

Need to fight on all fronts

Born in Northfield Minnesota in 1949, Peter Agre joined the Johns Hopkins School of Medicine faculty in 1984 and became Professor of Biological Chemistry and Professor of Medicine. In 2003, he shared the Nobel Prize in Chemistry with Roderick MacKinnon for discovering aquaporins, a family of water channel proteins found on the cell membrane. He is presently University Professor and Director of the Malaria Research Institute at the Bloomberg School of Public Health (Baltimore, USA). Dr. Agre was recently in India to mark the decadal celebrations of the Indo-US Science & Technology Forum and spoke exclusively to Biotech News.

Biotech News (BTN): We have been trying to figure out a cure for malaria for the last 100 years. Will we ever be able to eradicate malaria like we have done with small pox and polio?

Peter Agre (PA): The scale of malaria remains large despite major advances for more than a century. Malaria of course had come under control sometime in the past to give political leaders confidence that it is no longer a current issue of great importance. But it has a bad habit of coming back. In India this is a significant problem and I suspect that public health statistics are not so precise. The diagnosis is never so clear in poorer areas where modern medical facilities are not available. In places like Burma the situation is enormous. In Africa more than 1 million children die of malaria every year. So the scope is very large. And what we've learnt in the past, also because of good efforts made here in India, is that malaria can be brought under control by serious public health steps. We've learnt that when malaria goes away the partial immunity an individual develops after surviving it, declines. So the problem with malaria control is that if malaria comes back due to decline in immunity it is much more severe. Control measures can make the problem appear temporarily better but subsequently, become much worse. So we must be very careful.

Malaria is not a neighborhood problem as mosquitoes don't respect any border. If one neighborhood takes care of malaria and the adjoining one does not, the mosquitoes will bring it right back.

BTN: How far are we from a malaria vaccine today? What are the big ideas as far as the malaria vaccination is concerned?

PA: The logic to vaccine of course is quite clear that if people can become partially immune by having malaria, should we not in some artificial way

provoke that immunity or even increase it? The disappointment is however that none of the efforts have been particularly effective.

If we think of the diseases that have been actually conquered by vaccines, what comes to mind is polio and small pox. While small pox has actually been conquered, polio only has been brought under control. The virus is still out there and it can still come back. So we have to maintain vigilance.

Unlike Small Pox and Polio which are of viral origin, malaria is caused by a complicated parasite having more than 5000 genes. It is a unicellular organism and is a very wily and sinister competitor that goes through three different stages during its life cycle.

Simple analysis says that some of these may be amenable to a vaccine. Efforts are being made by very gifted and dedicated scientists. I hope some of them succeed, but right now the positive analyses are limited. There is a large vaccine trial that was announced a couple of years back in Africa with a manufactured vaccine which shows partial efficacy in one population but not in another. Partial efficacy is not prevention of malaria but only amelioration of symptoms. Those affected had less severe symptoms temporarily. So it's far from a success. I would not recommend one of my children to come to a malaria endemic region based on the current vaccines alone. It would be too risky. So while some of the research efforts should of course be concentrated on developing malaria vaccines, that is not enough. That is like gambling in which you can pick the winner. But what if we don't pick the winner? There is clear evidence that improved public health measures, improved diagnosis and medical treatment of malaria also play a large role. The vaccine may succeed, but looking at things critically, I feel that we still have a long way to go.

BTN: What are the strategies apart from vaccination to get a handle on malaria?

PA: If we observe how malaria has been brought under control, it always the same answer: mosquito control. Malaria was endemic in the U.S. up until the World War II. So before the invention of DDT (that work, by the way, received the Nobel Prize) before modern medical treatment of malaria, it was brought under control and then eliminated. Control measures included simple public health standards e.g. building homes with screened porches, building homes away from the swampy areas, elimination of standing water through drainage etc.

Cuba has eliminated malaria by relentless application of public health measures. No high tech activities, basically public health measures: mosquito control, patient identification, treatment and follow up. This is when malaria is out of control in Haiti, an island just 30 miles to the east of Cuba. An island of course is protected. If we are able to eliminate malaria from all parts of an island, then it is gone forever. This occurred in Sri Lanka as well as Zanzibar in the past. But in continents like Asia or Africa, it is hard to control it at every place at the same time but it will still respond to public health measures.

BTN: Malaria in India is largely linked to *P. falciparum* and *P. vivax*. There is a debate on whether we should have a combined vaccine for both or address the two separately. What are your views?

PA: Vivax and Falciparum are both described as malarial parasites but they are quite different in many ways. Hence the nature of the vaccine by and large would be specific for one, or the other. Just like flu vaccines that we have in the US are strain specific. It does not confer lifelong immunity to flu but the current strain of interest can be addressed. In order to have a vaccine which can take care of both, ►►

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► I think a new strategy must be employed. We have some creative young scientists at Johns Hopkins who are looking at transmission blocking vaccines. The logic of a transmission blocking vaccine is not to prevent you from getting malaria but to prevent you from giving it to others. That involves the biology of Anopheles mosquitoes. One approach undertaken by a very talented young scientist - Rhoel Dinglasan - at Johns Hopkins is developing vaccines specific for the binding site in the gut of the mosquito which should prevent either, or both. This is a theory and is yet to be proven. If there were a universal malarial vaccine that is effective, that will be tremendous. You never predict who gets the Nobel Prize but I will consider success in finding such a vaccine above most other Nobel prizes, certainly above my own.

BTN: What is your opinion on the status of malaria research in India? Do we have the right institutions and the institutional structures to address the challenge of malaria in India?

PA: I spent a wonderful day at the Indian Institute for Malaria Research, New Delhi during the current visit to India. They have modern new HQs with labs which are state of the art. And more important than the facilities are the talented young scientists coming from all over India doing their doctorate in malaria research. Some of them have worked in top US labs and have returned to India. So I am optimistic that you are making excellent efforts here.

In addition to these efforts, there is a series of 10 centers called the International Centres of Excellence for Malaria Research (ICEMR) worldwide, and I happen to be the Director of the Southern African one. Two of them are targeted for the subcontinent of India. One headed by Pradeep Rao from University of Washington,

second by Jane Carlton from New York and they will be collaborating with your Malaria Institute here, to do surveillance throughout India looking for changes in the evolution of the parasite of the mosquito. In a partnership great things can happen. I am optimistic about this and I see this as a very positive step taken by the Government of the U.S. And Government of India to work together for the betterment of all.

BTN: What is your advice to Indian policy makers in the health sector on priorities and challenges in the battle against malaria?

PA: This is an important question. I am optimistic for India. Last night I had a wonderful opportunity to speak with your former president Dr. APJ Abul Kalam. Here is a very wise gentleman, scientifically trained, who is looking at the future of India. I would like American Govt. leaders to have this kind of wisdom. He is not looking for soft, glitzy visits, photo-ops but for hard scientific collaborations. So even though resources may be a constraint in India as they are in the U.S, priorities must be set and I believe they are being set. I don't have access to the figures but I think significant resources are being made available. But more important than the dollars is to put this in front of the young talented Indian scientists. That's where I think India is unparalleled. In the US we have extremely good universities but are seeing a declining interest in science by our young people. India has marvelously talented, enthusiastic young scientists. They are the future and they will make this all happen. So I think that in addition to the budget we have to make sure that the laboratories are sustained not just in times of plenty but constantly. One of the problems in the U.S. is that we have this boom-bust cycle that impacts scientific research. It is like treating diabetes two weeks every



month. So funds are to be made available with long term commitments, of course with in-built accountability, so that scientists can predict what lies ahead. I think a particularly valuable exercise would be a collaboration between India and the United States.

BTN: Drug resistance is a key issue in finding a stable therapy for treating malaria. What are the options?

PA: Excellent question. Here we in academics have to come off our pedestal a bit. For a long time in the U.S., university scientists have looked down upon industrial scientists as weak, profit-driven, perhaps a little bit greedy. But I think we need each other. I think we need each other very badly. I happen to sit on the board of Glaxo Smith Kline's Center in Spain called Drugs for Developing World. They have announced a new policy wherein their facilities would be opened for the exploration and development of new medicines for treatment of TB and malaria. Patents generated in the process would go into a pool. This is not about making money, but about making medicines. I think that is a



There are right now many candidate medicines with their therapeutic potential against malaria still unknown. Previously Chloroquinin was very effective against malaria but then resistance against Chloroquinin emerged. It probably emerged somewhere in S.E. Asia. It seems that the drug resistance occurs where medical release is less thoroughly regulated. They are so many fake medicines in the markets. So the organisms are getting a small sense of the medicines and they become resistant. The current treatment of choice Artemesin and combination therapy is very effective but just last year the evidence for partial resistance to Artemesin has emerged. If partial resistance gets worse that is problematic.

If we simply stop and say that given the current knowledge we will do no more basic science it may well be that within a decade or so, we will be without any effective medicines against malaria. Disaster will occur worldwide. So we must keep the pressure on and development of medicines will be a very important part of all this. We hope that vaccine development efforts will succeed. But it is such an important problem that we cannot

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keep all our investments in any one platform. We have to hedge our bets so to speak making sure we are looking for proper leads wherever we can get them.

BTN: What message would you like to send to researchers working on the problem of malaria in India?

PA: First message is to those who are established in their field. The work that we do is more important than all the personal benefits and recognition that we may, or may not get, in our lifetime. It is some thing much larger, as what we are doing is for humanity. Second message is to youngsters who are trying to decide whether they should go for science, or play it safe. My urge is to tell them: go for it!. Science can lift things beyond anyone's expectations. It may inflict some personal hardships but the rewards are tremendous. And it is a special opportunity for young scientists in India to do something significant for not only themselves and their families but for their country and the world as a whole. I am an optimist. If I had to predict the next malaria Nobel, I will say that it will be awarded to some young person going to school somewhere in India, as we talk. ■

IYBA INNOVATIVE YOUNG BIOTECHNOLOGIST AWARD

Applications are invited for the 'Innovative Young Biotechnologist Award' (IYBA)-2010. Instituted by DBT in year 2005 to identify and nurture outstanding young scientists (upto 35 years of age) with innovative ideas and desire to pursue research in frontier areas of biotechnology, IYBA consists of financial support for a project and Cash Award/fellowship for the awardees. Awardees having a regular employment will receive a cash award of Rs One Lakh every year during the course of the project in addition to grants-in-aid of upto Rs. 50 Lakhs for a project. The awardees, those who are not in the regular employment will receive a fellowship of Rs. 40,000/- p.m. and shall be attached to a Senior Scientist (Mentor) in a University, Research Institute, Medical/Agriculture/ Veterinary College or any other institute of repute. It is expected that the awardees will work independently and the Mentor will facilitate the awardees research efforts.

Applications (2 copies) neatly typed on plain paper in the prescribed format along with enclosures & certified copies to be sent to Dr. T. Madhan Mohan, Adviser, Department of Biotechnology, Block-2, CGO Complex, Lodi Road, New Delhi 110 003, so as to reach latest by 15th December, 2010. Soft copy of the application also needs to be sent to: iyba.dbt@nic.in. For more details and application format, please visit DBT websites:

For more details on Bio-CARe, please visit DBT at <http://www.dbtindia.gov.in/iyba.htm> / <http://www.btisnet.gov.in/iyba.htm>