

How to reconnect US academic and industrial researchers to better utilize Chinese hamster ovary 'omics in bioprocessing

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It is estimated that biopharmaceuticals market is over US\$125 billion worldwide [1], where Chinese hamster ovary (CHO) cells are used to manufacture over half of these products [2]. CHO cells are preferentially used for biopharmaceutical production due to their ability to perform human-like post-translational modification of the protein, ease of culturing in large-scale bioreactors and protein expression stability [3,4]. The recent publications of the CHO genome has opened up our ability to develop improved processes for recombinant protein therapeutic production [5–7]; however, federal funding related to CHO 'omics and bioprocessing is still limited in the USA [4]. This article strives to increase awareness of the need for better communication between academic and industrial researchers in education, intellectual property (IP) and federal funding in the USA to better leverage CHO 'omics in bioprocessing.

One might ask why would industrial and academic researchers outside the USA be concerned about this shift in research priorities in the USA? The USA has a leading research infrastructure and is a driver of innovation in biotechnology [8]. And, if the USA were to falter, the world economy in biotechnology would be harmed. Over half the public biotechnology and biopharmaceutical companies are US-owned and employ over 65% of the world's workers in this field in public companies [9]. Additionally, these US companies represent approximately 80% of the global market capital, spend 80% of the world's research and development funds, and generate 80% of the world's revenue in

biotechnology and biopharmaceuticals in the public sector [9]. In the private biotechnology sector, US companies also dominate as venture capital funding for US companies represents approximately 70% of the global total [10]. Additionally, in science and engineering graduate education, the USA educates each year approximately 176,000 international graduate students out of approximately 561,000 total graduate students, where roughly 30% of these international graduate students will return to their native countries [11]. And, when considering chemical engineering graduate student enrollment, a dominant supplier of engineers to bioprocessing, the international student percentage increases to 50% [11]. These education numbers and the growing number of biotechnology companies in China, India and Brazil with bio-similars and innovative products indicate that biotechnology is transitioning to a more global industry where the USA plays a critical role. Consequently, changes in research priorities in USA will affect graduate research based education, and subsequently impact CHO 'omics bioprocessing-related academic research and employees destined for a global economy.

If one was new to biotechnology research, one might believe that CHO 'omics research began in 2011 when the first public draft CHO genome sequence [5] was published [7,12,13]. Or, those new or not familiar with the variety of 'omic terms might think all CHO cell bioprocessing problems had been solved [14] or that the remaining problems are only of industrial interest. When, in reality, academic and industrial researchers had been



Sarah W Harcum

Department of Bioengineering,
Clemson University, 301 Rhodes,
Clemson, SC 29634-0905, USA
Tel.: +1 864 656 6865
Fax: +1 864 656 4466
harcum@clemson.edu

quietly and slowly using ‘omic data to better understand the relationship between the culture environment and the product quantity for nearly 30 years. An early example used ‘omics data to determine the underlying mechanism for sialylation when galactose was provided as the carbon source instead of glucose [15]. This work also required the sequencing of the *Cricetus griseus* α 2,3-sialyltransferase IV gene [16]. Current ‘omics studies focus on a wide variety of issues such as nutrient limitations [17,18], waste accumulation [19–21] and glycosylation variations [22,23]. Future studies will be able to quantify genome instability, unexpected apoptosis and incomplete protein processing of the biopharmaceutical. Since CHO-derived biopharmaceuticals cost between US\$2000 to over US\$20,000 per gram [24], it is these high manufacturing costs that, in part, contribute to the increasing healthcare costs in the USA, which is a concern for all [25]. As biochemical engineers, we have the tools to address these bioprocessing cost issues; however, the lack of communication in the USA between and among academic and industrial researchers impedes progress. To bridge this communication gap, several areas need to be openly addressed, principally undergraduate and graduate education, IP rights and federal funding priorities. Furthermore, these areas impact each of the other areas, such that separating the causes and effects will be a challenge that also must be openly addressed.

Education

Dr Charles Cooney recently gave a presentation at the American Chemical Society National Meeting in Dallas (17 March 2014) where he provided a retrospective on the first 50 years of biotechnology [26]. In that presentation, he brought up several points with regards to education that are indirectly changing the federal funding climate. He stressed that students will need many tools to be able to connect technologies across disciplines. Plus, he questioned if we as educators were providing our students the tools necessary to solve open-ended problems with imperfect and incomplete information. It is this last point that I think needs to be examined further. Are academics getting the right training to be able to teach students to solve these open-ended problems? Which is similar to the sentiment expressed in the National Academy of Engineering report, *Educating the Engineer of 2020*, ‘Engineering curricula must focus on developing skills that enable them (the students) to address the unknown’ [8]. And further, are we preparing our students to be able to synthesize engineering practice with social policies and cultural, economic and political changes [27]. Yet, does the current climate of federal funding stress fundamental research so much that, even in engineering, our

graduate students, who will become future academics, do not value application-driven research? It is now very possible for a new faculty member to secure a tenure-track faculty position with no industrial experience. And over that last 30 years, the disconnect between engineers in practice and engineers in academe has grown [8,28]. In 1984, the Engineering Research Center (ERC) funding mechanism at the National Science Foundation (NSF) was initiated at the request of both the White House and the National Academy of Engineering to address this disconnect between the system of engineering education and the practice of engineering. Biotechnology benefited greatly from this initiative as the Biotechnology Process Engineering Center at the Massachusetts Institute of Technology was one of these early ERCs. And, the third generation ERC program solicitation (2013) still stressed the need to educate graduate engineering students to be ‘highly effective in industrial practice’ and added entrepreneurial and globally competitive perspectives to the graduate training [28]. Conversely, beyond this special program, these applied-oriented graduate training goals are not emphasized, since most faculty members were trained outside ERCs. Additionally, the pressures that promotion and tenure committees put on faculty to publish can be at odds with research in an industrial setting. So, how can these new academics obtain these skills themselves and where are they to learn to value application-driven research? First, we need to open lines of communication with respect to the complex and profoundly important challenges in biopharmaceutical manufacturing.

Federal funding

Research training and education related to biotechnology in the USA is primarily funded at the federal level through agencies such as the NSF and NIH, where peer review is used to rank research proposals, and ultimately determine which projects will get funded. In the peer-review process, fellow academics are wary of projects that appear too industrially focused and relegate these research project to be ‘too applied’ and ‘something industry should be doing’, whereas this same project is viewed by industrial researchers as ‘too basic’ because the anticipated results are not specific to a commercial product. These contradictory comments link back to the changes in education. Additionally, there is little incentive to include industrial interactions on federal proposal in the USA. For example, at NSF in the division that supports biotechnology research, Chemical, Bioengineering, Environmental, and Transport Systems, only 2% (~US\$1 million) of the 154 funded biochemical/biotechnology projects (US\$49 million) are classified as Grant Opportunities

for Academic Liaison with Industry projects [29]. In contrast, approximately 5% of all bioscience research and training on behalf of the UK public (BBSRC) research grant funding in 2014 went to projects that were classified as Industrial Partnership Awards totaling over £54 million [30], where industrial interactions are required [31]. If we desire our students to be able to solve open-ended problems with imperfect and incomplete information, academics need to interact with industrial researchers to expose students to such problems. One mechanism to increase these interactions would be for industrial researchers to serve on NSF and NIH proposal-review panels. The industrial researcher would need to articulate the connection and importance of 'fundamental' 'omics and application-driven research and improved healthcare costs.

In addition to the applications nature of bioprocessing research, CHO cells were not considered a model organism by NSF or NIH, until just recently. Specifically, on 25 April 2014, the *C. griseus* (Chinese hamster) genome reached the automated queue for Eukaryotic RefSeq Genome annotation and was released 2 May 2014. This process to have the CHO cell species recognized as a RefSeq began in 2012, but took 2 years to meet the requirements for RefSeq status. The National Center for Biotechnology Information (NCBI) requires that a genome be public and deposited in the International Nucleotide Sequence Databases, which includes DNA Data Bank Japan, European Nucleotide Archive and GenBank®. NCBI sets priorities based on the quality of the genome assemblies, community interest, biological, evolutionary, or economic importance, public availability of supporting transcript evidence and availability of gene annotation in the International Nucleotide Sequence Databases records. This designation is a major milestone. Prior to 2011, many US researchers provided individual *C. griseus* and CHO cell sequences (not counting patent-related sequences, which are mostly attributed to companies) to Genbank, including Dr Pamela Stanley at Albert Einstein College of Medicine [32–36], and my own research group [16,37]. However, until the efforts of several US academic research groups including the University of California – San Diego, University of Delaware, Stanford University and Johns Hopkins University combined with international programs to collaborate, the public CHO genome effort lagged behind the private collaborative efforts of the University of Minnesota and the Bioprocessing Technology Institute of Singapore [4–6,13,38]. Thus, the *C. griseus* and CHO genome sequences being processed at NCBI are attributed to China and Germany. Moving forward, completion of the annotated Chinese hamster genome will greatly impact bioprocessing; similar to

how the completion of the Human Genome Project in 2001 profoundly increased our understanding of human diseases. For example, CHO genome stability can formally be assessed and quantified and complex multiscale models can be developed that combine transcriptome, proteome and metabolome data to predict cell behavior. Both of these research focuses might appear application-driven, yet principally use fundamental techniques well suited to academics.

Another driver that has limited federal funding in CHO bioprocessing-related research has been the exclusion of bioprocessing from several initiatives related to manufacturing. Only as recently as fiscal year 2012 was 'nano-bio manufacturing' included in Advance Manufacturing requests to Congress. And in fiscal year 2014, the only 'bio-manufacturing' initiative was part of the Industry/University Cooperative Research Centers Program (I/UCRC), which is an industry, academe and government partnership program primarily supported by industry. Consequently, this program is not a suitable funding mechanism for most academics pursuing application-driven research ideas. Hence, NSF does not truly include any facet of biotechnology or mammalian bioprocessing in the Advanced Manufacturing, yet, bioprocessing uses manufacturing controls that are far more primitive than the control systems used in the automotive or computer manufacturing industries, while these industries were supported under the Advanced Manufacturing initiatives. Specifically, the NSF Engineering Directorate's Division of Civil, Mechanical and Manufacturing Innovation has an Advanced Manufacturing Cluster that supports fundamental research leading to transformative advances across scales, with emphases on efficiency, economy and minimal environmental footprint. Predictive and real-time models, as well as novel experimental methods for manufacturing and assembly of macro, micro and nanoscale devices and systems are supported. Additionally, advanced sensing and control techniques for manufacturing processes are supported [39]. These same fundamental studies are needed in the biotechnology and CHO cell 'omics fields to allow transformative advances to be made with respect to productivity and production costs, which would directly and significantly impact healthcare costs.

The recent NSF sponsored Workshop on Advanced Biomanufacturing (June 2013) was a move forward toward bringing applied research to academics [40]. Mainly, the workshop report focused on product development, where advanced manufacturing of products includes products that have high-level design, are technologically complex, innovative, reliable, affordable, better and/or solve a society's problem. Though,

the workshop report overstated the gains in advanced manufacturing in (bio)pharmaceutical manufacturing and thus did not report process technology gaps within advanced biomanufacturing, where advanced manufacturing of process technology includes control systems to monitor and/or control processes, continuous processing computer modeling, simulation and analysis, information technologies, advanced robotics, automation, sustainable and green processes and technologies, new industrial platforms, custom manufacturing, and manufacturing across scales. The process-control technologies used in the biotechnology field are archaic with respect to bacterial systems and are practically nonexistent with respect to CHO bioprocessing. CHO 'omics will be greatly enhanced by studies between scales, as these types of studies are necessary to implement advanced control algorithms. To make this significant paradigm shift in the field of controls, fundamental validation studies will be required that are not commercially driven, thus these studies may be best suited to be conducted in an academic setting in partnership with industry, where the results can be shared with the entire CHO cell culture community. Second, we need to shift funding priorities to include 'omics applications in bioprocessing and advanced manufacturing integration into mammalian cell bioprocesses.

Intellectual property

The Bayh–Dole Act (12 December 1980) permitted a university, small business or nonprofit institution for the first time to choose to pursue ownership of an invention instead of relinquishing those rights to the federal government, if federal funds had been used to sponsor the research. This Act was enacted with hopes to increase the commercialization of patents, as most US-owned patents were not licensed. The Bayh–Dole Act, in practice, has made interactions in the USA between companies and universities in bioprocessing, more difficult by erecting perceived barriers to collaborations. University legal councils are now perceived by the biotechnology industry to take the position that the university must own all rights to an invention. Thus, many companies think it is easier to avoid working with academics. This hurts both the students and the company. Specifically, the company now has fewer highly trained individuals with desired skills. In fact, US managers searching for biochemical engineers bemoan the lack of trained individuals in the US, and eventually go to Europe to find qualified employees. In Europe, like the UK, there are close collaborations between industry and academics, which are supported by federal funds.

Obviously, the Bayh–Dole Act has stimulated US universities to patent IP as evident by the high number

of biotechnology-related patents originating from US universities, over 2000 in 2013 [41]. Additionally, more universities are receiving a greater fraction of their budgets from industry; however, the biopharmaceutical/bioprocess industry has been less interested in working with academics due to perceived IP issues. How to break the perceived IP barriers in bioprocessing/biotechnology, the big question. There are several parts to this question and its potential solution. First, we, as a cell culture community, need to gain a better understanding of why bioprocessing/biopharmaceutical collaborations lag other closely related fields. A recent study examined the industry–university interactions in the agricultural biotechnology industry through a series of interviews with academic and industrial researchers, where these interviewed researchers were already working together [42]. Research environment and IP concerns were highlighted in the survey. The survey was able to identify areas where the industrial and academic researchers had similar and dissimilar perceptions. Also, the survey was able to identify what motivates a person to conduct research. Both groups of researchers had very similar perceptions of the research environments for the two cultures. The two groups generally agreed on the advantages of working together: new research funds and tools, students and postdoctoral support, expanding scientist network, and enhancing product development [42]. The perceived greatest disadvantages to collaboration were potential conflicts of interest, communication restrictions, material transfer inhibition, de-emphasis of non-proprietary research and lawsuits over IP issues. Industrial researcher's perception of the Bayh–Dole Act were the most diverse, where some industrial researchers were extremely negative and others were extremely positive [42]. Those that had negative opinions felt that funding academics was similar to funding the competition. Those that had favorable opinion cited that the Bayh–Dole Act allowed for protecting IP as opposed to requiring publication [42]. Unfortunately, the only major conclusion reached by the study was that the two cultures have not converged as had been suggested might occur due to the Bayh–Dole Act [43].

A similar survey instrument of the biopharmaceutical (cell culture, in particular) industrial and academic community might provide insight into barriers to collaboration, real and perceived; however, for this type of survey to be more meaningful, the level of industrial–university interactions desired and currently achieved should be assessed. Academic and industrial researchers not currently engaged in collaborations should be surveyed as well, as they are more likely to have opinions about barriers. Another critical issue with all surveys is the participation rate. Therefore, this sur-

vey should be given at a national cell culture conference attended by both academic and industrial researchers, where they are rewarded for their participation. Of course, the results of the survey would need to be widely disseminated in an open access forum in order to reach individuals who did not participate in the survey. Additionally, a critical analysis of the data would be required and concrete attainable solutions proposed. Third, we need this data and analysis to gain a better understanding of the barriers to academic–industrial collaboration within the cell culture community.

Potential solutions: cooperative/forum

After discussions with academics and industrial researchers from Australia, Canada, China, England, Germany, India, Ireland, Korea, Portugal, Singapore, Switzerland and Taiwan, it became apparent that CHO ‘omics bioprocessing researchers in the USA must take charge and change how we do research. Since we cannot change federal laws or immediately affect changes in federal funding, our best recourse is to join together to share resources. An industrial researcher suggested a clearinghouse/forum in mammalian cell bioprocessing. It would need to be an inclusive group that included any academic or industrial researcher who wanted to participate. The CHOgenome.org might serve as the initial clearinghouse. Ultimately, for this to be successful, physical resources would need to be shared as well. To enable physical resource sharing funding would be necessary. One potential funding source could be something like the Industry & University Cooperative Research Program (I/UCRC; NSF 13–594) [44] with

its update: Biological and Cellular Bio-manufacturing (NSF 14–048) [11]. This mechanism requires a lead institution, cost sharing, industry support (buy-in), marketing plan and membership agreements. One vision of the Mammalian Bioprocessing Center would be a forum for academic and industrial researchers to develop innovative approaches to improve mammalian cell biopharmaceutical manufacturing, biopharmaceutical purification and biopharmaceutical characterization methods. Both NSF initiatives, the ERC and I/UCRC Program Solicitations attempt to address the IP issues by providing center-wide IP policy guidance and sample membership agreements. Potential questions that this forum might address are as follows. What is the root cause of the lactate metabolic shift? How best to purify ‘fragile’ molecules? Are we using best practices for process control in the biotechnology industry? This mechanism may or may not be the best funding mechanism to foster transformative education and collaboration changes, but I hope this perspective stimulates further discussions to strengthen research in CHO ‘omics bioprocessing research.

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