

EMBL



European Molecular Biology Laboratory
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Laboratoire Européen de Biologie Moléculaire

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PRESS RELEASE

Scientists decode genomes of mosquito and malaria parasite

...opening new perspectives on ancient epidemic

Source articles:

Holt et al, "The Genome Sequence of the Malaria Mosquito *Anopheles gambiae*."

Zbodnov et al, "Comparative Genome and Proteome Analysis of *Anopheles gambiae* and *Drosophila melanogaster*."

Christophides et al, Immunity-related genes and gene families in *Anopheles gambiae*.

Science, Oct. 4, 2002

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NEWS BRIEF:

Scientists decode genomes of mosquito and malaria parasite

...opening new perspectives on ancient epidemic

London, Heidelberg

Press Embargo until 1400 US Eastern Time, Oct. 2, 2002

The journals *Science* and *Nature* report this week that international groups of scientists have cracked the genetic codes of two organisms implicated in malaria, one of the world's most serious infectious diseases. Researchers have completed the genomes of the one-celled malaria parasite, *Plasmodium falciparum*, and the mosquito *Anopheles gambiae*, the most important carrier of the parasite. Just over a century ago, scientists proved that *Plasmodium* enters the human bloodstream through the bite of an infected *Anopheles* mosquito, starting the human disease cycle. Today's landmark achievements hold the promise of greatly accelerating the search for methods to control the malaria epidemic, which puts at risk 40% of the world's population and causes over one million deaths per year. Scientists will be able to capitalize on an unprecedented amount of information now available about many thousands of mosquito and parasite genes.

Sequencing the mosquito genome was accomplished by a cooperation involving the US company Celera Genomics, the French national sequencing center (Genoscope), mosquito experts from the European Molecular Biology Laboratory (EMBL) in Germany, Notre Dame University in the USA, the Pasteur Institute in Paris, and the Institute of Molecular Biology and Biotechnology in Crete (IMBB). The main funders were the National Institute of Allergy and Infectious Diseases (NIAID/NIH, USA), the French Ministry of Research and the World Health Organization (WHO).

In the context of EMBL's central interest in functional genomics, three research groups from the EMBL were involved in this work. Fotis C. Kafatos, the Director-General of EMBL, was one of the founders of the international mosquito genome consortium and helped steer its work. A study led by an EMBL senior scientist, Peer Bork compared the mosquito genome with that of the fruitfly *Drosophila*. They discovered that almost half of the more than 13,000 genes of *Anopheles* are also found in *Drosophila*, which will facilitate subsequent studies on their functions. They also revealed how these genes are organized in the mosquito chromosomes.

The mosquito genome is now freely and easily accessible through the efforts of Ewan Birney's group on the Internet at the homepage of the *Ensembl* genome database project, <http://www.ensembl.org>. *Ensembl* is a collaborative project of the European Bioinformatics Institute in the UK (EBI, a branch of EMBL) and the Sanger Centre on the Wellcome Trust Genome Campus.



A further collaborative study, led by Kafatos' group, analyzed 242 genes that are part of the ancient but powerful immune system of the mosquito. They discovered that the immunity genes evolve exceptionally rapidly, probably to deal with a constantly changing set of microorganisms.

The findings will give researchers a head start in understanding why only a small number of mosquito species - out of nearly 3,000 - can transmit human malaria. Follow-up studies may also reveal weaknesses in the parasite that can be exploited by new therapies.

"The international collaboration that we have built to sequence and analyze the mosquito genome will continue to work closely together in answering fundamental questions about the disease," Kafatos says. "We are introducing and standardizing novel experimental methods, and expanding the collaboration to involve more scientists in countries which are directly and terribly affected by malaria. Over the next years, this should give us a good chance of transforming this wonderful information into real strategies against the disease."

Links:

At <http://www.embl.de/oipa> you can find the following:

- Pictures accompanying this EMBL Press Release;
- A teaching kit on malaria for high schools;
- Tips and tricks for browsing genomes

EMBL and our sister organization EMBO are hosting a major Conference on Science and Society with the theme, "Infectious Diseases: Challenges, Threats, and Responsibilities," from Nov. 8-9 this year. Details can be found at the website: <http://www.embl-heidelberg.de/ExternalInfo/stefans/>

The mosquito genome can be viewed at <http://www.ensembl.org>



FEATURE ARTICLE

Scientists decode genomes of mosquito and malaria parasite

...opening new perspectives on ancient epidemic

London, Heidelberg

Press Embargo until 1400 US Eastern Time, Oct. 2, 2002

New genomes promise insights into malaria

This week, the journals *Science* and *Nature* report that international groups of scientists have cracked the genetic codes of two organisms implicated in malaria, one of the world's most severe infectious diseases. Researchers have completed the genomes of the one-celled malaria parasite, *Plasmodium falciparum*, and the mosquito *Anopheles gambiae*, the most important carrier of the parasite.

The achievement is a historical as well as scientific landmark. Just over a century ago, scientists proved that *Plasmodium* enters the human bloodstream through the bite of an infected *Anopheles* mosquito, starting the human disease cycle. Those discoveries led to new ways of fighting one of the worst diseases in human history.

"Today's landmark achievements hold the promise of greatly accelerating the search for methods to control the malaria epidemic," says Fotis C. Kafatos, Director-General of the European Molecular Biology Laboratory (EMBL) in Heidelberg. "Scientists will be able to capitalize on an unprecedented amount of information now available about many thousands of mosquito and parasite genes."

Sequencing the mosquito genome was accomplished by a cooperation between the US company Celera Genomics, the French national sequencing center (Genoscope), mosquito experts from the European Molecular Biology Laboratory, Notre Dame University in the USA, the Pasteur Institute in Paris, and the Institute of Molecular Biology and Biotechnology in Crete. The project was made possible by major, essential support from the National Institute of Allergy and Infectious Diseases (NIAID/NIH, USA), and the French Ministry of Research. Additional support came from the World Health Organization (WHO), the McArthur Foundation, the European Commission, the Wellcome Trust, and EMBL.

Celera Genomics and Genoscope carried out the actual sequencing. The project was coordinated by a consortium organized over a year ago by Frank Collins (Notre Dame), Fotis C. Kafatos, and Paul Brey (Pasteur Institute).



“The industrial-scale approach to genome sequencing has made it possible to take on projects of this size and scope,” Kafatos says. “As the research community was forming the cooperative network necessary to sequence the mosquito genome, Rob Holt and his team from Celera joined forces with Jean Weissenbach’s team from Genoscope and did the mosquito sequence in an impressively short period of time.”

Funding had been secured by July 2001, and milestones came quickly after that. The DNA sequence was completed in the following November; the information had been assembled into a coherent sequence map by March 2002, and by May 2002 the data were ready for in-depth analysis.

Three research groups from the EMBL were involved in this work. Kafatos helped found the international consortium and steer its work. He joined a study led by an EMBL senior scientist, Peer Bork, which compared the mosquito genome with that of the fruitfly *Drosophila*. They discovered that almost half of the more than 13,000 genes of *Anopheles* are also found in *Drosophila*, which will facilitate subsequent studies on their functions. They also revealed how these genes are organized in the mosquito chromosomes.

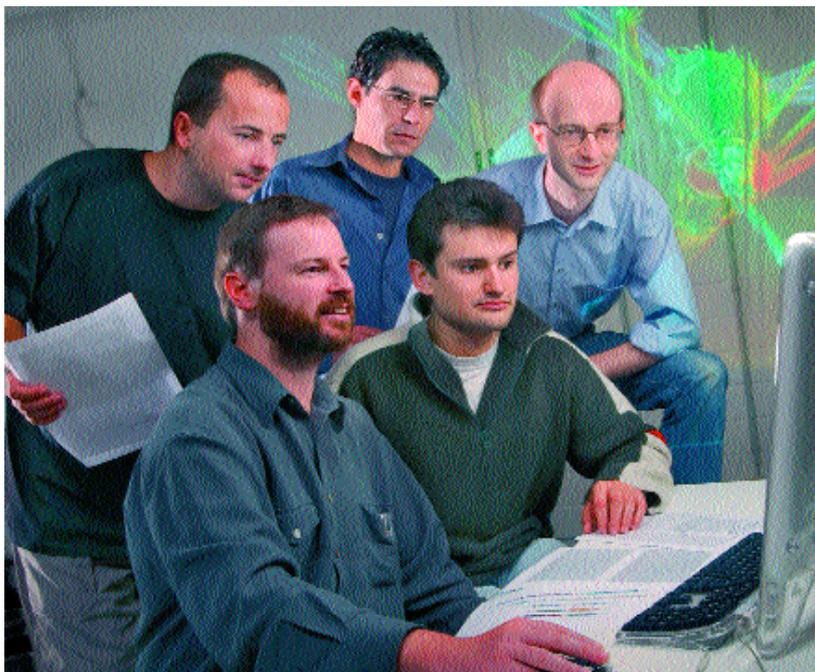
The science of malaria

Scientists hope that the new information can be combined with analyses of the human genome to yield new strategies to combat the disease. The genome projects have revealed thousands of new genes in both mosquito and parasite. The analysis has already provided

Fotis C. Kafatos, Director-General of the EMBL



Photo: Marietta Schupp, EMBL



Clockwise, from 12 o'clock:
George Christophides,
Christian von Mering,
Eveny Zdobnov,
Peer Bork,
Ivica Letunic

Photo:
Maj Britt Hansen, EMBL

crucial information about how the mosquito immune system evolved and how it responds to the presence of the parasite.

“Armed with what we are now learning,” says Kafatos, “we will be able to bring a range of new molecular tools to bear on the problem of malaria. Additionally, the genome projects have brought together many research groups that will continue to work in a tight collaboration on problems directly related to the disease.”

Malaria has plagued humankind throughout recorded history and probably much longer, evolving hand-in-hand with our species. According to Kafatos, “The same ‘stealth techniques’ by which the parasite evades the human immune system have made the development of a vaccine extremely complicated.”

Plasmodium has a very complex lifecycle which depends on both mosquitoes and man. Thus it can be fought on either front. Major battles have been won by using pesticides and destroying mosquito breeding grounds – particularly in Southern Europe, where the disease was an enormous problem a century ago.

In other parts of the world, the disease rages on, especially in sub-Saharan Africa. It infects nearly 300 million people every year and results in over two million deaths, mostly among children. Malaria has entire countries and economies in its grip, and in the absence of a breakthrough, the prognosis is bleak. Mosquitoes and parasites have steadily evolved resistance to pesticides and medications. And global warming will probably lead to a major spread of the disease to new regions.

While many researchers are focusing on *Plasmodium's* effects on the human body, the mosquito can serve as an equally important battleground in fighting the disease. Kafatos’



own research group has been studying what happens when the mosquito digests parasites during a meal. That, too, is an infection, and it evokes a response from the insect's immune system.

One fact that has continued to puzzle researchers is why so few types of mosquitoes can transmit malaria. There are nearly 3,000 species of mosquitoes in the world. While many of them feed on infected animals, only half a dozen members of the *Anopheles* family pass the parasite to new hosts.

"Insects have an ancient but powerful immune system which usually completely eliminates infectious organisms," says George Christophides, a postdoctoral fellow in Kafatos' lab who headed one of the current mosquito studies. "*Anopheles* mount a defense against *Plasmodium*, too – it just isn't effective enough. We think that the parasite is able to exploit some weakness that is specific to this group of mosquitoes. The trick will be to find that weakness, then to use it against the parasite."

Having the complete DNA sequences of the three organisms involved – parasite, mosquito, and human – is an essential step in achieving this goal, he says. Researchers need to understand how immune systems recognize and respond to a *Plasmodium* infection. Usually that response is orchestrated by cells' genes. These contain the recipes for proteins, the "worker molecules", and switching a gene on or off can result in a change in a cell's chemistry or behavior. Specific proteins are responsible for recognizing an infection, spreading an alarm signal, and triggering an immune response.

Different types of mosquitoes have nearly identical sets of genes. But in *Anopheles*, *Plasmodium* survives and grows during an approximately three-week journey through the mosquito body – from the digestive organ to the salivary glands. If it arrives there intact,

As it travels through the body of a mosquito, the parasite that causes malaria undergoes stages of its lifecycle that depend on the cooperation of mosquito genes.

Graphics by Adam Richman





the parasite can be passed into a human or animal in a bite. Researchers believe that small genetic differences between *Anopheles* and its close relatives allow this to happen. Finding the culprit genes has been virtually impossible until now. But new technologies permit scientists to monitor the behavior of thousands of genes – even whole genomes – at a time. This requires a complete catalogue of the genes they want to monitor, however, and until two years ago, the list comprised only a few hundred mosquito genes. The situation has dramatically changed thanks to the genome project, an international collaboration headed by the US company Celera Genomics.

“The fact that about thirteen thousand genes were identified in *Anopheles* is one of the big surprises from the analysis,” says EMBL Bioinformaticist Peer Bork. “That number is similar to the genome of the fruitfly *Drosophila*, although mosquitoes have a third again more DNA.”

The fruitfly genome is playing a crucial role in figuring out what functions the thousands of unexplored mosquito genes might have in cells.

“The principle is to compare a new genome to a closely-related one which is far better understood,” Bork says. “Geneticists have been working on *Drosophila* for a hundred years. The same approach is helping us understand human genes using what we know about the mouse.” Evgeny Zdobnov, Ivica Letunic and Christian von Mering from Bork’s group teamed up with the Kafatos lab to conduct a complete comparison of the two genomes.

Flies and mosquitoes diverged from a common ancestor probably about 250 million years ago. Since then, their genomes have evolved independently. Even so, the study was able to relate about half of *Anopheles*’ genes to clear counterparts in the fruitfly. A gene’s closest relative in another species typically performs the same basic functions. So the new study has produced a wealth of predictions about the functions of the new *Anopheles* genes.

It has also produced some fascinating insights into evolution. “People have thought that some types of species evolve faster than others,” Bork says. “Now we have hard numbers to actually measure this. The pufferfish – whose genome was finished just weeks ago – shared a common ancestor with humans about 450 million years in the past. This is almost twice the time of the split between mosquitoes and flies – yet there are more differences between the genomes of the insects. It suggests that insects evolve considerably faster than vertebrates.”

Kafatos’ group, with help from Bork’s lab and numerous other groups in Europe and the U.S., focused more closely on genes that might be involved in immunity. They discovered 242 good candidates in the mosquito. Still a large number, but their identification will mean a huge leap forward for molecular biologists working on malaria-related questions.

Here, too, the study produced insights into evolution. Not all types of genes evolve at the same rate. The study revealed that immunity genes have changed faster than other types.

“As time goes on, various events make extra copies of genes in an organism, which then undergo mutations and changes of their own,” Bork says. “If extra copies of a gene don’t take on their own functions and become useful to the organism, they usually disappear fairly quickly. We’ve found eighteen ‘families’ of immunity genes in the mosquito and fly, and these families have added on new members at a considerably faster rate than those involved in other biological processes. This suggests that immunity is subject to special



evolutionary pressures. As an organism evolves, it behaves differently – maybe it eats different foods, or moves into new environments. This brings it into contact with new pathogens. Insect immune systems can't 'learn' to cope with new diseases like ours do – flies and mosquitoes don't produce antibodies. So spinning off new genes is probably a good way for the primitive immune system of insects to cope with new diseases."

In addition to the research projects, scientists at the European Bioinformatics Institute (EBI), a unit of the EMBL in Hinxton (UK), have played a key role in putting together the genomes of mosquitoes, humans, and mice and making them available to the research community. The genomes can be accessed by scientists and the public at the *Ensembl* project website: <http://www.ensembl.org/>. Ensembl complements *Anopheles* information (Anodb) established and maintained by the group of Kitsos Louis at the IMBB in Crete.

Ensembl is a collaborative project between the EBI and the Sanger Centre, which is funded by the Wellcome Trust. "Scientists like Fotis Kafatos and Peer Bork are adding to our understanding of mosquito genes on a daily basis," says Ewan Birney, who heads the EMBL side of Ensembl. "Researchers need access to that information as quickly as possible. They also need to be able to view a mosquito gene in the context of the fruitfly, human genes against the backdrop of the mouse. It's a massive computational task that Ensembl is set up to deal with."

Birney adds that Ensembl provides open data access, and has been designed so that the complete system can be duplicated and run on a local computer network with modest resources. "As a result, our team has been working with researchers in South Africa to bring this genomic information to countries that are directly affected by malaria, giving their own researchers access to this crucial information."

Kafatos and his colleagues regard the completion of the genome and their comparative analysis as "the end of a beginning." The real value lies in the fact that scientists will be able to bring a wide range of new molecular tools to bear on the problem of malaria. New technologies such as DNA chips, combined with new methods to study the functions of mosquito genes, should allow scientists to pinpoint genes specifically involved in malaria.

"The international collaboration that we have built to sequence and analyze the mosquito genome will continue to work closely together in answering fundamental questions about the disease," Kafatos says. "We are introducing and standardizing novel experimental methods, and expanding the collaboration to involve more scientists in countries which are directly and terribly affected by malaria. Over the next years, this should give us a good chance of transforming this wonderful information into real strategies against the disease."



About EMBL

The European Molecular Biology Laboratory is a basic research institute funded by public research monies from 16 member states, including most of the EU, Switzerland and Israel. Research at EMBL is conducted by approximately 80 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, Outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and an external research programme in Mouse Biology in Monterotondo near Rome. The cornerstones of EMBL's mission are: to perform basic research in molecular biology, to train scientists, students and visitors at all levels, to offer vital services to scientists in the member states, and to develop new instruments and methods in the life sciences. The Laboratory also sponsors an active Science and Society programme. Visitors from the press and public are welcome. For more information see the EMBL website at:

<http://www.embl-heidelberg.de>

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