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Vincent Lee on integration of drug delivery and discovery

Interviewed by Rebecca N. Lawrence

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What inspired you to pursue drug delivery research?

It was entirely by accident. To begin with, I never dreamed of being a scientist. I set out to become a medical doctor. I owe my scientific career to three former professors at Ferris State College in Big Rapids (MI, USA), where I received my pharmacy education. They were Prof. Everett Nienhouse in organic chemistry, the late Prof. Thomas Mikkelson in pharmaceutics, and Prof. Brandt Rowles in clinical pharmacy. They piqued my interest in research. It was Tom who was instrumental in enrolling me at the University of Wisconsin, the birthplace of pharmaceutics. There I met my former mentor Prof. Joseph Robinson and now my best friend. Joe introduced me to drug delivery research and challenged me to do the very best. I should add that 20 years ago, drug delivery was almost entirely physicochemical in thrust. Joe was among the few visionaries who broadened the definition of drug delivery by adding a biological dimension.

Can you tell me a bit about the pioneering work that has been taking place in your lab at USC?

My work deals with the delivery of challenging molecules, including peptides and proteins, in the eye, the lungs and the gut. My main goal is to understand whether the entire array of drug transport mechanisms in the GI tract also exist in those mucosae for which absorption is an incidental function, as in the eye and lung. A related goal is to determine the baseline efficiency of a particular drug absorption mechanism and subsequently the degree to which it can be increased through formulation engineering.

My research team has made several contributions to drug delivery in the past 20 years. First, we have developed an approach to gain insight in the substrate-binding domain of membrane-bound drug transporters. This is of value in drug design. Second, we discovered that the epithelial cells lining the respiratory tract and the conjunctiva of the eye were equipped with the same array of drug transport mechanisms that exist in the GI tract. This fascinating finding makes us wonder whether this scenario also holds true in other absorptive epithelia.

Our third contribution concerns optimization of drug delivery to the eye. As you know, drugs in eye drop preparations can be absorbed into the bloodstream to cause possible harm to the susceptible patient. A decade ago, we discovered that it was possible to minimize drug absorption into the bloodstream by drug design because the two principal mucosae responsible for drug absorption into the eye and into the bloodstream are not exactly the same. To date, the vast majority of ophthalmic drugs are derived from those originally designed for oral use, which by necessity are well absorbed. It is tempting to select the few candidates that are best absorbed orally for further evaluation. If this ophthalmic drug selection paradigm prevails, we must resist the temptation to select the most potent and the best absorbed orally for the sake of minimizing systemic liability. Our work suggests that it might be prudent to go with those molecules that are not necessarily on the top of the list for oral absorption and potency, and then to use the prodrug approach to tailor-make a molecule that is more compatible with the physicochemical properties of the cornea (the gateway to drug absorption into the anterior segment of the eye), the conjunctiva and nasal mucosa (the port of drug entry into the bloodstream).

In the future, with respect to ocular drug delivery, my team seeks to understand the nature as well as the magnitude of the constraints limiting the access of topically applied drugs to reach the back of the eye for treating vision-threatening conditions, such as macula degenerative disease. Our goal is to devise ways to overcome each of these constraints by focusing on increasing the efficiency of transport mechanisms already present. We are testing the hypothesis that there exists a small library of endogenous absorption promoters that are produced and stored in the epithelial cells and which are meant to act locally and transiently. If this hypothesis is proven to be correct, the next step is to screen existing excipients and then create new ones that will unleash these enhancing molecules.

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We adopt the same strategy in optimizing respiratory drug delivery. This essentially is a bioengineering feat: molecular engineering, formulation engineering and device engineering. Few drug molecules are currently engineered for lung drug delivery, and we are just beginning to see the emergence of an improved generation of devices that are designed to faithfully deposit the correct dose in the alveolar region, time after time. This stringent requirement is crucial for drugs with a narrow therapeutic index (e.g. insulin). Other investigators are pursuing formulation engineering, principally particle engineering.

Finally, in oral drug delivery, my team focuses on designing peptides that are smart enough to promote their own penetration (as exemplified by Pz-peptide that enhances transport in between cells). We are also focussing on understanding the endogenous transporter protein, PepT1, with respect to substrate-binding domain, its compartmentalization in the cell following biosynthesis, and regulation of its distribution between the apical membrane and the intracellular store. We are particularly interested in manipulating this ratio with the same excipients mentioned earlier in situations that warrant such a strategy.

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Do you think that drug delivery should take a more important role in R&D to improve drug therapy?
I think drug delivery will be increasingly important in this era of genomics. We all have the same types of proteins but not necessarily an identical copy of each. For some proteins, a single amino acid difference can be highly significant for activity or lack thereof. For the first time, we are on the verge of having the means to respond to the well-known phenotypic differences in drug response in a heterogeneous patient population. If pharmaceutical companies are going to respond to pharmacogenomics – and there is every indication that they are, to varying degrees – then instead of producing one blockbuster drug aiming at a huge segment of the population, they might begin to produce drugs for a stratified population. As consumers, I can foresee us all having our own drug formulary that is grounded in the science of genomics. Because drug design cannot be the only answer to this therapeutic challenge, drug delivery must be brought forth to fill the void.

Are large pharmaceutical companies being conservative in the area of pharmaceutical delivery?
I think pharmaceutical companies are being traditional (rather than conservative) in the sense that, generally speaking, they tend to be reluctant to launch the first product in a controlled-release platform. Controlled-release technologies are currently thought of as a way to maintain a competitive position for as long as possible and therefore these technologies are not usually brought forward until the patent is about to expire. For some drugs, launching them in a controlled drug delivery platform is the only way to go. Omeprazole is a good case in point. In this genomics era, I envision that a pharmaceutical company might consider launching one drug simultaneously in different presentations targeted for different phenotypes. To realize this might require a quantum change in the way drugs are tested for safety and efficacy and evaluated for regulatory approval.

Do you think drug delivery research can really contribute to reducing rising healthcare costs?
I think some drug delivery research might improve quality of life by reducing the incidence and severity of side effects and consequently decreasing healthcare costs. There is a misconception that controlled-release technology is expensive. Although this might be so on a per-unit basis, we really should be looking at the cost of total therapy. I think we need better documentation of the pharmacoeconomics of drug delivery systems. I am very pleased to see some pharmaceutical companies that embrace drug delivery are taking pharmacoeconomics very seriously. Transdermal fentanyl is a good example of a product with large economic benefits for postoperative pain, as is transdermal scopolamine for motion sickness.

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Do you think we should move our attention to prodrugs rather than concentrating so much effort on drug delivery systems?
Absolutely. Whenever possible, drug delivery requirements should be addressed in the grand drug design scheme. After all, prodrugs are a drug delivery system. Despite several commercial successes afforded by prodrugs, new chemical entities are generally favored. Going back to genomics, I do feel that prodrugs could provide the type of fine-tuning that might be required.

Do you think there is a future for peptide, protein and oligonucleotide targeted delivery?
Certainly, because we need all the help we can get to defeat some of the worst diseases. Our preference is to use small molecules but we need to have other sets of tools to meet every therapeutic challenge.

Do you think that enough time and attention is being focused on brain drug delivery considering the rising healthcare costs attributed to an increasing incidence of CNS diseases?
No, definitely not. It is puzzling why billions of dollars are spent on drug discovery for CNS disorders but much less on drug delivery when the challenge posed by the formidable blood–brain barrier is legendary. There are surprisingly few laboratories working actively in this area. The ones that come to mind immediately are Dr Pardridge's group at UCLA, Dr Zlokovic's group at the University of Rochester, Dr de Boer's at Leiden University, Dr Sugiyama's group at the University of Tokyo and Dr Terasaki's group at Tohoku University.

What do you think the future holds for improving gene and vaccine delivery?
I think the future will probably involve more non-viral than viral gene delivery. Our body is conditioned to combat viruses. Synthetic materials offer more flexibility in design, and quality control will not be as problematic. We can mix-and-match the components to ensure the system can get into the cell. The current status in gene delivery is that promising *in vitro* findings abound, but that there is still some distance to go in meeting the pharmacokinetic challenges *in vivo*. Thus, most work focuses exclusively on getting the gene into its target cell, but the ultimate challenge is how to direct the genetic material to the site of action. Towards that end, we need to pre-empt the body from removing the gene vector before it reaches its destination. A case in point is the administration of viral vectors of the CFTR gene, which has overlooked the mucus barrier between the virus and the cell. Finally, we are still rather empirical when it comes to dosing regimen.

What are the main problems with clearing/excretion of viral and synthetic delivery systems from the body?
Good question. More work is needed in this arena. I think it would be fascinating to know how our body would clear, for example, the dendrimers that are being tested as a gene delivery platform.

I would very much like to see drug delivery in the limelight.

Do you think that the 'flatter-is-better' paradigm in drug delivery research, which focuses on pharmacokinetics, is as important as pharmacodynamics?
There is no doubt in my mind that we need to pay more attention to pharmacodynamics. As an example, albuterol in two different formulations achieve different pharmacodynamics despite similar pharmacokinetics. I am

convinced that we need to find a better way to measure drug pharmacodynamics. The challenge facing us is that the appropriate marker might not be that obvious. Moreover, we need to concentrate more on the individual than on the population – one size does not fit all. We are beginning to recognize that each of us is unique and, for some drugs, this uniqueness might be important.

Do you agree that the future of drug delivery is limited because some systems induce immune responses and also because of problems with cell targeting and membrane penetration?
No, I think we need to be more optimistic. We need to operate on the assumption that Mother Nature is very protective and so the body's natural instinct is to deter the entry of foreign substances through multiple mechanisms. I think that in some way, she anticipated that people would be very creative. But to what degree can we 'outsmart' Mother Nature?

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What are the most recent and innovative delivery systems available at the moment?
There are many: Pardridge's work on designing the right molecular packaging system to get the drug across the blood–brain barrier is very innovative, as is the porous particle technology developed by Edwards and Langer for lung delivery. Noteworthy developments on the horizon are tissue engineering and drug delivery platforms on a chip.

I would very much like to see drug delivery in the limelight. Unfortunately, the history of drug delivery is to fix a problem that drug discovery cannot solve and therefore delivery has always taken a backseat. I hope that in the changing dynamics of drug discovery, pharmaceutical companies will take a long look at the big picture and gain a good understanding of some of the drug delivery challenges ahead.

I am convinced that future challenges in drug delivery will be driven by biology. There must be a team effort: hopefully, the biologists will be able to identify more of the hurdles and then the engineers will design systems to overcome them. We therefore need to train future generations of scientists differently. I hope to see a common drug delivery vocabulary that everyone must have and I extend this to the drug discovery medicinal chemists. The way we train scientists at the moment tends to 'pigeon-hole' them. If you are a medicinal chemist, you might never think of publishing a paper in any journal other than a chemistry journal. But if you are trying to fine-tune drugs using prodrugs, why should it not go to a journal whose main focus is drug delivery?

Do you think collaborations in drug delivery research between industry and academia are important relative to 'pure' drug discovery collaborations?
Yes, I think it is, but I think our mission should go beyond establishing a concept. I fully support the notion that you have drug discovery in the laboratory, but you need feasibility studies and it is not in the mission of universities to go beyond this. Therefore, to translate this knowledge into something that is tangible, we need another vehicle. I do not see anything wrong with having a company in a university setting that is grounded on promising allowed patent applications. This could be an incubator mechanism to establish the feasibility of your company. I think small companies make a much more significant impact than many large pharmaceutical companies as I often wonder how committed big pharma are.

What would you like to have achieved by the end of your career?
There is no end. I hope to have contributed in a small way to the intellectual and personal growth of the next generation of scientists who are key to advancing the frontier of drug delivery. In terms of knowledge, I hope to gain an appreciation for the grand visionary scheme Mother Nature devised to build a system of checks and balances in epithelial solute transport. Research is essentially following one's instinct in pursuing a moving target. My research today is very different from what it was when I began my independent research career at USC almost two decades ago. Therefore, it might be impossible to forecast what I could be pursuing two decades from now. For the time being, however, I want to know why some drug transporters are so tolerant of diversity in chemical structures and to understand how Mother Nature regulates the distribution of transporters within the cell. I wish to listen in on the dialogue between what determines the signal within the cell and what determines the distribution of the proteins within the cell.

I hope that someday I would be able to discover and/or create an excipient (possibly polymeric in nature) that would, by remote control, orchestrate the trafficking of certain drug transporters between the absorptive membrane and the intracellular store. My biggest dream of all is to be able to deliver drugs to the back of the eye for the treatment of macular degeneration without going through invasive procedures.

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