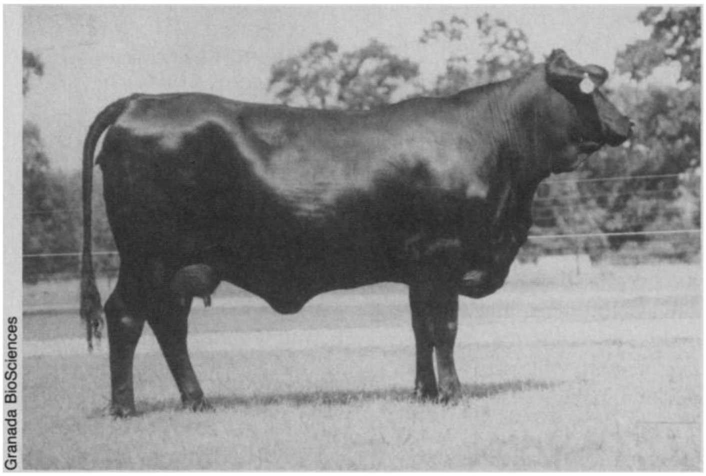
Research News

An Animal Genome Project?

Animal researchers hope to piggyback on the human genome project as they set out to map the genomes of cows, pigs, sheep, and chickens

COULD THE FANCY NEW TOOLS behind the $3-billion human genome project help build a better T-bone steak? That's what a group of animal researchers is arguing, and they are hoping to convince the federal government to kick in some funds to launch a genome project of their own.

The enterprise they envision has a decidedly practical bent. They are not trying to find all the genes of, say, a pig, or to decipher its complete genetic instructions, as is the plan for the human genome. Rather, they are seeking the genes that control fat deposition in cattle, so they can get a leaner steak on the U.S. market and a fattier one on the Japanese market. They want to increase disease resistance and boost the milk production of cows and the litter size of pigs. While the human genome project has been likened to the quest for the Holy Grail—the desire to find, among the twisted strands of DNA, what it is that makes us human—here the grail is, in short, a better piece of meat.


Granada BioSciences

The new breed. *Granada's Brangus cows, a cross between a Brahman and an Angus, are ideal for gene mapping.*

The awareness that gene mapping may have a lot to contribute to the animal sciences has been slow in coming—more so even than in the plant sciences. For many plant breeders, skepticism vanished about 5 years ago. That's when Native Plants Inc., a biotech firm in Salt Lake City, came up with the first of the new genetic linkage maps for a major crop—corn—and then sold the map and the DNA markers used to make it to a handful of companies for a reported $2 million a pop.

Once word of the Native Plants sale got out, plant breeders started asking: "Why are they paying all that money?" recounts Charles Arntzen, dean of the College of Agriculture and Life Sciences at Texas A&M University, who adds, "It was consciousness-raising."

The reason the animal researchers are coming so late to gene mapping, they say, is because it is a lot harder in animals than in plants, for several reasons. And while the animal work is not any tougher than mapping in humans—in fact, it will be easier—funding is certainly a lot scarcer. But the would-be mappers are convinced that if they play their cards right, animal agriculture may in fact be the first beneficiary of the ample funds the National Institutes of Health and the Department of Energy are spending on the human genome project. That's because cows are turning out to be a lot more like people, at least genetically, than many suspected. And thus the fine-resolution genetic maps of the human chromosomes now being developed at great expense can guide the search for animal genes as well.

But first the animal scientists must convince their own sometimes stodgy research establishment to launch the project, which is why they met in late February at the Banbury Center at Cold Spring Harbor Laboratory on Long Island. Conference organizer James Womack, a geneticist at Texas A&M, brought together researchers working on all the major domestic animals, as well as some human gene mappers, for advice. And he brought in a representative from the Department of Agriculture, which is already beginning to come around, he says.

Indeed, USDA has just established a committee, headed by Womack, to look at animal genome mapping, with instructions to report back in December. There is talk—but no commitment—of $10 million for next year. The meat producers, who finance a hefty share of animal research, may prove tougher to sway, says Womack, but even so, there are signs of progress.

And as was the case with plants, the biotech companies don't seem to need any convincing. Genmark, a new company started by human gene mapper Raymond White of the University of Utah and executives at Native Plants, is already gearing up to map the genomes of important farm animals.

While the goal of the embryonic animal genome project is more modest than that of the human endeavor, it is remarkably ambitious nonetheless. For one, when compared with their counterparts in human genome mapping, the animal mappers are starting from ground zero. Surprisingly little is known about the genomes of domestic animals, as quickly became clear at the 2-day meeting. The cattle map—a representation of landmarks and genes along the chromosomes—is the furthest along, says Womack, but it is still rudimentary. At this stage, Womack has identified syntenic groups—groups of genes that belong together—but he doesn't know which chromosomes most of them reside on. That map is still sufficient to demonstrate the remarkable degree of genetic conservation among cows, mice, and men, he adds.

And after the cattle map, it's all downhill. "If you have 30 seconds to spare I will go over the goat map," quipped Jay Hetzel of CSIRO (Commonwealth Scientific and Industrial Research Organisation), who helped organize Australia's fledgling animal genome project.

But the biggest obstacle is that the traits that matter, like fat deposition or milk production, are controlled not by one gene but by many. Tracking down a single gene is tough enough—it took dozens of labs nearly 10 years, and cost an estimated $50 to $200 million, to find the cystic fibrosis gene. And here researchers are talking about three, or five, or perhaps a dozen or more genes that all play a part in these quantitative traits.

Finding the genes involved in such complex traits is formidable. Indeed, although researchers are beginning to tackle that problem for human disorders, like cancer and heart disease, in which many genes play a role, few people predict success anytime soon (*Science*, 30 March, p. 1540).

"In humans, I shudder at the thought of attacking polygenic traits—and these obviously are the ones you are interested in. With the tools available now, they are very hard to get at," said Victor McKusick of Johns Hopkins University, one of the human gene mappers brought in for advice. "In man, at any rate, I am very pessimistic of trying to make sense of susceptibility to high blood pressure, epilepsy, or schizophrenia. One might be rather pessimistic at getting at these [polygenic] traits in animals, too. But I don't want to throw cold water on the whole idea."

True, it won't be easy, but plant research has shown it can be done, responded Andrew Paterson of Du Pont, referring to his recent work with Steven Tanksley at Cornell University and other colleagues and the work of Tim Helentjaris at Native Plants. Using a special kind of DNA marker known as a restriction fragment length polymorphism and a technique called interval mapping, they tracked down the five genes that have a major influence on soluble solid content in tomatoes—a highly desirable trait for tomato precessors.

What's more, say the scientists seeking animal genes, they have one distinct advantage over their counterparts trying to decipher the human genome. Said Alan Teale of the International Laboratory for Research on Animal Diseases in Nairobi: "We can construct populations to study, which presumably you [human geneticists] can't."

Just how hard the animal project ultimately turns out to be will depend, to a large extent, on how many genes are involved in the complex traits the mappers are seeking. Until recently, it was thought that perhaps 100 genes contributed just a bit to each trait, explains Womack, who adds that if so, "then we are in trouble." And that is why the tomato work, which suggests that just a handful of genes is involved, is so encouraging. Moreover, it seems to be true not just for soluble solids but for other traits as well, says Helentjaris of Native Plants. "We always find a certain number of major genes." For yield in corn, six or seven genes account for a high percentage of the variation, he says. For insect resistance, it comes down to two or three genes. And for drought tolerance in tomato, three genes.

Helentjaris sees no reason why the same gene mapping strategies shouldn't work for

Plant Maps, Public and Private

Will the genetic map of cattle go the way of the tomato map, with two independent versions, one public and one private, and a lot of duplicated effort? That was the nagging question at the Banbury Center at Cold Spring Harbor Laboratory in late February, where a group of animal geneticists met to launch a project to map the genomes of domestic farm animals.

What happened with plants, recalls Tim Helentjaris, a molecular geneticist at Native Plants Inc., a Salt Lake City biotech firm, is that companies were far quicker than the U.S. Department of Agriculture to see the economic potential of the new genetic linkage mapping techniques. As early as 1982, several researchers in both industry and academia realized that these techniques, already being used to track down human disease genes, could help them find the genes that control disease or insect resistance in corn, for example, or soluble solids in tomatoes—the stuff tomato paste is made of. And the companies jumped right in. Native Plants was the first out with "a real map and real data" on corn in 1984, says Helentjaris, but others, like the seed giant Pioneer Hybrid, quickly followed suit.

By the time the USDA got around to funding plant maps a couple of years ago, the private efforts were already well under way. And the companies, understandably, were not keen on handing out their maps for free—especially when they could sell them, like Native Plants did with its corn map and DNA markers, for a reported million or two per buyer.

But that meant that other researchers who wanted to track down, say, tomato genes, essentially had to duplicate the work—find their own DNA markers, test them in their own line of plants, and so on. The upshot: plant scientists ended up with two different tomato maps, one developed by Helentjaris at Native Plants, and the other by Steven Tanksley at Cornell University—a situation that the Banbury participants held up repeatedly as something to avoid.

"For corn, it is even worse—there are four or five maps. Companies didn't want to share. And we are as much a part of it as anyone," says Helentjaris. While even the companies don't think this situation is ideal, they defend it as a fact of life. "It costs an awful lot to develop a linkage map," says Native Plants president Peter Muldrum, who nonetheless admits that having two maps "is a legitimate problem. It would be better if we had a single standardized map available to all."

Others say that for tomato, at least, the current situation is not much of an impediment. "Tanksley is so far ahead of everyone else, and his map is in the public domain," says Joe DeVerna of Campbell's Institute for Research in Davis, California. DeVerna adds that it is not clear who would want Native Plants' map at this point.

Efforts are now under way to glue the various maps together, Helentjaris says, "but it is a hell of a lot more work to do it after the fact." Native Plants, meanwhile, has offered to give USDA its corn map so the agency won't have to duplicate that effort as part of the genome project it expects to launch next year—a burst of generosity that Muldrum attributes to the company having exhausted its customer base for the expensive map.

So will the company make its other maps available to USDA too? "We are still a profit-oriented company," says Muldrum. "It depends on our potential customer base. If USDA asked us in 1986 for the corn map, we probably would have said 'no.' "

And now the animal gene mappers may also have to confront the issue of private versus public maps. While USDA is deciding whether to launch an animal genome project, Genmark, a biotech company started in part by Native Plants executives, is hard at work churning out the DNA markers needed to construct a cattle map. And already, would-be cattle mappers are asking whether those markers will be available to them.

Since the Banbury meeting, where the question came up repeatedly, Genmark has been sorting out its policy, says Michel Georges, who is leading the company's cattle mapping effort. "We want to avoid having two different maps, but we can't afford to make the markers freely available." The company's compromise position, says Georges, is to collaborate with "groups we believe have projects of economic value." And through these collaborations, Genmark's map could at least be tied together with those being developed in the public sector. ■ **L.R.**

complex traits in animals as well, though gearing up will be harder. And the effort will be worth it, he says, because "the potential impact is really big in animals. Animal breeding is so much harder than plant breeding that any tool you can add will help."

But before the animal scientists start tracking down the economically important traits, they need genetic maps of the major domestic species—cows, sheep, pigs, chickens, and maybe horses. A genetic linkage map consists of DNA markers, which are simply short detectable pieces of DNA, evenly spaced along the chromosomes. The marker positions are determined by looking at how often two of them are inherited together: if they consistently show up together, they are "linked" and must reside close together on a chromosome. The map allows geneticists to locate an unknown gene between two of these landmarks, narrowing the hunt considerably.

And here the animal mappers have another advantage over researchers working on the human map: they don't need to find the precise locations of the genes they are interested in, at least to start. Knowing roughly where the genes are on the chromosomes would allow animals to be bred with unprecedented precision through what is known as marker-assisted selection.

If the mappers can find markers close to the genes they want—the genes for, say, fat deposition—they could then scan the DNA of a bull to see if the telltale marker is there and then match him with the perfect cow, significantly boosting the chances of getting a calf with the desired qualities. Or, instead, they could analyze the DNA of embryos "to see if the animal is best suited for the parade ground, stud farm, or glue factory," as Paterson of Du Pont describes it. Eventually, the map could help to find the genes themselves so that they could be introduced directly into animals by genetic engineering techniques, but that is years away.

And because the animal genes don't have to be precisely located, the mappers don't need a very detailed map. The human project has as its goal a genetic map with markers spaced every 2 to 5 million bases. For animals, 20 million bases apart would be sufficient, and 5 million would be fantastic, the animal mappers say. Thus, with a concerted push—and the hoped-for $10 million from USDA—the maps could be completed in 3 or 4 years.

For cattle, Womack and several other researchers are already gearing up. Michel Georges, a vet turned molecular geneticist at Genmark, is scouring the cow genome, looking for the highly variable DNA markers needed to construct the map. He has found nearly 200—and thinks 400 is about all he'll need. Womack is also looking for markers, as is Hetzel in Australia.

And others are coming up with the herds in which to test these markers. For these linkage studies, geneticists need large multigenerational families with lots of siblings—six is about minimum. That's where plant mappers have it easy: they can easily get 100 progeny per cross. But with cows, that takes a little assistance. It turns out that Granada BioSciences, Inc., in Texas has been constructing the perfect herds for genetic mapping, though the company didn't set out with mapping in mind. Granada's Michael Wilson has been crossing two genetically distinct subspecies of cattle—the humped *Bos indicus* and the humpless *Bos taurus*—superovulating the female and then using embryo transfer to get as many as 10 or 20 offspring for each set of parents.

Granada is now giving DNA from these animals to Womack for his genetic mapping project. And if all goes well in the three-way collaboration Womack is engineering, he will soon have Genmark's probes to test in Granada's cattle.

In Australia, though, Hetzel will continue to ferret out his own markers and map them in the herds he is creating because "there is some question about how available the commercial probes will be." What he and others at the Banbury workshop fear is that animal mapping may go the way of plant mapping, in which two sets of maps have been developed for several crops, one in the private sector and one public (see box on p. 551). "We should avoid that, but it almost certainly will happen if Genmark does not release its probes," said Paterson.

And unless there is public funding for an animal genome project, there will be no public maps, say the Banbury participants. Many of them are on Womack's committee, which will report back to USDA in December. But judging from the February workshop, there is little question about what they will recommend. ■ **Leslie Roberts**

What to Do with an Animal Map

Cattle will likely be the first farm animals for which researchers produce a genetic map. And although many of the participants at the recent Banbury Center meeting talk of the benefits of a cattle map in terms of dollars per steak, Alan Teale of the International Laboratory for Research on Animal Diseases in Nairobi has a different use in mind for the map, whenever it is done.

Teale doesn't want to produce a leaner steak. Rather, he wants to provide food for a protein-poor region of Africa. To do so, he wants to track down the genes that control resistance to trypanosomosis, better known as sleeping sickness.

Because of this tsetse-borne disease, some 10 million square kilometers in Africa are unsuitable for cattle. Eradicating the tsetse fly will be difficult if not impossible, and prospects for a vaccine are dim, says Teale. Short of those two options, resistant cattle would be a tremendous boon. Teale considers them "a backstop that might save you from catastrophe."

One breed of cattle, the N'Dama, are resistant to the parasite, but they are scrawny and are poor milk producers. Teale wants to use the genetic map now being developed by James Womack of Texas A&M University and others to find markers associated with the resistance so that he can introduce it into the popular Boran breed, though he admits at the outset that he has "absolutely no idea how many genes are involved."

Although the cow genetic map has been garnering the most attention so far, pig maps may well be next. At the University of Illinois, Larry Schook, Harris Lewin, David McLaren, and Matthew Wheeler are just starting to look for markers with a grant from the National Pork Producers Council. They want to find the genes that control the huge litter size in the Chinese pig, a fat, homely animal reminiscent of a Shar-Pei dog. The Chinese pig has 20 or so piglets per litter, as opposed to eight or ten in the litters of domestic animals, but the meat is too fatty. If the group can find markers close to the genes, then they can select for them to breed the large-litter trait into the domestic pig. ■ L.R.

Chinese pig. *Good litters, bad meat.*