scale trial of gp160 alone. As a step in this direction, NIAID announced at the meeting that it plans to begin small trials next spring that pit the MicroGeneSys vaccine against those made by California biotech companies Chiron and Genentech. The trials will focus on safety and on the ability of the vaccines to stimulate immune responses. But small trials like those, which gather data primarily on "surrogate markers" of AIDS progression (such as changes in CD4 cell counts and the amount of HIV in a patient's system) will not answer the question of whether a therapeutic AIDS vaccine can extend life. Answering that question, say many AIDS researchers, will require larger trials that measure "clinical endpoints," such as development of specific opportunistic infections or death.

Yet before starting such a large-scale trial, researchers would like convincing surrogate marker data indicating that the vaccine will work. And from the "purisitic" vantage point, Fauci told the meeting, the scientific data do not yet meet that requirement. But scientific considerations clashed at the meeting with the demands of AIDS activists, who want access to therapeutic vaccines. Against a backdrop of signs saying "You diddle, we die" and "MicroGeneSys is not the enemy," AIDS activist and panelist Mark Harrington argued that "there is nothing else on the horizon, and this is a precious opportunity...to really answer the question, once and for all, with clinical endpoints, whether this approach is going to pay off."

The panelists were responsive to this point of view and spent much of the meeting discussing the merits of a "large, simple trial" that would compare a few therapeutic vaccines. As described by Susan Ellenberg, head of biostatistics at NIAID's Division of AIDS, such a placebo-controlled trial would attempt to assess only one measure: whether a vaccine could reduce AIDS-related illnesses or deaths by one-third. Because it takes so long for people with HIV infection to develop symptoms, it would take 30,000 patients to answer the question in 2 years—or 14,000 patients in 5.

If a large, simple trial of several therapeutic AIDS vaccines results from the furor over the $20 million appropriation, several AIDS activists would be satisfied. David Gold of the Gay Men's Health Crisis said that he would like to think that "much good" could stem from a "sleazy action." But, in the minds of many researchers who were disappointed by the lack of focus at the meeting, there's a long way to go, scientifically, to reach that goal. At the panel's next meeting, scheduled for 23 November, Fauci promises a fuller discussion of scientific issues. And that's none too soon. Healy, Kessler, and the secretary of defense—who jointly have oversight of the large-scale test of the MicroGeneSys vaccine—by law only have until April to speak their minds.

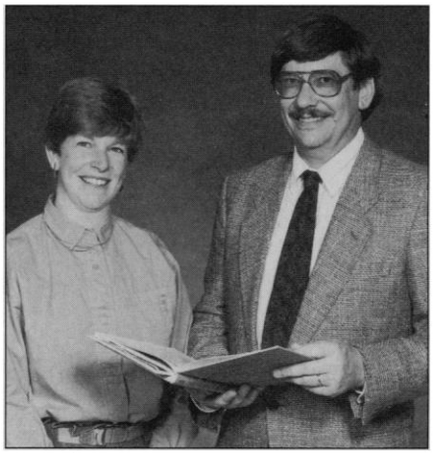
–Jon Cohen

CANCER RESEARCH

Closing In On Melanoma Susceptibility Gene(s)

As the hot summer sun fades to a distant memory and the winter chill sets in, concern about malignant melanoma, a cancer often connected with excessive sunbathing and its accompanying ultraviolet radiation, may go into hibernation for most people. But when spring break rolls around, health columns in newspapers and magazines will again be filled with articles about the dangers of America's obsession with a "healthy" suntan. In the scientific world, however, melanoma is a topic for all seasons, and recent reports, including a powerful statistical analysis published on page 1148 of this issue of *Science*, indicate that investigators have drawn a bead on the location of a gene crucial in a large majority of the cancers, especially the hereditary cases that make up about 10% of all melanomas.

Pinpointing the actual gene could take years, and there is a debate over whether it is the only gene that predisposes to melanoma, but the new research has buoyed investigators' hopes. "What's exciting [about these latest observations] is that this is a tumor where there is great potential for disease prevention and control," says oncologist Mark Green of the Mayo Clinic in Scottsdale. "This is a disease where we can clearly win, and unraveling the genetics is extremely important." That task is becoming ever more urgent since the incidence rate for melanoma has risen faster than that of any other cancer except lung cancer. Each year, more than 32,000 Americans contract melanoma and nearly 8000 die annually from it, despite the fact that the cancer is rarely fatal if detected and treated early. Researchers are hoping that this latest research will lead to a genetic test that could be used to warn those predisposed to the disease to avoid the sun and check their skin frequently. In the long run, identifying genetic abnormalities involved in melanoma could lead to new therapeutic strategies.



Implicating chromosome 9. Lisa Cannon-Albright and Mark Skolnick.

For the past half-decade or so, the search for melanoma genes has been largely a tale of three chromosomes, specifically the short arms of chromosomes 1 and 9 and the long arm of chromosome 6. In the late 1980s, investigators began trying to nail down the location of a hereditary melanoma gene by conducting genetic linkage studies in families with a history of melanoma and dysplastic nevi—pigmented moles that in some cases appear to be tumor precursors. These studies seemed to hit paydirt in 1989 when Green, then at the National Cancer Institute (NCI), and collaborators from NCI, the Massachusetts Institute of Technology (MIT), the University of Pennsylvania, and Collaborative Research Inc., published a landmark study in *The New England Journal of Medicine* that provided evidence that a gene on chromosome 1 was linked to hereditary cases of melanoma.

Shifting focus. In the years since, however, a number of other groups, using different sets of families, have obtained contradictory results that find no indication of linkage to chromosome 1. These results prompted a sometimes bitter debate between members of Green's collaboration and some of the opposing groups over whether the findings were skewed by differences in the sizes of the families studied or by differences in the families' sun exposure—a factor that could affect the incidence of noninherited sporadic melanoma. Most important, the chromosome 1 issue became mired in a controversy over the relevance of dysplastic nevi to melanoma and the diagnostic criteria used to identify the moles. "It led to a great deal of acrimonious back and forth that plagued the field and clearly slowed work in the area," recalls Green. "Interest began to wane in looking at that part of chromosome 1." As a result, while some researchers, such as the NCI group, continued to pursue a chromosome 1 gene, and still do so today, a number of other investigators began to explore other areas of the genome like chromosome 6, where data suggest there is a gene that acts late in the cancer progression.

In the last year or so, however, the melanoma spotlight has shifted to chromosome 9, when three lines of evidence converged to implicate a region called p21 that lies in the middle of the chromosome's short arm. Some of the earliest hints pointing to that site came

STEVE PROEHL/THE IMAGE BANK

Too much sun. Melanoma incidence is rising fast.

out of studies on melanoma tumors. For instance, in this month's issue of the *Proceedings of the National Academy of Sciences*, Jane Fountain, a postdoc in David Housman's lab at MIT's Center for Cancer Research, and her colleagues narrow the candidate region for a melanoma susceptibility gene down to a 2 or 3 million base-pair section lying between two genetic markers labeled IFNA and D9S3.

Their conclusion was based on what researchers see as a kind of "chromosomal chaos" on chromosome 9. Fountain and her colleagues found that a large majority of the tumor cells had the region between IFNA and D9S3 either deleted or rearranged on one of the two copies of chromosome 9 each cell carries. Furthermore, in 10% of the melanoma cell lines, another marker, D9S126, that resides between the two was deleted from both copies of chromosome 9. Such disarray strongly suggests that this stretch of DNA plays a role in the progression of the cancer, although the mayhem could merely be the result of changes brought upon by the cancer.

Buttressing this tumor work is a second line of evidence from a single cancer patient, a 34-year-old woman who has eight separate melanoma sites and what appear to be multiple precursor moles. An alert dermatologist referred the patient to the genetics department at Yale University's Medical School. There, postdoctoral researcher Elizabeth Petty and her co-workers discovered that every cell in the woman's body had a flawed copy of chromosome 9. The woman apparently had a germline mutation, specifically a translocation between chromosomes 9 and 5. Further work with genetic markers revealed that the affected region of DNA was the same as that isolated by Fountain's tumor studies. To Petty and other melanoma experts, this coincidence, coupled with the woman's remarkable number of melanomas, strongly suggests that a tumor suppressor gene resides within the p21 locus, and that its loss predisposes the patient to frequent cancers.

The final piece in the chromosome 9 jigsaw may now have fallen into place with the publication in this week's *Science* of a genetic linkage study from a multi-institution collaboration led by Lisa Cannon-Albright at the University of Utah medical school. Using two of the same markers as Fountain, IFNA and D9S126, Cannon-Albright and her colleagues analyzed the inheritance pattern of melanoma in 10 Utah families and one Texas family. They report that the odds overwhelmingly favor the conclusion that this stretch of DNA contains a gene that predisposes people to familial melanoma. By one estimate in the paper, there is less than one chance in a trillion that a melanoma gene is not linked to the markers. To cancer researchers, this study wipes away almost all doubt that chromosome 9 plays an important, and potentially initiating, role in a great deal of melanomas. "People have been looking for positive linkage studies for quite a long time and the results have been controversial at best," says Bert Vogelstein, an oncologist at Johns Hopkins University Medical School. But this latest study, he continues, is "very compelling" and "it's extremely unlikely that this linkage is due to chance."

"This a disease where we can clearly win, and unraveling the genetics is extremely important."
–Mark Green

Solid data. This new finding should escape a lot of the criticism that struck both sides of the chromosome 1 debate. For one thing, Cannon-Albright and her colleagues ignored dysplastic nevi, focusing their attention only on clear cases of malignant melanoma. And for another, they were able to concentrate on what Cannon-Albright calls "a unique set of families." Past studies looked at smaller families that had few incidences of melanomas in their history, says one of Cannon-Albright's co-authors, Mark Skolnick, also of Utah's medical school. Their group, however, was able to draw upon the Utah Population Database, which goes back eight generations to the early pioneers and—thanks to Utah's high fertility rate—contains information on very large families. In one family, for instance, they sampled 53 members that had had 22 cases of melanoma.

Nevertheless, the Utah report is certainly not the final word on whether the chromosome 9 gene is the only gene that predisposes to melanoma. Indeed, it will probably rekindle the debate about genetic heterogeneity: More than half the families in the study showed no linkage to chromosome 9, keeping alive the possibility that hereditary melanoma can be triggered by another gene on a different chromosome—perhaps chromosome 1. "The area of controversy that will remain is that we have some families that are positive and some that are uninformative," admits Skolnick, who says the collaboration next plans to investigate the latter families to see if there is any evidence of linkage to chromosome 1.

The chromosome 1 issue will also gain new life at this week's meeting of the American Society of Human Genetics when a team at NCI, which participated in the 1989 study, presents a new linkage analysis of the families from the original report, plus seven others. This time, the researchers looked only at melanoma cases and not dysplastic nevi, and "we continue to find evidence for a melanoma locus on chromosome 1," says Alisa Goldstein, a NCI genetic epidemiologist. And when they look for linkage to chromosome 9 in the same families, she adds, their early results have been ambiguous if not outright negative.

How can this confusing picture be resolved? A number of researchers have speculated that melanoma may prove similar to colon cancer, a disease resulting from the accumulation of a series of genetic changes. In this model, explains Nic Dracopoli of MIT's Center for Genome Research and senior author on Fountain's paper, the deactivation of the proposed tumor suppressor gene on chromosome 9 is the initial event, perhaps changing the skin's melanocyte cells into precancerous moles. From there, continues the speculation, mutations on chromosomes 1 and 6 may provide the impetus for tumor progression and metastasis. Dracopoli acknowledges, however, that this theory is far from being proven and many, like the NCI team, take issue with it, asking why their families then show no apparent linkage to chromosome 9.

In any case, now that the linkage study has provided strong evidence of a melanoma gene on chromosome 9's short arm, the next step will be to sift through the 2 or 3 million base pairs to identify the proposed tumor suppressor gene. That's no easy task: The region could contain hundreds of genes, says Fountain, but "with luck, it might take a year." In the meantime, investigators will also try to sort out the puzzling questions about melanoma genes on chromosomes 1, 6, and elsewhere and what their relation may be to the one on chromosome 9. Just as the genetic mutations leading to many cancers appear to progress in a series of small, but vital, steps, so, it would seem, does research on the dreaded disease.

–John Travis