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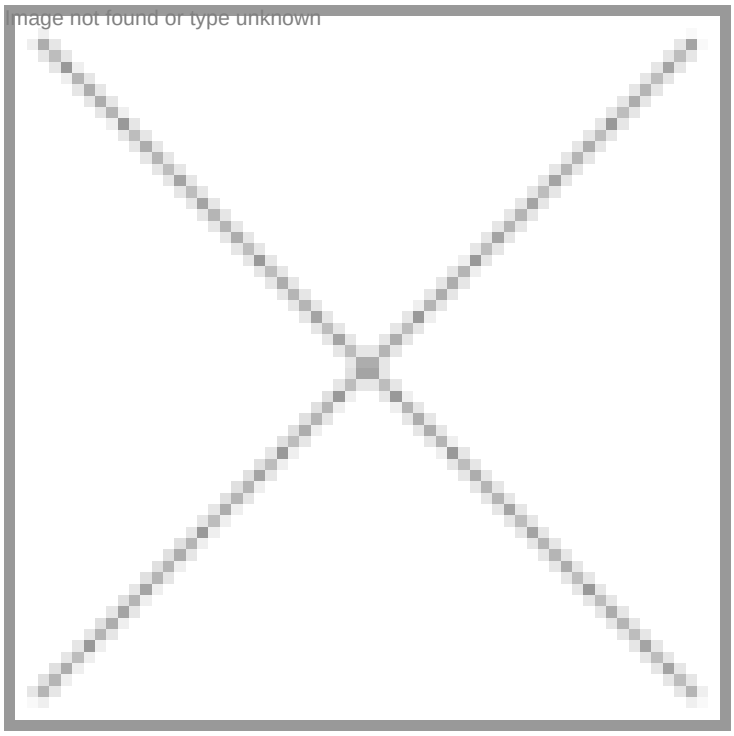
The breakthrough really is to explore new chemical classes for TB treatment'

21 March 2012 | News | By BioSpectrum Bureau



Novartis Institute for Tropical Diseases (NITD) is a public-private partnership between Novartis and the Singapore Economic Development Board and involves more than 100 international scientists in Singapore. NITD conducts R&D for major tropical diseases and provides teaching and training for graduate students and post-doctoral fellows, building capacity to address medical challenges in the developing world.

Why is it difficult to tackle Tuberculosis?
TB is particularly difficult for two reasons. The first reason is that you have to do several combinations of tests. You need to conduct several series of tests with diffirent compounds and see which one works out. The second reason is that the duration of the treatment is very long. You have to wait for many years for the clinical studies to give a result.

And during this time you need to follow the patients, sequence the bugs and support the patients, which is extremelly expensive. Since we are a commercial organization, we have decided that although we can allocate large funds to drug discovery to make new drugs, we cannot afford as a commercial organization to pay hundreds of millions in an area when there will be no returns.

What are your main objectives?
We want to contribute to new drugs that would be effective specifically on those bacteria that have become resistant. That is the first key goal of this Institute. The second goal is to shorten the treatmetn duration. There are a few drugs being developed by certain partners of the TB Alliance. These drugs will work on resistance as they have a new mechanism, but we dont know if they will be able to shorten the treatment.

How has your drug development journey been until now?
Our researchers not only try to develop drugs that work against resistance but develop drugs which would reduce the duration of treatment. Usually the drug development cycles take 50 years from the moment you select the target until you have a drug that you can give to patients after registration. When we started in 2002, TB was neglected in research and we had a very few people working on it.

What various infrastructure and technology are being used by NITD?
We have set up all the tools to do drug discovery for TB and we are testing our libraries and we are designing new drugs. And with a lot of trial and errors. We are doing most of the modern experiments, applying modern science to this field and this takes a lot of time. Essentially we are now at the level where we have all the state of the art assays, we have high throughput screening for CDTs, We have a big biosafety level 3 laboratory, which means that we can work on the TB bacteria, we can do experiments with infected rats in here which only few labs can do.

We have now selected a few members from chemical families, what we call chemical scaffolds, that seem to atleast have the properties that show them to be effective against resistant strains . We take these chemical starting points, which are not drugs yet, and need to do a lot of chemistry as these are only molecules that kill the bacteria. But there are lots of problems like they are not soluble or too expensive or they dont go through membranes. And that is the whole process of drug discovery and development and medicinal chemistry which takes a long time.

Could you shed some light on the 'not-for-profit' adopted by NITD?
We have generated a large amount of science and published a lot of papers. We have shared our results with the public and other scientists, we have put it in public databases so that other people dont try and make the same mistakes that we have done and take those molecules that we have published and do things that we did not think of doing. In the pharma industry they usually keep research data as propriety as a competitive advantage. But we have dedicated this institute here to the neglected diseases of the developing world where we do not expect any financial returns and hence we can be much open with our information.

Who are your partners?
The Bill and Melinda Gates Foundation, GSK and the TB Alliance.

What do you think is the most positive and negative aspect of the 'not-for-profit' functioning of your organization?
The positive aspect of the not-for-profit model is that we can work along with some of the Indian drug manufacturers, who have the expertise and can produce cheaper drugs as compared to others. The negative aspect is that while for us, making these TB drugs is a contribution towards medicine, many companies who do not do the research, take what is already done and copy it. For them its a business. So the only thing they want is, to sell alot. You need to sell the drugs only to the people at the right time along with combination of other drugs. This does not optimize your sales but it saves people. And so that is a matter of grave concern.

What do you think are the major obstacles that are hindering the complete eradication of TB from the world?
TB is a disease where there is huge medical need and not enough research activities. TB is an old disease that has been with mankind for quite some time and there have been few very good drugs. These drugs are about 40 years old and usaghe of the drugs for such a long time has led to increase in the number of resistances and thus these drugs do not work anymore. There is a family of TB, which is recent, called TDR, that is Total Drug Resistance where nothing works. And we are seeing an increased number of patients showing this type of resistance. TDR was not much apparent nine years ago but now it has exploded all over the world.

Moreover, you have to work for six to eight months with a combination of drugs to treat TB and as you can imagine this is extremely difficult to sustain in countries like India or Africa. It is very difficult to have people to take the drug everyday at the right time, in the right combination for nine months. Especially since these drugs work quite well, the patients feel no

symptoms after two months and they stop taking the drugs. What happens during this time is that you kill the selective bacteria and you have kept the more resistant ones. This leads to resistance.

Another thing that makes everything very slow in TB is that the bacteria grow very slowly and it takes week to do an experiment. And this problem is faced even in the in-vivo testing cos when u see that these drugs will kill the bacteria in a dish u need to verify that in an animal model and that takes even more time. So the turn around time is several weeks and this has nothing to do with modern science. Modern scince cannot make the bacteria grow faster. So that remains the bottleneck. That is why after one year we are only in the very early part of the pipeline.

What are your most important concerns that continue to be associated with the treatment of TB?
Clearly, the concern with new drugs is how to control them such that they will never be used in an inappropriate manner. For example, if a new drug or a new antibiotic is used alone and is not used in combination with another drug, then there is a high probablity that within a year or so there will be resistance from the microbe. It takes 15 years to make a new drug and we lose it in one year due to inappropriate usage. Once you have developed a drug, you should use it in a way such that you will not loose it immediately. Another concern is the cost of drug development in TB. Developing a drug for the poor people is not cheaper than developing a drug for the rich people. The science and the technology involved is the same.

How are these concerns being addressed?
The World Health Organization (WHO) is addressing the drug control problem. It is trying to tell the people that if you continue to use TB drugs inappropriately, you will be unable to control the problem.

What do you think is the future of Tuberculosis drug development?
The future is to use the techniques that have never been used for TB before. So the breakthrough really is to explore new chemistries, to adress the disease and to kill the bacteria with weapons that have never been seen before. The real breakthrough will now come by applying all our knowledge to find new chemical classes and bring them into this field of research.