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INTERVIEW

# Interview with the Theme Issue Editors of Antibody-Drug Conjugates

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**What do you think holds the key to your success as a pharmaceutical scientist?**

**Dr Kulkarni:** I have been a student of science since my early high school days in India. This was partly due to the tremendous emphasis that educational institutions as well as parents in India put on science, technology and medicine as the preferred careers of choice and partly due to having some excellent science and mathematics teachers in high school. The teachers made these subjects highly interactive, engaging and fun. My pharmaceutical scientist career took off when I started my graduate studies at the University of Southern California under the tutelage of Dr Vincent H.L. Lee. His mentorship as well as the support of my fellow graduate students at that time really helped me become a good scientist and prepared me for the 'real world' scientific research and development that takes place in renowned institutions all around the globe. Not only was I mentored on the technical aspects but a strong emphasis was also put on behavioral aspects (presentation skills, mentorship skills, honesty, integrity, leadership etc.). This dual emphasis was key to my development as a pharmaceutical scientist as well as a leader and made my transition to the industry very smooth. I have been blessed with excellent mentors/managers/supervisors during my industry career who have morphed me into an independent thinker and leader. I feel very fortunate to have been part of such excellent organizations as Allergan and Celgene where cutting edge science and research combined with wonderful development opportunities have painted a good career path for me.

**Dr Gukasyan:** Adhering to the practice and delivery of sound, fundamental, basic science is central. Having this concept as a core value is essentially the engine that sustains a successful career in pharmaceutical research. In modern business practice the other key factors are being able to be nimble and work seamlessly within multidisciplinary team settings. Efficient and data driven decision making is critical and holds rewards in multiple levels.

**What do you consider to be your key research accomplishments?**

**Dr Kulkarni:** To-date, I believe my biggest research accomplishment is my PhD thesis. That thesis was the culmination of 5 years of hard work and dedication. It really was the first 'true' research project of my career. I have published 13 manuscripts and 2 book chapters over the past 10–12 years but I still consider my PhD thesis as a key research accomplishment that entrenched me into the world of pharmaceutical research.

**Dr Gukasyan:** Drug delivery science and technology has been the central theme of my career. Specialty in the field of parenterals (ophthalmology and intravenous injectable, or nanotechnology based formulations) has been very helpful and productive. It has provided powerful support in drug discovery, as well as development, in addition to being a platform to working across important therapeutic areas. A solid peer reviewed publication track record, contributions and participation in the generation of intellectual property has combined best of both worlds; lessons learned and education of the science community as well as delivery of critically needed medicine to patients all over the world.

**What was the turning point in your career?**

**Dr Kulkarni:** A key turning point for me was the choice of pharmaceutical sciences over engineering. During high school and college years, I was always focused on physics, chemistry and mathematics with very little focus on biology, physiology,

and biochemistry. My goal was to get admission into a Bachelor's program in an engineering discipline at the esteemed Indian Institute of Technology (IIT). However, I missed the admissions criteria and did not qualify for the IIT program.

As a result, I looked at other options and decided to pursue a Bachelor's in pharmaceutical sciences at the University of Mumbai – Institute of Chemical Technology (UICT), one of the highly ranked institutes in Mumbai for a pharmaceutical career. This was a bold choice considering my lack of focus on biology, physiology, and biochemistry. However, my successful career path following that choice has taught me that flexibility, adaptability, and accepting challenges by getting out of your comfort zone are key ingredients to success.

**Dr Gukasyan:** It has been a true roller coaster ride, in every sense of this cliché figure of speech. Reflecting back, I have to admit that there have been multiple ones. However, there is a common thread which has tied them all together. Continuous learning, improvement, and advancement, from all the successes and failures have been recorded in my career through my passion for teaching. In addition to my day job(s), I never lost the interest to mentor and teach young scientists and healthcare professionals about pharmaceutical research. Sharing my knowledge and personal experience through case studies and discussions remains an important tool in shaping my career path. More turning points will come, undoubtedly, in this winding path that is truly undefined by nature.

**Who has most influenced your research career?**

**Dr Kulkarni:** There are several individuals who have influenced my research career over the years. These include my high school and college science teachers, my graduate school colleagues and my past and current colleagues in academia as well as the pharmaceutical industry. But the most influential people have been my current and previous supervisors (Dr Moghaddam and Dr Shen) and my graduate thesis mentor Dr Vincent H.L. Lee. These 3 individuals have morphed me into the scientist and leader that I am today. They have been a blessing for my career progression and development.

**Dr Gukasyan:** The honest answer lies somewhere between the community network of outstanding expert researches that I have been privileged to work with and learn from during the past twelve years, and the individual who opened up the doors of pharmaceutical research to me as a young undergraduate student with a passion for making medicine (later on Vincent H.L. Lee became my PhD advisor). This is a very tight nit industry, spanning from academia to government, and there are lots of seeds for nurture and support for anyone with passion, commitment, and genuine interest. I have to also mention PhRMA, because my introduction to the field as a Fellow sparked a career which was recently come full circle with a PhRMA Working for Health Champion Award.

**Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does this mean cutting-edge science will not likely be featured in journals like Pharmaceutical Research?**

**Dr Kulkarni:** I do believe that cutting-edge science has always been featured in Pharmaceutical Research. It's affiliation with the American Association of Pharmaceutical Scientists brings Pharmaceutical Research at the center stage of cutting edge research in pharmaceutical sciences. It has a broad audience and routinely gets articles from high performing, reputed laboratories from all over the globe. In my knowledge, it is one of the premier journals for publishing research related to drug delivery, drug targeting, nano-technology, formulations research, membrane transporter research and many more. In addition, it is being led by several world renowned scientists on its editorial as well as review team. I believe, this focus on quality as well as cutting edge science will make Pharmaceutical Research the journal of choice for pharmaceutical scientists for years to come.

**Dr Gukasyan:** A controversial topic indeed, but an important one to continue to debate upon. It remains a core value for me, as an individual development plan almost, to make the time and effort to publish. There is a fine balance between this requirement for all scientists and the competitive nature of the business we're in. As long as the system remains healthily balanced, where there is always the incentive and opportunity for innovators to be rewarded, I believe that there will be a plethora of forward looking publications, critical case studies, and post-hoc features of experimental breakthroughs that will be in press for perpetuity.

**Where is the field of Antibody-Drug Conjugates going, and how do the articles in this theme section fill the gap?**

**Dr Kulkarni:** Antibody-drug conjugates (ADCs) is a rapidly evolving field. The interest in this therapeutic modality has sky rocketed over the past decade. With the recent approvals of CD-30 directed Adcetris® (brentuximab vedotin) and the Her2 targeted Kadcyla® (ado-trastuzumab emtansine) and several others in various stages of drug discovery and development, this field is poised to advance at an increasingly rapid pace. Most of the applicability of ADCs has been in the oncology indications but researchers are also evaluating their potential in other therapeutic indications. That is reflected in Dr Shen's article in this theme issue where she discusses the role of ADCs in Ophathalmology.

Some think ADCs as an extension of monoclonal antibodies but in reality, ADCs are much more complex since they have the linker and payload conjugated to the antibody of choice. The ADC field is still trying to gain a deeper

understanding of the mechanisms that govern ADC activity, the strategies to select optimal ADC targets, optimize linker-payload combinations to have maximal therapeutic window, devise translational strategies for effective bench-to-bedside translation, and understand the regulatory approaches that will govern ADCs in the future. In addition, significant effort is also ongoing to generate novel approaches for production of antibodies and ADCs that could help us intricately control the design and stoichiometry of ADCs.

This theme issue is very timely and covers all the areas mentioned above. We have contributions from some of the key players in the field and their opinion represents the current state-of-art. I believe this issue will be tremendously helpful for the readers of Pharmaceutical Research.

**Dr Gukasyan:** Looking at the collection of high caliber contributions within this themed issue two things come to mind. Oncology, being the so to say low hanging fruit, promises to deliver on target (no pun intended). There will be a number of extremely valuable ADC medicines delivered to the cancer patient in the next decade, with the potential of making this terminal disease a chronic one. The second point, which to me holds more value, is the application of ADCs in other non-oncology therapeutic areas. If this is reduced to practice, the technology can be considered a true platform and success for our field of expertise.

### What are the challenges for designing and using novel ADCs ?

**Dr Kulkarni:** Since ADCs are a hybrid of small molecule (linker and payload) and large molecule (antibody), the key challenge in designing and using novel ADC's is the significantly complex multi-parameter optimization that is required during lead selection. The optimization process is also a hybrid of small molecule development and biologics development. In addition, selection of an appropriate target (homogenous expression in target tissue, high expression on the cell surface, minimal sink, ability to get internalized etc.) could make or break an ADC program.

Another challenge, which are not specific to an ADC program but does play an important role is the lack of predictability from preclinical models to human. Regulatory guidance is also scarce for ADC development, however with the recent approval of 2 ADCs, the regulatory aspect of ADC development is becoming more clear. There is significant communication within the scientific community on strategies to overcome these challenges and conferences/meetings such as the World ADC summit, which takes place every year, are fertile grounds for such discussions as well as for imbibing new cutting edge research in this arena.

**Dr Gukasyan:** I think the experts have spoken on this within our themed issue best. A three prong approach that spans discovery to commercial development resonates within articles featured here. Target validation is going to be a key deliverable, with the second part of predictably translating it from bench to bedside. Lastly, technological breakthroughs that the industry continues to take major risks in by substantial investments, will provide the highest level of purity, potency, and molecular definition exemplified within future generations of ADC drug products. I would like to see on the third horizon some medicines from the ADC field designed with the patient at their core, which combine best of disease biology, pharmaceutical research, and engineering for self- administration, −medication.

### What is the key to developing successful collaborative relationships, and how can your company help?

**Dr Kulkarni:** A key factor to successful collaborative relationships is to treat both sides as equals. The collaborators need to understand each other's strengths and then leverage those strengths in a symbiotic relationship rather than just being additive, or worse, diminutive. Understanding what each collaborating partner brings to the table, keeping an open mind, being flexible and always thinking win-win is what makes collaborations highly successful.

Celgene has been developing several successful collaborative relationships in recent years. The number of collaborations have grown exponentially over the past 5 years. They include relationships with academic institutions, small biotech companies, and other organizations that are the epitome of cutting edge research/science. Not only have these relationships enriched Celgene's scientific pool but they have also significantly enhanced the collective scientific knowledge that Celgene now has access to, in order to come up with better therapies in the future, lead innovation and change, and show passion for the patient.

**Dr Gukasyan:** Knowledge sharing is a powerful tool. Every organization has its own channels and definitions for achieving this, i.e., presentations, publications, teaching, etc. While in essence the burden falls on the individuals' shoulders to get this done, I think some of the most fruitful collaborations and partnerships (to the core definition of the word) have been forged at such forums. It is up to us to find mechanisms to establish these networks, and to avoid looking back at them as opportunities lost, but stay within the scope and rules defined by the mission of the company that one represents.

### What is your philosophy of providing internship or curricular practical training for graduate students in pharmaceutical companies?

**Dr Kulkarni:** I strongly believe in providing internship and/or curricular practical training (CPT) for graduate students in

pharmaceutical companies. I believe that strong collaboration between industry and academia is very essential. Individuals who understand basic and fundamental research (academia) in combination with the process of converting these ideas into real life therapies/technologies (industry) are a significant asset to the pharmaceutical sciences. Internship and CPT opportunities provide graduate students with a good view of both sides of the coin. It helps them broaden their thinking and look at the big picture.

I was fortunate to do an internship during my Bachelor's program and it helped me tremendously. I understood the benefit of that opportunity and am striving to do the same for future students. As a result, I am a visiting lecturer at the USC School of Pharmacy and the graduate students highly appreciate the industrial perspective that I (as well as other industrial lecturers) provide them during the lectures. Allergan and Celgene also have internship programs that the interns have found highly beneficial.

**Dr Gukasyan:** It is a community effort, and I can attest to the fact that every participant in the industry contributes to this in some way. Beyond external academic relationships, Pfizer Inc. for example has very competitive and renowned corporate programs for students. Summer student internships offered at Pfizer detail opportunities to hundreds of undergraduate and graduate level students with interest in learning what the industry is all about. Also, the Pfizer post-doctoral corporate program is a terrific opportunity for more lengthy and expert-area specialized positions within the corporation, with a chance to gain experience and publish your cutting edge research.

### What challenges face the pharmaceutical sciences?

**Dr Kulkarni:** Pharmaceutical sciences is an amalgamation of different disciplines. One of the key challenges facing the pharmaceutical sciences is keeping up with the rapid pace of technological and scientific advancements in each of those disciplines and implementing the needed changes in curricular training of graduate students. In other words, there needs to be a strong effort in preserving the relevance of curricular programs in Universities. This will ensure that these student scientists of tomorrow are well trained and well prepared for challenges in the future.

Another key challenge is the availability of adequate funding for junior faculty members. This is very important for developing good educators and research mentors of the future.

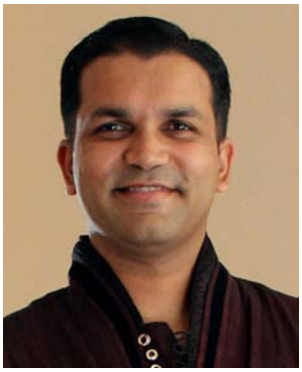
**Dr Gukasyan:** Pharmaceutical research at its core is very patient centric. In one way or another, all experts in this area work with or influence patient lives. Keeping this mission in mind, I think one of the biggest challenges is going to be managing the patient itself in the age of information sharing and technology. Access to medicine, technical information about it, ways of using it, will all merge within mass-personalized media/technology, and we have to find efficient ways of providing transparent knowledge along with new cutting edge medicines to a more informed global patient population.

### What are your views for collaboration between industries and universities?

**Dr Kulkarni:** I believe that collaboration between industries and universities is very crucial. The steady flow of well-educated researchers that are strong scientists, independent thinkers and possess good leadership qualities are a boon for the overall pharmaceutical industry. In addition, a significant number of new therapeutic targets, ideas, and technologies are generated from the basic research that occurs in various laboratories across universities. Graduate students working on these targets and ideas enter the workforce (as university professors or industrial researchers) and champion them for successful application. Furthermore, several universities are affiliated with hospitals that provide them with rich data set from patients – a highly valuable resource for ideating the potential therapies of the future.

Industries, on the other hand, have strong expertise in taking an idea and converting it into a product. Several pharmaceutical industries have very productive collaborations with universities whereby they leverage the academic excellence at Universities and help convert those visions/ideas into reality.

**Dr Gukasyan:** This is an essential part of the business that continues to provide a new lifeline to the pipeline. Among many academic relationships and collaborations, opportunities appear endless on the surface. There is a strong push to open up, globalize, and share data along with information. A few major precompetitive areas have been identified, which I feel will pave the way for new opportunities of collaboration in the future. Public databases and consortia are just a few of the existing tools out there which are trailblazers in this concept. From platform delivery or diagnostic technologies (like emergence of healthcare nanotechnology), drug side effect databases (or opportunities for new indications, another way to look at it), excipient safety information libraries, and clinical trial details are all current mechanisms for such precompetitive collaborative research.



**Ashutosh Kulkarni** Ph.D received his Bachelors in Pharmaceutical Sciences from the University of Mumbai and his Ph.D. in Pharmaceutical Sciences from the University of Southern California in 2004 under the supervision of Dr Vincent H.L. Lee. His Ph.D. thesis focused on "Structure –Function Relationships of the Mammalian Intestinal Dipeptide Transporter hPepT1" Following graduation, he joined Neurion Pharmaceuticals as a Scientist in their Neuroscience department. In 2006, he moved to Allergan Inc in their Pharmacokinetics and Drug Metabolism department working on several development projects and contributing to a number of IND and NDA submissions. He was a key member of several non-clinical teams and was responsible for driving DMPK strategy and studies for those projects. In 2011, he joined Celgene as a Principal Scientist in their Pharmacokinetics and Drug Metabolism department. At Celgene, he has driven DMPK strategies for several discovery programs, some of them leading to development candidate nominations and has been a Project team leader for 2 early stage projects. He has a broad knowledge of the entire discovery and development paradigms, has authored or co-authored 13 publications, 29 abstracts and 2 book chapters, has given several invited presentations, and has been a visiting lecturer at the USC School of Pharmacy for almost 8 years.

**Hovik Gukasyan**, PhD received a BS in Chemistry from the University of Southern California with an academic minor in Biology. In 2003 he received his PhD in pharmaceutical sciences from the same institution under the supervision of Professor Vincent H.L. Lee. His publication track record includes 30 peer-reviewed research articles, including 2 book chapters, 79 abstract presentations as posters or invited talks. With more than 12 years industrial experience, Dr. Gukasyan is currently Senior Principal Scientist within the Drug Product Development support line at Pfizer Global R&D in San Diego, CA. His primary area of research lies in the development, characterization and application of novel drug carrier systems (nanotechnology, targeting, and controlled delivery devices), drug discovery and repositioning. In addition, Dr. Gukasyan is Lecturer at the University of Southern California School of Pharmacy in Los Angeles, CA, at the University of California – San Diego Department of Mechanical and Aerospace Engineering in San Diego, CA, and at the KGI School of Pharmacy in Clairmont, CA.