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It's all about delivery: interview with M. N. V. Ravi Kumar

M. N. V. Ravi Kumar is interviewed by Stella Bennett, Commissioning Editor. He is the Professor at Department of Pharmaceutical Sciences, Texas A&M Health Science Center in College Station. His research in drug delivery has won him numerous awards including the British Pharmaceutical Conference Science Medal, UK (2009), Tom Gibson Memorial Award by British Society of Plastic Surgeons and the Royal College of Physicians and Surgeons, UK (2008), Indian National Science Academy (INSA) Medal for Young Scientist, India (2007). He was awarded Alexander von Humboldt Research Fellowship, Germany (2002). He was appointed to Guest Professor/Distinguished Foreign Professor at Seoul National University (South Korea); University of Navarra (Spain); University of Torino (Italy) and Shandong University, (China). Since 2003, he supervised about 41 students that include MS: 20; PhD: 7; Postdocs: 10 and Visitors: 4.

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Q You originally trained in physical science & applied chemistry; what began your interest in medicine, & specifically in drug delivery?

I had my first opportunity to work on a drug delivery project during my Master's course work for 6 months during 1995 which motivated me to pursue a long-term project that led to a PhD in 2000 both in chemistry departments at different institutes. If I look back to analyze what I did then I feel very embraced as drug delivery then to me was to sustain the encapsulated drugs as long as possible in a test tube. Subsequently, I did my first postdoc at University of Kentucky, Lexington in cancer research during 2000–2002, where I started to understand biology and medicine followed by another postdoc (Humboldt fellowship) at Saarland University, Germany in gene delivery (2002–2003). Though I was awarded an extension of Humboldt fellowship, I decided to return to India in 2003 to take up my first faculty position (Assistant Professor) at National Institute of Pharmaceutical Education and Research (NIPER) Mohali. Just before heading back, I had spent significant time on identifying the

area that I wanted to build my research program. This became all the more important as I was one of the first faculty members in the department of pharmaceuticals without a pharmacy degree. The parameters I considered for choosing my area of work were ongoing activity in the country, NIPER's research needs and a bit on what the industry could be looking for, and I felt oral drug delivery would be ideal. This became apparent for other scientific reasons to as why nanosystems are not explored much for oral delivery when these are believed to be taken up intact enhancing the oral bioavailability. I guess at NIPER my drug delivery research program started to take shape (and still taking shape now) with some basic understanding of pharmaceuticals and the basis for delivering drugs or drug-like compounds.

Q Could you describe the work currently being conducted at the Texas A&M Rangel College of Pharmacy?

For about good 12 years, we have used commercial polyesters (we still use) and worked on about 15–20 different drugs or drug-like compounds and the idea was to see if we can

convert injectable to oral, cut down the dose and frequency and always depended on animal models unlike my MS and PhD work. While there is a big deal of work going on around the globe on targeted drug delivery and attempting to establish mechanisms of these nanosystems absorption, distribution, elimination and of course the safety using model systems, we never attempted to do that then may be, I have more questions than answers. One of the questions I felt very important was how we optimize ligand–receptor stoichiometry with commercial polyesters, mostly if not always confined to end terminal functionality. Once we have something to answer the functionality problem then further questions started, what are the ligands to target a particular receptor, somehow I am not a big fan of large peptides or antibodies. At last, we have few ideas to work with that I started believing will help us understand the mechanisms and also possible translation. My group currently is making biodegradable designer polyester-based polymer compositions with variable molecular weights and functionality and methods for making pharmaceutically effective nanosystems for receptor-mediated delivery across the biological barriers, for example, GI tract. The designer polymers go beyond the currently available polyesters in that they allow optimization of ligand–receptor stoichiometry which is one of the key factors to achieve ideal receptor-mediated delivery of the encapsulated compounds, while receptor itself can be debatable. We are screening small molecule ligands for receptor-mediated delivery. We have some excellent cell and animal data to backup this hypothesis and more studies are underway. We believe the success of this polymer platform will allow single or multiple ligand functionalization, deliver single or multiple drugs, conversion of invasive to noninvasive administrations as well as potential to minimize attrition rates in the drug discovery. Next few months, we should have some publications coming out on these designer polymers, while couple of provisional patent applications are filed.

Q What do you think the future holds for nanoscale drug delivery?

I guess very bright, but one should understand ‘nano’ cannot be a one-stop solution to everything in drug delivery. In particular I think there is a high expectation from the nanoscale systems in the area of targeted drug delivery where I believe a reality check is important. I think we need to go little beyond demonstrating statistical significance and be realistic. One of the major benefits of the ‘nano’ could be coming from its ability to offer minimum effective dose regimen.

Q You studied for your undergraduate & postgraduate degrees in India – could you share your thoughts on the innovation & opportunities in Indian pharmaceutical research at present?

Academically, there is a big change at policy level where the government initiated National level institutes exclusively for pharmacy education along the line of Indian Institute of Technology (IITs) model of which the first one came up at Mohali, Punjab that I was part of until I moved to UK in 2008. I guess now there are total seven of them in different states and three more planned taking the tally to ten. So definitely there is a lot happening and huge potential. I think the public–private partnership becomes critical for the success of these institutes and industry should come forward to help these institutes grow. Whether we like it or not, translation is the ultimate goal of the academic research we conduct and that happens only with industry involvement. All the new institutes have academic mentor institutes help them develop, in addition they should have had industry mentors as well.

Q What do you think has been the biggest advance in the field of therapeutic delivery in the past decade?

There are quite a few, for example, Abraxane (paclitaxel) that is still increasing its portfolio of cancers that it can manage; Bydureon (exenatide) once a week injection is a glucagon-like peptide-1 agonist used in Type II diabetes; DaTscan (Ioflupane I¹²³) is a radiopharmaceutical used for striatal dopamine transporter visualization using SPECT brain imaging for adult patients with suspected parkinsonian syndromes (PSs); Raplixa (fibrinogen) to help control bleeding from small blood vessels when conventional surgical techniques, such as suture are ineffective or impractical.

Q You once described your belief that the future of therapeutics will involve a combination of engineered drug molecules & traditional or herbal medicine. Could you please elaborate on this for our readers?

I still believe the same. One of the things that unsettle my thought process is the approach to drug discovery for managing the diseases or their complications, for example, cardiovascular diseases, Alzheimer’s disease, Parkinson’s disease, diabetes, cancer or when they co-exist, are believed to be initiated or progressed by a variety of molecular pathways but the discovery is very much focused on single target or path, I fail to understand this approach, likewise the targeted delivery approaches. In this context, there is a lot of literature describing the ability of natural compounds to act on a wide range of molecular pathways, but not much work

is done in establishing product profile that facilitates the use at large. In this direction, we have demonstrated the ability of drug-like compounds, for example, epigallocatechin gallate, ellagic acid, curcumin, co-enzyme Q₁₀ to minimize lipid abnormalities, endothelial dysfunction, insulin-sensitization, oxidative stress/inflammation, hypertension and organ damage in rodent models. In conditions like diabetes (in Type 1), these compounds have no influence on glucose reduction (at least from our studies) but have other actions to delay complications where one might consider a traditional glucose-lowering drug. However, the overall success of these drug-like compounds depend on efficient delivery systems.

Q Are there any changes you would like to see in the next few years across the field of drug development & design, & therapeutic delivery in particular?

Yes, of course. The delivery approaches should consider the drug, the disease and the room available for improvement when applied to existing drugs while efforts should be placed in early drug discovery program that can help minimize attrition rates. This then has to be put on patient benefits and economy landscape, as marginal improvements will not help the cause. I wish to see more work (drug delivery, nanomedicines) done in areas other than cancer where a patient could be on drugs life-long. While, in cancer

it is important to switch the gears toward low dose, more frequent dose regimen (metronomic therapy) than focusing on maximum tolerated dose and targeted approaches. There is a huge gap between development, delivery, efficacy and safety, where majority of work is focused around development and short-term evaluation. It is important to come up with simplified methods of formulation that permits scale-up which not only helps advance academic research to industry practice but also helps generate data on chronic administration of the nanosystems collecting more information on their safety aspects. Finally, I would like to see the application of delivery technologies for drug-like compounds, it is all about delivery after all.

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