Perspective

'Stealth' corporate innovation: an emerging threat for therapeutic drug development

Dimitrios C. Mastellos[1], Anna M. Blom[2], E. Sander Connolly[3], Mohamed R. Daha[4], Berhane Ghebrehiwet[5], Piet Gros[6], George Hajishengallis[7], V. Michael Holers[8], Markus Huber-Lang[9], Taroh Kinoshita[10], Tom E. Mollnes[11,12,13], Robert A. Montgomery[14], Bryan P Morgan[15], Bo Nilsson[16], Ruben Pio[17], Daniel Ricklin[18], Antonio M. Risitano[19], Richard J Smith[20], Ronald P. Taylor[21], Alberto Mantovani[22], John P.A. Ioannidis[23], and John D. Lambris[24]

[1]National Center for Scientific Research 'Demokritos', Aghia Paraskevi, Athens, Greece
[2]Department of Translational Medicine, Lund University, Sweden
[3]Department of Neurological Surgery, Columbia University, New York USA
[4]Leiden University Medical Center, Leiden, Netherlands
[5]Department of Medicine, Division of Rheumatology, Allergy and Immunology, Stony Brook University, NY, USA
[6]Department of Chemistry, Faculty of Science, Utrecht University, Utrecht, Netherlands
[7]Department of Microbiology, School of Dental Medicine, University of Pennsylvania, Philadelphia PA, USA
[8]Division of Rheumatology, Departments of Medicine and Immunology, University of Colorado School of Medicine, Denver CO, USA
[9]Institute of Clinical and Experimental Trauma immunology, University of Ulm, Ulm, Germany
[10]Research Institute for Microbial Diseases Osaka University and Laboratory of Immunoglycobiology, Immunology Frontier Research Center, Osaka University, Osaka, Japan
[11]Department of Immunology, Oslo University Hospital, and University of Oslo, Oslo, Norway
[12]Research Laboratory, Nordland Hospital, Bodø, and K.G. Jebsen TREC, University of Tromsø, Norway
[13]Centre of Molecular Inflammatory Research, NTNU, Trondheim, Norway
[14]Department of Surgery, NYU Langone Transplant Institute, NY, USA
[15]Systems Immunity Research Institute, School of Medicine, Cardiff University, Cardiff, UK
[16]Division of Clinical Immunology, Uppsala University Hospital, Uppsala, Sweden
[17]Program in Solid Tumors, Center for Applied Medical Research (CIMA), University of Navarra, IDISNA, CIBERONC, Pamplona, Spain
[18]Department of Pharmaceutical Sciences, University of Basel, Switzerland
[19] Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples Italy
[20]Molecular Otolaryngology and Renal Research Laboratories, Carver College of Medicine, University of Iowa, USA
[21]Department of Biochemistry and Molecular Genetics, University of Virginia, USA
[22]Istituto Clinico Humanitas, Humanitas University, Milan, Italy
[23]Meta-Research Innovation Center at Stanford, and Departments of Medicine, of Health Research and Policy, of Biomedical Data Science, and of Statistics, Stanford University, Stanford CA, USA
[24]Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, USA.

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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 in 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 which spans the entire spectrum of corporate structure. 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 may not be easy to invest a lot of funds on high-risk ideas. 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.

The reliance of research on public funding should invoke a strong sense of accountability, primarily towards 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 mainly achieved through several rounds of review by expert scientists before the described research product (e.g. drug target/candidate) can reach the public domain in peer-reviewed publications. Taxpayers 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. These opportunities can only be nourished by robust scientific evidence and peer-validated technologies in developing innovative patient treatments [2]. Naturally, similar requirements regarding transparency and data integrity should also apply when such research is partially or fully conducted by start-up companies, regardless of whether academic or other (e.g. clinical) investigators are involved.

Rigorous scientific scrutiny at all steps of the discovery process is essential, regardless of whether this innovation is generated in university laboratories or biotech cubicles. With great clinical impact comes even greater responsibility to communicate and engage with the scientific community through clear and irrefutable 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 biopharma research to advance its pipeline of products through clinical development should not create impediments in the way of maintaining data transparency and open access to research. Industry-based research should not only be communicated between company executives, investors, stock brokers 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 for 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 may be a more prominent issue for research covering the early stages of the discovery to clinical validation pipeline, usually conducted by smaller companies (including start-ups), than for larger biopharma 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 corporate intellectual property protection from competition holds a prominent place, especially for early stage research [3]. Most major pharmaceutical companies, at critical checkpoints of technology development, engage in peer review of their technologies or products. However, it is the aspiring startups and biotech small- or medium-sized enterprises that tend to rely more on media hype than on actual scientific evidence, in an effort to direct, as early as possible, investor funding towards their products [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 finally, data openness [5].

Placing these general considerations into perspective, *Cristea* and colleagues recently evaluated the lack of peer-reviewed evidence from healthcare unicorns [6]; that is, biotech startups with promising technologies and market valuations that exceed the 1 billion threshold. Many startups had secured exceedingly high market valuations despite a lack of peer-reviewed publications to support their 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 this analysis to the complement system drug space and investigate whether similarly obscure corporate practices fuel 'stealth' innovation among startups active in the clinical development of complement therapeutics.

We should stress that most of the clinical indications currently targeted in the complement drug space are designated as rare or orphan diseases [7]. Therefore, the small numbers of treatable patients and the projected low financial return of orphan medicines, impose commercial risks that have been counterbalanced by the enactment of special legislation (e.g. US Orphan Drug Act). These offer several incentives to companies 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/III) for a wide spectrum of complement-mediated diseases [9,10,11]. A growing number of startups have engaged in developing complement-targeted drug candidates, alongside established pharmaceutical companies that have also initiated complement drug programs within their highly diversified portfolios [9]. In exploiting the rekindled interest of the biopharma industry to target this innate immune system, several startups have managed to acquire exceedingly high market valuations that likely reflect mounting investors' interest in what appears to be a rapidly evolving field of commercial, not only clinical, opportunity. Yet, 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 startups 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 including the term "complement' in the title/abstract/keywords and also in extracted meta data (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-targeted therapeutics, excluding usage 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 and thus large global healthcare companies with recently initiated complement drug programs were not included in this analysis. Our search yielded quite striking results with regard to a group of startups/medium-sized enterprises which are either publicly listed on the stock exchange or privately held (**Figure 1**)

As shown, companies with the highest market valuation tend to make less of their research results accessible to the scientific community through peer-reviewed publications. With regard to publicly listed companies with known market valuation, with few exceptions (such as Omeros and the Germany-based InflaRx which both have a notable publication record), there is an inversely proportional 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., but also raises awareness about a 'stealth' research culture that may have infiltrated the complement drug discovery space, disengaging industrial innovation from evidence-based scientific documentation.

It should be noted that InFlaRx's impressively high market cap of 1.05B declined precipitously under the pressure of the recently released (June 5th, 2019) negative results from its multi-center

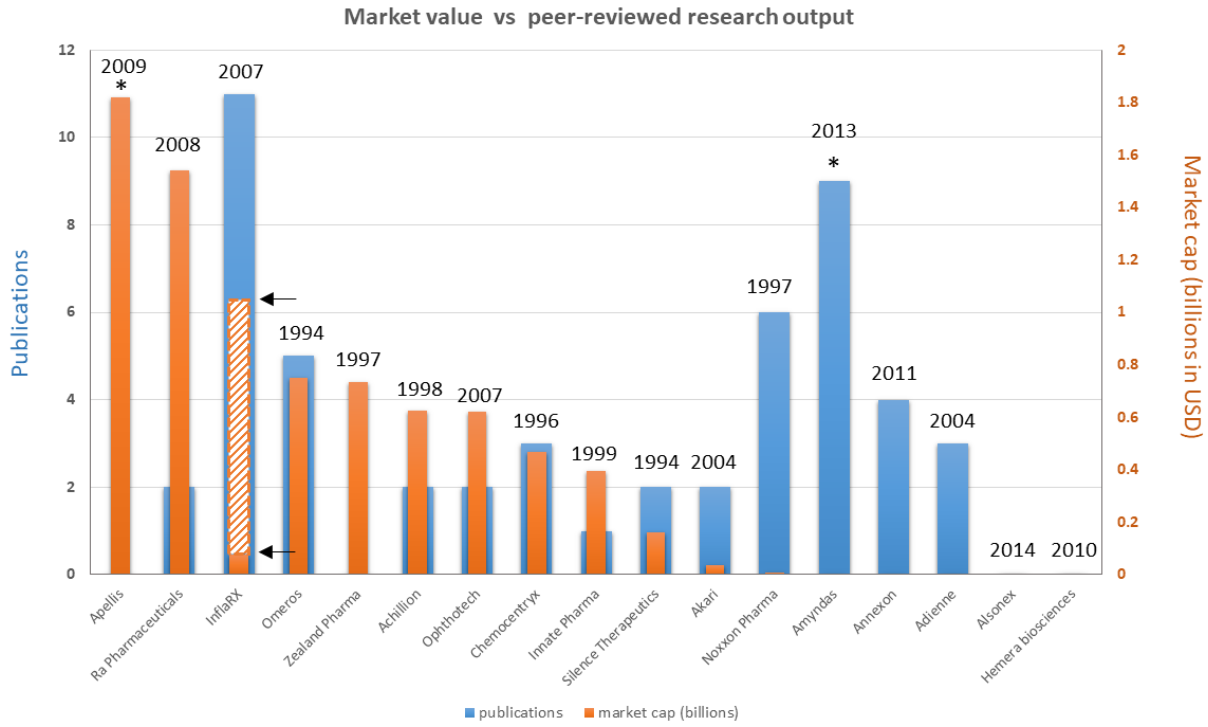

Figure 1. Market valuation of complement-related drug development companies vs research output (peer-reviewed publications of company-sponsored research) validating their complement-related technology or drug candidate. All market caps have been retrieved through Yahoo's finance search engine: https://finance.yahoo.com/ and converted for uniformity to USD based on currency exchange rates, as of 07/30/19. Our analysis has included five privately held companies (not listed on stock exchange). These are Amyndas, Annexon, Adienne, Alsonex and Hemera Biosciences. The valuation of these private companies was retrieved through the CBInsights platform and is available in the online supplement. For reasons of conformity market values for these companies are shown as zero in this graph. Publications refer to peer-reviewed papers (original research articles, reviews and editorials) retrieved through Elsevier's Scopus search engine. Conference presentations, conference proceedings or corporate presentations and investor/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 available online as a supplement. The year in which each company was founded is depicted on top of the respective bar. The asterisks denote that these companies clinically develop different versions of the same C3- inhibitory peptide, compstatin. The dashed bar indicates the market cap of InFlaRx before the announcement of the failure of IFX-1 in the Phase II trials in hidradenitis suppurativa.

Phase II study evaluating the efficacy of its lead product, the monoclonal anti-C5a antibody IFX-1, in patients with the rare skin disorder hidradenitis suppurativa (HS) [12]. In the wake of this news the company's stock plummeted, losing more than 90% of its original value, with the current market cap of the company reduced to 75M (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 HS in particular was based on weak evidence, a

single recent publication with limited translational data, perhaps insufficient to support a full commitment to clinical trials for HS [13]. The case of InflaRx further illustrates that occasionally a combination of media hype, investors' 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 C5aR1 antagonist that prevents activation of the same effector pathway in complement-mediated inflammatory disorders. Of note, Chemocentryx stock value dropped sharply by 22% within two days following the announcement of the InflaRx trial results (data available in online supplement). It is worth mentioning that Chemocentryx's candidate drug, Avacopan, is currently in Phase III trials of ANCA-associated vasculitis and results are eagerly awaited in view of these developments [9].

The peer-reviewed maturity of a technology (i.e., pharmacology/biological efficacy of a drug candidate) is not necessarily reflected in the market valuation of the respective company. There is a 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 instance, several highly valued public companies have advanced their lead compounds into late-stage clinical development without having released in the literature any causative/mechanistic or preclinical evidence to support the feasibility of their clinical program. For example, Omeros Corporation has advanced its lead compound, the anti-MASP2 inhibitor OMS721, into two Phase III trials, in IgA nephropathy and aHUS respectively, without any relevant publication supporting proof of concept in these indications [9]. On the contrary, all Omeros-affiliated publications support the development of anti-MASP2 inhibitors as treatment options for cerebral, myocardial or gastrointestinal ischemia-reperfusion injury (data available in the online supplement). Apellis Pharmaceuticals, a public company advancing C3-targeted inhibitors through Phase II/III trials, has already achieved an impressively high market valuation of approximately $1.8B (**Fig. 1**), the highest among all of the complement-focused drug development companies, likely kindled by the release of non-peer-reviewed clinical results of ongoing trials. While clinically developing its lead drug candidate, a PEGylated compstatin–based C3 inhibitor APL-2, for several indications, Apellis has refrained from peer-reviewed publications, 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 in patients with paroxysmal nocturnal hemoglobinuria, without any published peer-reviewed evidence corroborating or benchmarking their technology against the standard of care in this specific clinical indication [14].

Our literature-based analysis was further extended to privately-held pharmaceutical companies developing complement therapeutics. For instance, Amyndas is a recently established startup advancing 3rd and 4th generation compstatins through Phase II trials that have been communicated in the scientific literature with 9 co-authored publications (**Fig. 1**). Alsonex, a biotech company 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, its development gains 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 investors' expectations. For example, the recent partnership of Zealand Pharma, a company with expertise in peptide-based therapeutics for metabolic diseases, with Alexion, the leading company in marketed complement therapeutics, for the joint development of C3-based inhibitors[15], made the headlines of biotech news channels [15]. While Zealand 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 C3 inhibition (see **Fig. 1**). Lastly, the recent partnership of UK-based Silence Therapeutics, a biotech with expertise in RNA interference technology, with Mallinckrodt Pharmaceuticals, to mutually develop their preclinical lead compound SLN500 as a C3-targeted RNAi therapeutic, was widely publicized in the media [16]. Despite a potential return of approximately $2.0B in combined milestone payments and commercial royalties, Silence has yet to produce any peer-evaluated line of evidence as to how this compound can achieve sustainable C3 inhibition in a therapeutically relevant context. The recently 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 startups by global healthcare leaders (e.g. Roche's announced acquisition of Spark Therapeutics for $4.5B in February 2019) have evidently garnered a lot of momentum for such approaches, as yet unsupported by transparent, evidence-based science and data openness [18].

To gain insight into the overall impact of the peer-reviewed papers produced by complement startups we examined how many of the papers shown in Figure 1 have received more than 30 citations in Scopus, as of 8/6/2019. We found that 14 out of a total 48 papers had more than 30 citations each, covering a time period from the inception date of each company to present, indicating that almost 1/3 of the research output from these companies has garnered significant attention from peers (a complete record of citations retrieved per publication, per company, is provided in a supplementary file).

We should caution that absolute number of publications is, of course, only a modest marker of the reliability of evidence. Also citation impact is only a modest marker of the extent of validation, let alone an indicator of the future potential of a drug under investigation. Despite clear limitations, the peer-review system is still regarded as the most reliable tool to evaluate scientific data. Nevertheless, it is important to examine peer-reviewed papers with a critical eye. Additionally, the inclination of both authors and editors to publish "positive", as opposed to "negative" results, has created a bias in the literature with important implications in 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 latter is Annexon's anti-C1q technology which, despite its sizeable impact in the literature (>560 citations, Scopus) has yet to overcome significant translational hurdles for clinical evaluation in neurodegenerative diseases.

Lastly, the credibility and concrete scientific base of a startup'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 Figure 1, we observed that only 4 out of these 17 companies were founded on the expertise of leading scientists with a sizeable impact on the literature, as deduced by their H-indices and total citations, (H>50 and total citations>20,000 according to Scopus). Although we acknowledge that this aspect is not a mandatory condition for the clinical success of any drug lead, it does provide an interesting perspective as to how 'thought leaders' in the field shape drug discovery efforts and become drivers of corporate innovation. Scientific advisory boards are also important to guarantee 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 biopharmaceutical research. At the same time, corporate data integrity and practices leading to scientific uncertainties are key issues that need to be dealt with in a transparent manner if these new therapeutics are to be translated into meaningful new therapies for patients. Despite a growing number of clinical trials being registered for the evaluation of complement-targeted drugs, peer-reviewed validation of new therapeutic concepts, targets and drug leads remains problematic, particularly in the case of startups that have secured large market valuations capitalizing on investor expectations and increased media attention. While we acknowledge that corporate innovation has to be protected through stringent IP policies, healthcare products that affect patients' lives, such as complement-targeting drugs, should undergo rigorous peer-reviewed validation before engaging sizeable resources and funds for clinical research and trials.

Disclosure statement

A. M. Blom has provided paid consulting services to Zealand Pharma.

D. Ricklin is the inventor of patents or patent applications that describe the use of complement inhibitors for therapeutic purposes, some of which are developed by Amyndas Pharmaceuticals He has also provided paid consulting services to Roche Pharma.

P. Gros has collaborated with, received research funding and/or research materials from the following biotech companies: Genmab BV and Merus BV.

G. Hajishengallis is an inventor of patents or patent applications that describe the use of complement inhibitors for therapeutic purposes in periodontitis, some of which are developed by Amyndas Pharmaceuticals.

V.M. Holers is a co-founder of Taligen Therapeutics and AdMIRx, Inc., both of which are complement therapeutics start-up companies. He receives Taligen-related licensing royalties from Alexion, Inc. and has equity interest in and consulting income from AdMIRx. He is also a recent or current consultant in non-complement areas to Janssen Research and Development, Amgen, Celgene, BMS and Trios.

M. Huber-Lang holds a patent on compositions and methods for the diagnosis and treatment of sepsis by C5a inhibitory strategies (US 7455837).

J.D. Lambris is the founder of Amyndas Pharmaceuticals, which is developing complement inhibitors for therapeutic purposes. J.D. L. is the inventor of patents or patent applications that describe the use of complement inhibitors for therapeutic purposes, some of which are developed by Amyndas Pharmaceuticals; J.D. Lambris is also the inventor of the compstatin technology licensed to Apellis Pharmaceuticals (i.e., 4(1MeW)7W/POT-4/APL-1 and PEGylated derivatives). He also provident paid consulting service to Achillion, Ra Pharma, Viropharma, Sanofi, Shire, LipimetiX, Baxter

D. C. Mastellos declares no competing interest.

T. E. Mollnes has received consultant fees from Ra Pharmaceuticals, SVAR Life Science and Alexion Pharmaceuticals.

R Pio is the inventor of patents that describe the use of complement-related proteins for cancer diagnosis, and has acted as consultant for Amadix.

A.M. Risitano has received research support from Alexion Pharmaceuticals, Novartis, Alnylam and Ra Pharma, lecture fees from Alexion, Novartis, Pfizer and Apellis, and served as member of advisory/investigator board for Alexion, Roche, Achillion, Novartis, Apellis and Samsung, and served as consultant for Amyndas.

R.P. Taylor has collaborated with, received research funding and research materials from the biotech company Genmab BV.

J. P.A. Ioannidis declares no competing interest.

Pending disclosures by remaining co-authors?

E. Sander Connolly

Mohamed R. Daha

Berhane Ghebrehiwet

Taroh Kinoshita

Robert A. Montgomery

Bryan P Morgan

Bo Nilsson

Richard J Smith

Alberto Mantovani

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