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US genome sequencing priorities decided

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MARYLAND - The US National Human Genome Research Institute (NHGRI) has just released its first list of high-priority genomes for sequencing. It includes the genomes of the chicken (*Gallus gallus*), chimpanzee (*Pan troglodytes*), several fungi, the honey bee (*Apis mellifera*), a sea urchin (*Strongylocentrotus purpuratus*), and the ciliated protist *Tetrahymena thermophila*. Accorded moderate priority are the ciliate *Osytrichia trifallax* and the Rhesus macaque (*Macaca mulatta*).

None of these projects has a start date yet, not even an estimated one. Large-scale sequencing on these organisms can't begin until the three big federally funded sequencing centers have finished their current projects on the mouse, the rat and *Homo sapiens*. "There would be a lead-in of quite a few months, and right now we have our hands full," says John McPherson, of the Genome Sequencing Center at Washington University School of Medicine in St Louis. "There's some upstream work before the sequencing, including physical mapping and construction of libraries. We would start doing some of that well in advance of the actual sequencing," he explains. His center will be sequencing chicken and splitting the chimpanzee sequence with the Whitehead Institute/MIT Center for Genome Research in Cambridge, Massachusetts. The third center is the Human Genome Sequencing Center at Baylor College of Medicine in Houston, which will be sequencing the honey bee genome.

The genome priorities list was devised in a unique process outside of the normal grant-proposal routine at the National Institutes of Health. Groups of researchers working on particular organisms were urged to collaborate with one of the three federally funded sequencing centers in putting together 'white papers' making the case for sequencing their favorites. NHGRI established a new review board, the Genome Resources and Sequencing Priority Panel (GRASPP), which reviewed the white papers and made its recommendations in March. Those recommendations were ratified by the National Advisory Council for Human Genome Research on Tuesday (21 May 2002) and made public on Wednesday.

The process is the reason why the status of genome projects on a number of large mammals, including livestock (cow and pig) and the so-called 'companion animals' (cats and dogs) remains undecided. So far, only the cow genome white paper has been submitted. "The dog community is currently preparing a white paper for this effort," says Elaine Ostrander, of the Fred Hutchinson Cancer Research Center in Seattle, long-time advocate for a dog genome project; she notes that they plan to meet the next deadline, 10 June 2002. NHGRI says it held off on the decisions because it expects white papers from the others too. Big mammal researchers are likely to be competing directly with one another for funding unless other sources of support turn up. "The considerable size of genomes in this group (the same size as the human genome), and budget limitations require careful decision-making. For some of these organisms, such as the cow and pig, there are potential major agricultural benefits that will likely lead to a partnership with the US Department of Agriculture," NHGRI says.

Before sequencing can begin, each of the three sequencing centers must negotiate with NHGRI to select an organism from the approved list, along with a strategy and timetable. The projects are expected to rely largely on the whole-genome shotgun strategy pioneered by the privately funded Human Genome Project at Celera Genomics. A project can begin after approval by the NHGRI Sequencing Advisory Panel. Depending on the organism, support for a project may come in part from other institutes at NIH, from the US Department of Agriculture, and perhaps from sources elsewhere in the world. Japanese

researchers say they have already begun to sequence the chimpanzee genome. China is known to be interested in the chicken sequence, and so are UK researchers.

A chimpanzee genome project has long been regarded as a sure bet, owing to our intense curiosity about how a creature can possess a nucleotide sequence that is 98.8% identical to our own and yet be something completely different. "Seizing this magnificent opportunity ranks among the highest basic science priorities in all of biomedical research," is how the chimp white paper puts it. The chimpanzee is now off limits as an experimental organism, but studying its genome is expected to illuminate many medical questions, such as why chimps don't get malaria or AIDS.

Although a chicken genome project may seem at first like a strange choice for immediate attention, researchers like Olivier Pourquié of the new Stowers Institute for Medical Research, opened in 2000 in Kansas City, Missouri, point to a long list of good reasons to sequence the genome. Pourquié's interest stems from the bird's long history as a model organism for developmental biology and a model for the study of viruses and cancer. Existing resources for chicken genetics are extensive, and it is likely to make a significant contribution to comparative genomics because of its evolutionary distance from mammals. "We're somewhere in the beginning of trying to make sense out of these genomes. So it's probably more difficult to compare genomes which are very closely related - for example, chimp and macaque and human - whereas at first it's probably easier to try to make sense using distantly related points. And then once we figure out the logic, we can try to apply it to more closely related species," Pourquié suggests.

In their white paper, fungus researchers argued for sequencing 16 organisms. The NHGRI advisory panels pared their recommended number to seven fungi, although NHGRI says final choice among the 16 is left up to researchers who are writing the proposals. On medical grounds, three likely choices are *Cryptococcus neoformans*, Serotype A, which causes meningitis, and human and mouse *Pneumocystis carinii*, the leading opportunistic infection associated with AIDS. Other top choices include established model organisms such as *Magnaporthe grisea*, a leading model for fungus-host interactions, and *Aspergillus nidulans*, a key model for the study of genetics and cell biology.

Tetrahymena thermophila is a free-living ciliated protozoan that has served as a model for molecular, cellular and developmental biology since the 1920s. Among other potential uses, its genome sequence is expected to be especially helpful for discovering the functions of human genes, in particular, the estimated thousands of human homologs not found in yeast. *T. thermophila* DNA amounts to only 6% of the DNA in a mammalian cell, but contains an estimated 30,000 genes, according to Eduardo Orias, at the University of California, Santa Barbara. Orias is coordinating the *Tetrahymena* sequencing project, which is to be carried out at the Whitehead. He has no idea when it will start but says that if the Whitehead can devote a substantial amount of its massive automated resources to the project, it could be completed in a month.

The genome sequence of the honey bee, an "insect endowed with a small brain but cognitive sophistication," would be valuable because it is a social species, like *Homo sapiens*, its advocates wrote in their successful white paper. The sequence would also have medical value for research on venom toxicology, allergy, infectious disease, parasitology, and even mental illness and gerontology, they argued. This would make sequencing its comparatively small 270Mb genome a bargain. Perhaps because the white paper was aimed at the medical funders at NIH, it did not much emphasize the honey bee's huge importance to agriculture. Crop plants and orchards depend heavily on its tireless pollination,

and are threatened by the current infestation of honey bee mites that have devastated hives all over North America.

Sea urchin advocates collected letters from 75 scientists urging sequencing of this model for the study of gene expression and gene regulation in development. There is also a long history of research on the cell biology and biochemistry of eggs, embryos and fertilization of the sea urchin. The white paper pointed out that decades of research money and effort already devoted to *S. purpuratus* would be leveraged "enormously" if the sequence was available, and "the value of the sequencing effort will be leveraged enormously by the already extant commitment of research effort to this model system."

NHGRI advisors also liked the proposals to sequence two other genomes, but put them at the end of the priority line. The ciliate protist *O. trifallax* is useful for studying eukaryotic cell biology and has a small, compact, junk-free genome that would be comparatively cheap to sequence. The Rhesus monkey is a long-established nonhuman primate model for medical research and the best model for HIV infection and AIDS.

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