx's impressively high market cap of US$1.05 billion decreased precipitously under pressure resulting from the negative results (released 5 June 2019) from its multi-center phase II study evaluating the efficacy of its lead product, the monoclonal antibody IFX-1, directed against the complement component C5a, in patients with the inflammatory skin disorder hidradenitis suppurativa[12]. In the wake of this news, the company's stock plummeted, losing more than 90% of its original value, with the market cap of the company reduced to US$75 million in August 2019 (https://finance.yahoo.com/quote/ifrx?ltr=1) (Fig. 1). Interestingly, while the company had published several papers on its main product (IFX-1), the decision to advance this candidate to trials for hidradenitis suppurativa in particular was based on weak evidence: a single publication (from 2018) with limited translational data, perhaps insufficient to support full commitment to clinical trials for hidradenitis suppurativa[13]. The case of InflaRx further indicates that occasionally a combination of media hype, investor impatience, loosely connected preclinical evidence and lack of sufficient peer-reviewed evidence for the targeted indication can drive corporate decisions into 'murky waters'. Of note, the market fall of InflaRx had parallel repercussions on the stock price of another complement-related biotech company, ChemoCentryx, which develops an orally available antagonist of the complement receptor C5aR1 that prevents activation of the same effector pathway (the pathway targeted by IFX-1) in complement-mediated inflammatory disorders. ChemoCentryx's stock value dropped sharply by 22% within 2 days (4–6 June 2019) of the announcement of the InflaRx trial results (https://finance.yahoo.com/quote/CCXI/?guccounter=1). It is worth mentioning that ChemoCentryx's candidate drug, Avacopan, is currently in phase III trials for anti-neutrophil cytoplasmic antibody–associated vasculitis, and the results are eagerly awaited, given these developments[9].

The peer-reviewed maturity of a technology (i.e., the pharmacology and/or biological efficacy of a drug candidate) is not necessarily reflected in the market valuation of the respective company. There is considerable risk of letting investors' decisions and market bias skew the direction of clinical research, irrespective of which drug candidate the evidence base suggests might be most efficacious. For example, several highly valued public companies have advanced their lead compounds into late-stage clinical development without having released into the literature any causative and/or mechanistic or preclinical evidence to support the feasibility of their clinical program. For example, Omeros has advanced its lead compound, the inhibitor OMS721, directed against the protease MASP2, into two phase III trials, for immunoglobulin A nephropathy and atypical hemolytic uremic syndrome, without any relevant publication supporting proof of concept for these indications[9]. On the contrary, all Omeros-affiliated publications support the development of inhibitors of MASP2 as treatment options for cerebral, myocardial or gastrointestinal ischemia–reperfusion injury (Supplementary Dataset 1). Apellis Pharmaceuticals, a public company that is advancing inhibitors that target the complement component C3 through phase II and phase III trials, has already achieved an impressively high market valuation of approximately US$1.8 billion (Fig. 1), the highest among all of the complement-focused drug-development companies, a valuation probably kindled by the release of non–peer-reviewed clinical results of ongoing trials. While clinically developing its lead drug candidate, the polyethylene glycol–conjugated, compstatin-based C3 inhibitor APL-2, for several indications, Apellis has refrained from publishing peer-reviewed articles, confining its research output to press releases, conference posters and corporate announcements about the status of ongoing clinical trials[9]. Similarly, Ra Pharmaceuticals has taken its lead compound, zilucoplan (RA101495), to phase III trials of patients with paroxysmal nocturnal hemoglobinuria, without any published peer-reviewed evidence confirming the drug's efficacy or benchmarking their technology against the standard of care in this specific clinical indication[14].

We further extended our literature-based analysis to privately held pharmaceutical companies that are developing complement therapeutics. For example, Amyndas, a start-up established in 2013, is advancing third- and fourth-generation compstatins through phase II trials that have been communicated in the scientific literature through nine co-authored publications (Fig. 1). Alsonex, a biotech company that is developing therapeutics for neurodegenerative diseases, offers another interesting example of how corporate innovation can gain leverage from academically led research results. While its lead compound (ALS-205) has not been registered in any publication so far, clinical development of ALS-205 has gained traction from the prominent academic publication record of its equivalent, PMX-205[9].

Our analysis further points to the consequences of insufficiently validated research in a setting that appears to be heavily influenced by media hype and disproportionately high investor expectations. For example, the partnership (announced 20 March 2019) of Zealand Pharma, a company with expertise in metabolic diseases, with Alexion, the leading company in marketed complement therapeutics, for the joint development of C3-targeted inhibitors[15] made the headlines of biotech 'news channels'[15]. While Zealand Pharma has a publication portfolio that supports its glucagon-like-peptide–related technology, it has yet to publish any paper related to complement-immunomodulatory peptides or inhibition of C3 (Fig. 1). Finally, the partnership (announced 18 July 2019) of UK-based Silence Therapeutics, a biotech company with expertise in RNA-interference technology, with Mallinckrodt Pharmaceuticals, for the mutual development of their preclinical lead compound SLN500 as a C3-targeting RNA-interference therapeutic, was widely publicized in the media[16]. Despite a potential return from the partnership of approximately US$2.0 billion in combined milestone payments and commercial royalties, Silence has yet to produce any peer-evaluated line of evidence of how this compound can achieve sustainable inhibition of C3 in a therapeutically relevant context. The rekindled interest of big biopharma in gene-therapy platforms for the treatment of chronic diseases[17], along with the excessively high, multi-billion-dollar buyouts announced for the acquisition of gene-therapy start-ups by global healthcare leaders (such as Roche's announced acquisition of Spark Therapeutics for US$4.5 billion in February 2019) have evidently garnered a lot of momentum for such approaches, as yet unsupported by transparent, evidence-based science or data openness[18].

To gain insight into the overall impact of the peer-reviewed papers produced by complement-based start-ups, we determined how many of the papers shown in Fig. 1 had received more than 30 citations in Scopus as of 6 August 2019. We found that 14 of a total 48 papers had more than 30 citations each, covering a time period from the inception date of each company to the present; this indicates that almost one third of the research output from these companies has garnered considerable attention from peers (Supplementary Dataset 1 provides a complete record of citations retrieved per publication, per company).

We should caution that the absolute number of publications is, of course, only a modest marker of the reliability of evidence. Citation impact is also only a modest marker of the extent of validation, let alone an indicator of the future potential of a drug under investigation. Despite such clear limitations, the peer-review system is still regarded as the most reliable tool for the evaluation of scientific data. Nevertheless, it is important to scrutinize peer-reviewed papers with a critical eye. Additionally, the inclination of both authors and editors to publish 'positive' results, rather than 'negative' results, has created a bias in the literature with important implications for the field of clinical therapeutics. Peer-reviewed papers, even when well cited, may still be suboptimal, flawed or largely irrelevant to the real translational value. An example illustrating the last is Annexon's technology directed against complement component C1q, which despite its sizeable impact in the literature (over 560 citations, according to Scopus) has yet to overcome substantial translational hurdles for clinical evaluation for neurodegenerative diseases.

Finally, the credibility and concrete scientific base of a start-up's lead technology may also be reflected by the record of scientific achievements and broader impact of its founders. Retrieving a set of impact metrics for the co-founders of the 17 companies in Fig. 1, we observed that only 4 of these 17 companies were founded on the expertise of leading scientists with a sizeable impact on the literature, as deduced by their *h* index (which measures productivity and citation impact of publications: the number of publications (*h*) for which an author has been cited by other authors at least *h* times) and total citations ($h > 50$ and over 20,000 total citations, according to Scopus). Although we acknowledge that this is not a mandatory condition for the clinical success of any drug candidate, it does provide an interesting perspective on how 'thought leaders' in the field shape drug-discovery efforts and become drivers of corporate innovation. Scientific advisory boards are also important for guaranteeing field expertise. However, information on the membership and level of involvement of these boards is often lacking[6].

Concluding remarks and outlook

The growing interest in complement therapeutics, as exemplified by a burgeoning pipeline of drug candidates currently in early or late-stage clinical development[9], has thrust complement drug discovery into the spotlight of biopharma research. At the same time, corporate data integrity and practices that lead to scientific uncertainties are key issues that need to be dealt with in a transparent manner if these new therapeutics are to be effectively translated into beneficial new treatments for patients. Despite the registration of a growing number of clinical trials for the evaluation of complement-targeting drugs, peer-reviewed validation of new therapeutic concepts, targets and drug candidates remains problematic, particularly in the case of start-ups that have secured large market valuations that capitalize on investor expectations and increased media attention. While we acknowledge that corporate innovation must be protected through stringent intellectual property policies, we contend that healthcare products that affect patients' lives, such as complement-targeting drugs, should undergo rigorous peer-reviewed validation before sizeable resources and funds for clinical research and trials are engaged. ❐

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Published online: 27 September 2019
https://doi.org/10.1038/s41590-019-0503-1

References

1. Chin-Dusting, J., Mizrahi, J., Jennings, G. & Fitzgerald, D. *Nat. Rev. Drug Discov.* **4**, 891–897 (2005).
2. Dahlin, J. L., Inglese, J. & Walters, M. A. *Nat. Rev. Drug Discov.* **14**, 279–294 (2015).
3. Grabowski, H. G., DiMasi, J. A. & Long, G. *Health Aff. (Millwood)* **34**, 302–310 (2015).
4. Ioannidis, J. P. A. *J. Am. Med. Assoc.* **313**, 663–664 (2015).
5. Amann, R. I. et al. *Science* **363**, 350–352 (2019).
6. Cristea, I. A., Cahan, E. M. & Ioannidis, J. P. A. *Eur. J. Clin. Invest.* **49**, e13072 (2019).
7. Orphanet. https://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN. Accessed 4 February 2019.
8. Luzzatto, L. et al. *Lancet* **392**, 791–794 (2018).
9. Mastellos, D.C., Ricklin, D. & Lambris, J.D. *Nat. Rev. Drug Discov.* https://doi.org/10.1038/s41573–019-0031-6 (2019).
10. Ricklin, D., Mastellos, D. C., Reis, E. S. & Lambris, J. D. *Nat. Rev. Nephrol.* **14**, 26–47 (2018).
11. Yang, K., Deangelis, R. A., Reed, J. E., Ricklin, D. & Lambris, J. D. *Adv. Exp. Med. Biol.* **735**, 301–313 (2013).
12. InflaRx. https://www.inflarx.de/Home/Investors/Press-Releases/06–2019-InflaRx-Announces–Top-Line-SHINE-Phase-IIb-Results-for-IFX-1-in-Hidradenitis-Suppurativa-.html. Accessed 31 July 2019.
13. Kanni, T., Zenker, O., Habel, M., Riedemann, N. & Giamarellos-Bourboulis, E. J. *Br. J. Dermatol.* **179**, 413–419 (2018).
14. Morrison, C. *Nat. Rev. Drug Discov.* **17**, 531–533 (2018).
15. Alexion. https://news.alexion.com/press-release/company-news/alexion-and-zealand-pharma-announce-collaboration-discover-and-develop-pe. (2019).
16. PRNewswire. https://www.prnewswire.com/news-releases/mallinckrodt-and-silence-therapeutics-announce-collaboration-to-develop-and-commercialize-rnai-therapeutics-for-complement-mediated-diseases-300887002.html (2019).
17. High, K. A. & Roncarolo, M. G. *N. Engl. J. Med.* **381**, 455–464 (2019).
18. Miller, J. *Reuters* https://www.reuters.com/article/us-spark-m-a-roche-hldg/roche-steps-up-for-gene-therapy-with-4–3-billion-spark-bet-idUSKCN1QE0L6 (2019).

Competing interests

A.M.B. has provided paid consulting services to Zealand Pharma. B.V.G. collaborates with and has received research materials from SomaLogic and Roche Pharma and has also provided paid consulting services for ClearView Health Care Partners and 1776 Health Care. B.G. is the holder of a US patent for a monoclonal antibody for the treatment of angioedema and a patent for monoclonal antibodies to both C1q and C1qRs for the treatment of various types

of cancer and has consulted for Diaccurate-Pasteur and Orion Pharma but has never received research support from any pharmaceutical company. P.G. has collaborated with and has received research funding and/or research materials from Genmab and Merus. G.H. is an inventor on patents or patent applications that describe the use of complement inhibitors for therapeutic purposes in periodontitis, some of which are being developed by Amyndas Pharmaceuticals. V.M.H. is a co-founder of Taligen Therapeutics and AdMIRx, receives Taligen-related licensing royalties from Alexion, has equity interest in and consulting income from AdMIRx, and is a recent or current consultant in non-complement areas to Janssen Research and Development, Amgen, Celgene, BMS and Trios. M.H.-L. holds a patent on compositions of matter and methods for the diagnosis and treatment of sepsis by C5a inhibitory strategies licensed to InflaRx. T.K. has received consultant fees and honoraria for lectures from Alexion. T.E.M. has received consultant fees from Ra Pharmaceuticals, SVAR Life Science and Alexion Pharmaceuticals. R.A.M. has received research funding from Alexion (the manufacturer of Soliris-Eculizumab) and Shire ViroPharma, has served as a paid consultant for Alexion, Shire ViroPharma and CSL Behring, has received travel honoraria from Alexion and Shire ViroPharma, has served on advisory boards for Genentech/Roche, True North/iPerian, Novartis and Hansa Medical, and received consulting fees from OrbidMed, GuidePoint Global, Sucampo, Astellas, and Shire and research grants from Immune Tolerance Network, ViroPharma, Hansa and Alexion. B.P.M. has received research support from GSK and served as an advisor for GSK, Roche, Alexion and Ra Pharma. B.N. is a shareholder and consultant in Tikomed and iCoat Medical. R.P. is the inventor on patents that describe the use of complement-related proteins for cancer diagnosis and has received consultant fees from Amadix and research funding from Dompé. D.R. is the inventor on patents or patent applications that describe the use of complement inhibitors for therapeutic purposes, some of which are developed by Amyndas Pharmaceuticals, and has provided paid consulting services to Roche Pharma. A.M.R. has received research support from Alexion Pharmaceuticals, Novartis, Alnylam and Ra Pharma and lecture fees from Alexion, Novartis, Pfizer and Apellis, and served as member of advisory–investigator boards for Alexion, Roche, Achillion, Novartis, Apellis and Samsung, and as a consultant for Amyndas. R.P.T. has collaborated with and received research funding and research materials from Genmab. J.D.L. is the founder of Amyndas Pharmaceuticals, which is developing complement inhibitors for therapeutic purposes, is the inventor of patents or patent applications that describe the use of complement inhibitors for therapeutic purposes, some of which are being developed by Amyndas Pharmaceuticals, is the inventor of the compstatin technology licensed to Apellis Pharmaceuticals (4(1MeW)7W/POT-4/APL-1 and PEGylated derivatives such as APL-2/pegcetacoplan), and has provided paid consulting services to Achillion, Ra Pharma, Viropharma, Sanofi, Shire, LipimetiX and Baxter.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41590-019-0503-1.