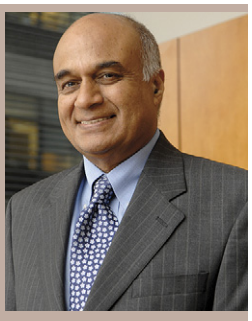
interview

Raju Kucherlapati talks about personalised medicine: breathing new life into old drugs

Interviewed by **Steve Carney**

Raju Kucherlapati

Professor of Medicine and the Paul C. Cabot Professor of Genetics at Harvard Medical School and Scientific Director of the Harvard-Partners Center for Genetics and Genomics



Raju Kucherlapati was born in India, where he completed his first degree. He later moved to the USA, obtaining a PhD at the University of Illinois and following this with a Postdoctoral position at Yale, before joining the faculty at Princeton. He later moved to the University of Illinois as Professor of Genetics. Following a period as Professor of Molecular Genetics at the Albert Einstein College of Medicine in New York, he moved to his current position as Professor of Medicine and the Paul C. Cabot Professor of Genetics at Harvard Medical School as well as the first Scientific Director of the Harvard-Partners Center for Genetics and Genomics. He is a member of the National Advisory Committee for Human Genome Research at the National Institutes of Health and Editor-in-Chief of *Genomics*. Raju Kucherlapati was a founder of Cell Genesys, Abgenix, Aveo Pharmaceuticals and Millennium Pharmaceuticals and currently serves on the boards of Millennium Pharmaceuticals and of privately held AVEO Pharmaceuticals.

What do you think are the toughest challenges that personalised medicine will need to overcome?

When people talk about the challenges that need to be overcome, different people have very different perspectives. Some think that one of the major obstacles is that there is not enough information to allow incorporation of genetic knowledge into clinical decision making. But, I don't feel it is accurate, because almost every week, there is a new discovery about some gene or its involvement in disease and how information about that can be useful for treatment. Some people believe that, however, the pharmaceutical companies may not be too excited about this idea of personalised medicine and that may be an impediment. My experience is that when we listen to many of the pharmaceutical executives they're all saying how important personalised medicine is, but if they could develop drugs that are going to be very effective, for the patient, then that would be very good business for them. So I think that that's not probably going to be an impediment as we move forward.

In my opinion, there are three major obstacles: demonstrating clinical benefit, establishing favourable cost efficiencies and ensuring broad awareness among patients and physicians. First it is important to show that if genetic and genomic information is used for clinical decision-making, that such incorporation results in better outcomes for the patient. The second major obstacle is to show that when we incorporate genetics and genomics in clinical decision-making, it is not going to increase the cost of healthcare. But incorporating genetics and genomics would indeed change the cost-benefit ratio for society. So when I talk about cost issues I'm thinking about it not for any one particular entity, not just for the pharmaceutical company, not just for the payers, but for the society as a whole. Then if we could show that the cost-benefit ratios are favourable, I think that it would be accepted. Third, we must make sure that physicians and patients are aware of the possibilities available with personalized medicine and how their lives can be changed.

Could you outline the details of the warfarin trial that you're about to start?

As I mentioned, one of the most important things in establishing personalised medicine is to demonstrate that the outcomes are going to be favourable. As you know, the way that we determine outcomes is clearly very well established for drugs in the United States. Drugs have to go through, phase one, phase two and phase three trials. Following these trials, they are submitted to the FDA and hopefully approved. For some drugs it may be possible or necessary to conduct, phase four trials. Based upon the results from those phase four trials, if conducted appropriately and

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published in appropriate journals, then practice guidelines may be altered in accordance with the results.

So, we felt that it was important to begin to think about that and to conduct these types of studies. One of the problems is that even though people have been doing these types of studies, most of the time, as far as genomic information is concerned, the trials are retrospective and tend not to have adequate numbers of patients to come to definitive conclusions. So we decided that we wanted to undertake a series of such trials, where we would be able to get definitive information and to test the hypothesis that incorporating genetics into the prediction of effective treatment regimes would, indeed, improve outcomes.

One of the first treatments we have chosen is the effective dosing of the anti-coagulant therapy, warfarin. In the United States, there are more than twenty million prescriptions for warfarin every year. Warfarin is a widely used drug and it has been around for more than fifty years. Warfarin is now a generic drug and several different companies manufacture it. However, despite its widespread use for a very long period of time, the precise dose of the drug that needs to be administered to patients is mostly done by trial and error, because of its poorly predictable pharmacokinetics. The dose of the drug that is administered to patients is very critical for their outcome. Too much of the drug could result in intracranial bleeding. Too little drug can result in stroke or other types of problems with these patients.

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Information is now available with respect to normal genetic variation in the population in cytochrome P450 genes and the vitamin K receptor genes that would enable us to try to define the appropriate dose for patients. So what we have started is a trial with warfarin in which the first part of the trial would be an open label trial to recruit about five hundred patients who have never been treated with warfarin. We would take a little bit of blood from these individuals and examine their DNA for genetic variants in the genes that I have mentioned and use that information, along with the clinical information, to try to make a decision about the right dose of drug that we would administer. In this part, it's an open label trial, so we would be able to learn, initially by treating these five hundred patients, what is the right nomogram or dosing algorithm for patients with particular clinical features and with a particular genetic constitution.

We believe that with the data from five hundred patients, we will be able to develop such a nomogram. Once we obtain such a nomogram, we are planning to conduct a prospective randomised trial in which one arm of the trial would be the nomogram alone, without genetics, and the other arm would be the nomogram that includes genetic information. We would then be able clearly to ascertain what the outcomes for these patients would be. We'd be testing the hypothesis that using this genetic information will indeed result in a significantly better outcome for the patients, in the short term and in the long term. If that is the case, then we believe that this would be a very strong example or a strong case for making personalised medicine in that field in reality.

What do you think the implications will be if this trial is successful?

This trial is being conducted with a number of different features. One is the conventional trial that we all know about, but at the same time, we also have a group of investigators who are pharmacoeconomists who are part of this trial. They will be involved in developing, initially, financial models and cost:benefit ratios, to determine what would be the effect in terms of the cost:benefit ratio of improving the outcomes for these patients by ten per cent, fifteen per cent, twenty per cent and so on and so forth. So we will have, not only information about the success of the trial, but also a quantitative measure of how economically successful this might be.

We believe that if the trial is successful and that we can also show that there is a very favourable cost:benefit ratio for the patient population as a whole then I think the approach could potentially become the standard of practice. Also, you might have seen from reports that the FDA is considering changing the label for warfarin, which could indicate that genetic testing might be beneficial for the patients.

'We will have a quantitative measure of how economically successful this might be'

I don't know what the precise wording of such a label change will be, but obviously the kind of information that the trial we are doing now will provide would be tremendously valuable for physicians to make well-informed clinical decisions.

Do you think that having very positive results from this trial will make people think about clinical practice and drug development? Will people will be looking for the personalised medicine approach earlier on in the scheme rather than as an add on at the end of the discovery process?

This is not the first time that a personalised medicine has been used. There are already drugs that are on the market, such as Gleevec™ and Herceptin® that use molecular genetic information to make decisions about treatment. We believe that as you get more and more examples of this nature then there will be a wider acceptance of the notion of personalised medicine. I think that as examples increase, there will be a wide scale adoption of personalised medicine for existing drugs. I think that will also stimulate the pharmaceutical companies to think more and more about you how they will be able to utilise these strategies to position their drugs.

I think there are good examples now and the one that comes to mind initially is Clozapine, which is a very effective atypical anti-psychotic but its use is restricted due to its propensity to induce agranulocytosis. If you could predict the likelihood of developing an adverse reaction, that drug could be much more widely prescribed than at present.

You're absolutely right. That's a great example of a molecule with significant types of toxicity associated with it, which could benefit from the introduction of genetic information. There has also been another report recently, that the FDA is considering changing the label for tamoxifen. Again, in this particular case, there are some women who take the drug, for whom there are significant toxic side effects. There is information to suggest that genetic variants in cytochrome P450 might be responsible for this toxicity. This is another example where if you could identify those individuals that will suffer adverse effects then you could tremendously enhance the utility of the drug.

So even with today's drugs there are lots of opportunities from our perspective as an academic medical centre, to have a very significant impact on healthcare. In each of these type of trials there will perhaps be other organisations around the world that either want to join us, or independently initiate similar trials and we hope that this would be a brand new enterprise at many academic medical centres.

Do you think that the current approaches to the development of personalised medicine are appropriate and useful? How is the HPCGG working to promote personalised medicine and directing and influencing its direction?

As I mentioned earlier, there are a number of different things that need to happen to realize personalised medicine.

The first issue is transmitting genetic information in an appropriate form to the physician. When you obtain genetic testing information, such as a sequence-based or genotype-based or expression profile-based information, or proteomic-based piece of information, the first thing you need to be thinking about is how to share it. There are two aspects to sharing genetic information: reporting standards and privacy protections.

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So, we have initiated a very serious effort together with the IT teams from Partners Healthcare, Brigham Women's Hospital and Massachusetts General Hospital, to coordinate standard reporting of genetic information and making it a part of the electronic medical record. In addition to the technical issues about how to structure the information and how you get it into the electronic medical records, we also must deal with all of the privacy issues as to who would have access to that information within the medical record. We believe we have been successful in dealing with all of the issues and now we have developed a mechanism where we should be able to do that. This could be the basis of a model that could be adopted around the world, to bring genetic information into the electronic medical record.

The second issue that we need to address is to provide knowledge-based decision support systems to the physicians. In other words, when a physician finds this information in the electronic medical record, there should be an algorithm that gives the physician all of the different choices that they could make. Then based upon their knowledge and the information that's provided, they would be able to make appropriate decisions.

You have just mentioned including information in electronic records. What about the question of standardisation of this sort of information?

This is a very, very big issue because very few hospitals and major academic medical centres have robust electronic medical records. Many Primary healthcare physicians don't even have electronic medical records. So in this country, there is a great effort to develop electronic medical records and the health and human services department is striving and advocating such records. All new records could be developed so that they could include standards.

A major issue facing the healthcare enterprise is how could you have all of the information located at a single place? Transporting the information to other places and to allowing it to be efficiently used requires standards. However, certain types of data such as images and so on and so forth, already have standards associated with them. We are working together with the National Institute of Standards and other "standards" bodies in the United States to try to develop similar types of standards for genetic and genomic information. We welcome other people from around the world to join forces in trying to develop such standards and recently there has been some effort made by an international group in Australia, to develop similar standards.

'We welcome other people from around the world to join forces in trying to develop such standards'

With respect to influencing the direction, as I pointed out earlier in the discussion, having all of this information, but with nobody knowing what it means and how that information will be utilised would be useless. That means that we should all be thinking about training physicians to be knowledgeable about genetics. It turns out that in the United States, genetics as a medical specialty has been attracting fewer and fewer people over the last few years. I think part of the reason for this is that, traditionally, genetics has been oriented primarily towards paediatric genetics or prenatal genetics. But now all of the things that we have been talking about are disorders that affect adults. So one of the things that we need to be thinking about is how do we train people in adult genetics and all of these newer methodologies and how they would be able to utilise that. So, the training of the future cadre of physicians who will be knowledgeable about genetics is very, very important.

There is a lot of discussion about what would be the most appropriate type of model for accomplishing these educational and training goals. We at HPCGG have instituted several programmes aimed at enhancing physician curricula. We run one of the largest training programmes in medical genetics, where we train both MDs and PhDs in various specialties of genetics. This includes medical genetics, molecular genetics, cytogenetics and biochemical genetics. We have also established a joint residency programme with internal medicine and now we are training people who are interested in internal medicine and genetics. We have started a joint programme with pathology to try to train people in a new field called molecular genetic pathology. So, we are advocating for change and providing the type of training models that any large academic medical centre will need if they are to embrace personalised medicine.

'We also need to be thinking about, not only how to educate future physicians, but also how to educate all of the practising physicians today'

Not only do we need to educate future physicians, but we also must educate all of the practising physicians today and this is a big challenge. There are some efforts that are underway to try to reach out to particular speciality organisations, and encourage them to organise meetings and workshops at their annual meetings to find out about how much knowledge and experience their members have in genetics. By knowing this, we might be able to increase their knowledge about genetics and inform them how they could be able to utilise all of these great tools to improve their patients' lives.

Do you think there is a perception that going into genetics in the past has been somewhat akin to a service industry rather than, the hands-on medicine that some of your colleagues would be practicing? Could you give a more positive message to young medics that this is a field that could be driving medicine rather than being a service?

You're absolutely right. I think that, in the past, people thought that geneticists would just do the diagnosis and then disappear. But actually it turns out that genetic knowledge of the sort that we are talking about is not only important in diagnosis, but is also important in prognosis and making treatment decisions. So as there are more and more examples of this, people will begin to recognise that genetic information is going to be very important not only in diagnosing some rare genetic disorder, but that it is going to play a very important role in the day-to-day treatment of patients that will be seen by the

primary healthcare physicians. Therefore, I don't think that everybody has to specialise in genetics, but they should be trained adequately and be sufficiently knowledgeable of when they should seek genetic information and how genetic information, when available, can be used.

I think this is one of the reasons why the joint training programmes we conduct with internal medicine are so important. We have also started new programmes here at Brigham Women's Hospital in which we are taking internal medicine residents and then trying to teach them intensively in genetics. These residents will be board certified in internal medicine only but by the time they have finished their three years of residency, they will also be very knowledgeable in genetics. Then they might go on to become specialists in cardiology or nephrologists or whatever, but they would be very knowledgeable about genetics. We believe that when they mingle with their colleagues and become a part of the fabric of medicine, then this knowledge and the importance of genetics would be disseminated to everybody.

What would you like to see happen in the next five years and the next ten years to advance this field to where you think it belongs?

The dream that I have is, first of all, to spread the knowledge about the role that genetics and genomics is playing and will play in the future. From a clinical point of view, the view that I have is that there is going to be a time within the next five to ten years when the physician will be able to incorporate all of the clinical and genetic information on his or her patients into an electronic medical record. So given the particular features that you have entered into the electronic medical record, you should consider doing the following genetic tests and those places where such tests are available. When the results come back, the electronic medical record would be able to suggest that, given all the clinical features and the genetic information, this is what kind of treatment you should consider.

'I think that there is an opportunity for genetics truly to transform the entire healthcare sector'

I also see that nowadays the payers are not certain about the utility of genetic information and therefore they're not sure how they should reimburse for costs associated with it. I believe that the kinds of clinical trial that I talked about are going to become an important fabric of clinical trials, both in the pharmaceutical industry and in academic medical centres. Since much of today's medicine is evidence-based, when you have strong evidence then the payers would consider reimbursement of that. Moreover, if you also have cost-benefit analysis associated with it, then it's very easy for the payers to see how payment for this would save them money in the long run.

Finally, I also see, not in the too far distant future, more and more drugs being developed by the pharmaceutical companies, in parallel with the genetic or genomic testing required for the selection of patients in which the drug will be most effective.

These are just a few ways in which I think genetics will truly transform the entire healthcare sector.