

# Postgenomics? A conference at the Max Planck Institute for the History of Science in Berlin

In 1997, Ernst-Ludwig Winnacker, Acting President of the Deutsche Forschungsgemeinschaft, posed the question: "In which direction will research go in a postgenomic era?" (Winnacker 1997). As the human and other genome projects begin to churn out massive amounts of sequence data, whose functional significance is at present poorly understood, that question is apposite. Winnacker elaborated on the problems faced by genome workers and the direction in which research must go: "Until now, the individual genes stood in the foreground. We will leave them behind us and ask how they contribute to the formation of individual cells, of cell communities, and of whole organisms.... We will go for an understanding of the whole." Winnacker's question—and the beguiling word "postgenomic"—formed the background for a conference (8–11 July 1998) titled "Postgenomics? Historical, Techno-Epistemic and Cultural Aspects of Genome Projects," which was organized by Hans-Jörg Rheinberger (Max Planck Institute for the History of Science in Berlin) and Lily Kay (Harvard University) and funded by the German Human Genome Project.

Although conferences on genomics and the Human Genome Project have become commonplace, this one was unique in three ways: significant attention was paid to the sequencing of nonhuman genomes; a successful effort was made to engage scientists, social scientists, and humanists in active discussion, not only of the usual ethical, legal, and sociopolitical questions raised by genomics, but also of basic epistemological questions about the conceptual framework and research strategies of molecular bi-

ology; and the conference brought together US scholars with those from several European countries (in addition to Germany), which encouraged wide-ranging cross-cultural comparative discussions. The conference included sessions based on pre-circulated papers and formal responses as well as daily panel discussions. As well as molecular biologists, the participants included developmental biologists, anthropologists, ethnologists, historians, lawyers, philosophers, and sociologists.

### From genetics to genomics

The conference began with a reassessment of the history of genetics, and in fact historical issues emerged repeatedly throughout the three days. Some of the historical questions raised (such as the role of informational thinking in the rise of molecular biology) were of well-known relevance to genomics (see Kevles and Hood 1992, Cook-Deegan 1994). In general, however, the historians tried to extend and contextualize received histories of genetics and to use that understanding to probe the scientific and human contexts of contemporary genome projects.

Garland Allen (Washington University, St. Louis) discussed the dichotomy between technical and popular understandings of the gene in the early decades of this century. This dichotomy resulted in popular misapprehensions about the assumed power of the gene. Although the limitations of genes as sole causal agents of phenotypes were scientifically recognized from the beginnings of genetics, that recognition rarely filtered through to the popular level. Using "feeble-mindedness" as an example, Diane Paul (University of Massachusetts–Boston) discussed eugenic measures that were proposed—and sometimes imple-

mented—in the 1920s and 1930s. What is striking is that negative scientific findings—for instance, that feeble-mindedness did not show a Mendelian pattern of inheritance—had negligible influence on social policy. This surprising story confirms Allen's dichotomy between technical and popular conceptions of the gene. Regine Kollek (University of Hamburg) noted that the gene is a polysemous concept (i.e., it has many meanings) and emphasized that the epistemic status of the gene (i.e., what it can really explain) must be specified in each context.

Turning to more recent history, Jean-Paul Gaudilière (INSERM, Paris) challenged the conventional story that, because genomics involves technological innovation (especially the introduction of large-scale computation) and has an applied orientation, it constitutes a radical departure from genetics. He noted that after 1940, much of classical biochemical genetics research was conducted in an applied medical context. Similarly, cancer research played a significant role in the development of molecular biology in the 1960s. Genomics should consequently be regarded as being in a continuum with these developments. The fact that medical expectations drove funding for molecular biology in the United Kingdom was further emphasized by Soraya de Chadarevian (University of Cambridge). Michael Lynch (Brunel University) analyzed various modes of representation of a single laboratory technique, polymerase chain reaction (PCR), from the laboratory bench to the advertising media.

John Beatty (University of Minnesota) discussed the origins of the US Human Genome Project, in which the Department of Energy, itself a successor to the Atomic Energy Commission (part of whose mandate was

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to study the mutational effects of radiation released at Hiroshima and Nagasaki), played a major role. Beatty attributed the decision to initiate the Human Genome Project partly to a perceived economic war between the United States and Japan that replaced the defunct Cold War in the minds of US policymakers in the late 1980s. Beatty's story complements received accounts of the origins of the Human Genome Project (such as Cook-Deegan 1994), which emphasize scientific, medical, and technological factors.

## Lessons from microbial genomics

Much of the conference was devoted to the accomplishments and present state of genome projects. Bernard Dujon (Centre National de la Recherche Scientifique, Paris) reviewed the status of the numerous nonhuman genome projects, ranging from bacteria to mice. Most striking in his account was the preponderance of microbial genome projects. Not only are all completed genomic sequences those of microbes (16 bacteria, with genomes ranging from 0.58 to 4.60 Mb, and one unicellular eukaryote, *Saccharomyces cerevisiae*, with a genome of approximately 12.07 Mb), but a wealth of additional microbial genomes are being sequenced. Dujon listed 46 bacteria, 8 archaea, and 7 unicellular eukaryotes. Genomics has thus been concerned primarily with unicellular organisms, many of which are of medical importance (e.g., *Mycoplasma genitalium* and *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis* and *Mycobacterium leprae*, *Neisseria meningitidis*, *Plasmodium falciparum*, *Trypanosoma rhodense*). Others are of economic (e.g., *S. cerevisiae*) or environmental (e.g., *Archaeoglobus fulgidus*) importance. Some are model organisms for fundamental research (e.g., *Escherichia coli* and *S. cerevisiae*).

Although medical and economic interests play a crucial role in organism selection for genome projects, they do not preclude important benefits for basic science (see Dujon [1996] for the lessons from the yeast genome project). Indeed, although at first mainly considered platforms for technological development, mi-

crobial genome projects have already produced several surprises. One of the most striking findings was the discovery that in all sequenced microbial genomes, a large proportion (typically approximately one-third) of open reading frames lack any significant homology with already characterized genes. The proportion of unknown genes further increases when the focus is on single-copy genes (i.e., genes that are not members of multigene families). This result suggests that there were significant biases in gene identification using classical genetic analyses. Because classical mutational analysis has failed to identify so many genes, it has potentially failed to uncover a wide range of genetic functions.

Microbial genomics has also taken the lead in functional analysis. For example, libraries of mutants have been produced for all *S. cerevisiae* "orphan genes" (those with no known

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function), and systematic functional assays are under development. Hybridization membranes and microchips now allow the transcription patterns of all genes to be characterized under different growth conditions. Finally, new methods also allow the study of intracellular localization and interactions of proteins in situ. Such snapshots of mRNA and protein accumulation at the level of whole cells constitute an invaluable resource for deciphering the corresponding complex networks of interactions.

Microbial genomics has also been innovative from a theoretical perspective. Deploying a single concept, that of a "neighborhood," Antoine Danchin (Institut Pasteur, Paris) introduced a potentially ground-breaking perspective linking genome organization to cellular structure and function. A neighborhood can be defined whenever there is a precise concept of "distance." In biology, distances can be defined in terms of recombination frequency, DNA or

amino acid sequence similarity, or codon frequency, among other ways. Physical proximity on chromosomes (i.e., low recombination frequency) is used to predict transcriptional units (operons) in bacteria, whereas sequence similarity is routinely used to assign functions to new genes. Comparison of codon frequencies in *E. coli* and *Bacillus subtilis* hints at a possible regulatory role of codon usage. The concept of neighborhood can also be applied to metabolic charts to derive families of functionally related enzymes or to identify functional complexes of cellular constituents (e.g., protein complexes, such as the *E. coli* RNA "degradosome," which is a multi-enzyme complex involved in RNA processing and mRNA degradation). Finally, the concept of neighborhood is already used routinely in the exploration of bibliographical databases; neighboring articles are defined in terms of the number of shared keywords (e.g., in the use of the NCBI Entrez software to explore Medline).

Danchin's view of the bacterial cytoplasm is that of a gel, traversed by a ribosome lattice, that undergoes relatively slow movements. In such a viscous medium, the diffusion of large molecules (e.g., tRNAs, mRNAs, and proteins) is limited, which significantly constrains gene transcription and translation (Danchin and Hénaut 1997). For instance, long mRNA threads are unlikely to move freely in the cytoplasm but are guided by the ribosomes during translation, leading to further channeling of the resulting protein products toward specific cellular locations. Consequently, Danchin argues that translation (not transcription) has to be the driving force in gene expression, thus inverting the usual representation, which starts with DNA and gives priority to the process of transcription.

Finally, statistical analyses of microbial genome sequences are proving to be powerful in revealing functional features, including the identification of regulatory loci. But statistical analyses of both yeast and bacterial genomes also have some limitations. For instance, important regulatory sites sometimes escape statistical screening. Also, a single polynucleotide stretch may have different regulatory effects, depending on its posi-

tion on the chromosome or on the presence of nearby regulatory sites.

## Of mice and men

Turning to multicellular eukaryotes, Hans Lehrach introduced the German Human Genome Project (launched in 1995) and research being conducted at the Max Planck Institute for Molecular Genetics in Berlin. These projects encompass various chordate genomes, including those of *Amphioxus*, zebrafish, mice, and humans. The main ideas driving Lehrach's projects are the search for maximal efficiency in the production of molecular data, the scaling up of sequencing and functional analysis, and correlative efforts to automate experimental protocols. For instance, in the case of the zebrafish, the production of libraries of cDNA clones, specific probes, and embryo labeling at various developmental stages is processed in parallel by a robotic array (Maier et al. 1997). Among the goals is the automation of the production of specific antibodies for the corresponding proteins. In this futuristic laboratory, the main tasks of a biologist might well consist of adjusting control parameters, selecting interesting data, and making them available to the scientific community through the World Wide Web.

For the human genome, Mark Guyer (National Institutes of Health) reviewed the history of the US project, assessed its achievements, and presented a set of goals for the next 5 years (Guyer and Collins 1995). The US Human Genome Project is well on track and perhaps even ahead of the original schedule. Mapping efforts have already led to the localization of tens of thousands of markers, and the 2005 target date for the completion of the entire sequence now seems easily achievable. Concerns such as sequence accuracy, continuity, assembly, and rapid public release are being addressed. In this context, it is not surprising that the 1998 goals consisted largely of reassessing the general objectives of the Human Genome Project in terms of sequencing capacity, quality, and accessibility. Bioinformatics, but also studies of the ethical, legal, and social implications of the Human Ge-

nome Project, are due for further financial support. Finally, and perhaps most important, the new goals explicitly emphasize the necessity of a concerted analysis of natural human sequence variation, as well as the need for further development of functional genomics. The decision to recognize and analyze natural human DNA sequence variation addresses one of the most important scientific criticisms of the original program of the Human Genome Project (Sarkar and Tauber 1991).

Related to the last issue is that of sequence diversity among human populations. It was addressed by Joan Fujimura's (Stanford University) discussion of the Human Genome Diversity Project, which was partly proposed as a corrective to a perceived bias in the Human Genome Project because the DNA being sequenced was collected primarily from populations of European origin (Cavalli-Sforza 1997). Although the "genome" being sequenced is in fact made of bits taken from cell lines of various origins, most of these were ultimately derived from "Western" individuals. However, the Human Genome Diversity Project, which attempts to trace human diversity by collecting DNA samples from people around the world, often from isolated populations, has met with much resistance and criticism. Understandably, representatives of indigenous groups generally consider the collection and transferred ownership of bodily materials objectionable, resist the potential economic exploitation of their DNA, and fear new, pseudoscientific justifications of racism. These disputes are yet to be resolved.

At the basis of large-scale sequencing initiatives always lies some faith in the predictive power of genomic sequences. In the case of the Human Genome Project, it is presumed that the availability of a good genetic map, together with the complete genomic sequence, will constitute a powerful tool for tracking genetic diseases and ultimately for designing appropriate therapies. The prospects of somatic gene therapy are often used to convince funding agencies to support basic research in genetics. Already advanced as an idea in the 1960s, the promise of gene therapy

embraces a wide variety of diseases. However, on the basis of an extensive anthropological study of the recent clinical experience with gene therapy treatment of cystic fibrosis in the United States, Alan Stockdale (Education Development Center, Newton, Massachusetts) reviewed problems related to gene therapy in general: frequent conflation of gene replacement with a full cure; exaggeration of medical benefits; deficiencies of the legal framework; and lack of education of both patients and physicians, as well as a failure of communication between them.

Despite much publicity and promises, few clear examples of successful applications of somatic gene therapy yet exist. The technical obstacle most regularly encountered is the poor efficiency of available gene delivery systems, which has led some scientists and physicians to promote germline gene therapy, a supposedly technically simpler way to achieve gene replacement than somatic gene therapy. This possibility was discussed at another recent symposium, "Engineering the Human Germline," held at the University of California at Los Angeles (20 March 1998). That discussion violated a virtual taboo that has been in place throughout the history of the Human Genome Project. However, manipulating the human germline was held to be too troubling a prospect to entertain in public, and, in Berlin, in a meeting held in a building almost adjacent to former Nazi torture chambers, eugenic fears were inescapable.

Nevertheless, several participants at the Berlin conference, including Charlie Weiner (Massachusetts Institute of Technology), initiated a discussion of the Summary Report of the UCLA symposium. The discussion that ensued was among the most searching at the conference. The general consensus was that there are strong prudential arguments against human germline therapy. As Rheinberger and Scott Gilbert (Swarthmore College) argued, at the present level of technical know-how, germline interventions in any species have a high probability of disrupting patterns of development. Sahotra Sarkar pointed out that these technical problems would almost certainly be solved eventually and noted that the real

issue is whether there are deeper ethical reasons to object to human germline therapy. A more systematic inquiry into the nature of these reasons is badly needed. Fujimura and Sarkar both argued that public discussion of these issues is desirable before any decision is made about developing human germline therapy.

Whether or not human germline therapy becomes technically feasible and socially acceptable, many participants at the conference agreed that the promise of genetic medicine had been exaggerated to the public. Rheinberger quoted the German molecular geneticist, Benno Müller-Hill (who is also one of the best-known critics of the Nazi abuse of genetics): "Now scientists are promising a massive betterment in preventive medicine after the 'holy grail' of the human genome has been attained, and 'man will be understood through his DNA.' I doubt all that. These promises cannot be kept. The public will become discontented when it realizes that all these expensive promises are not being fulfilled. Scientists should not sell hope" (Müller-Hill 1991). M. Susan Lindee (University of Pennsylvania) and Dorothy Nelkin (New York University) carefully documented the rise of the gene as a cultural icon, which partly explains the exaggeration of the gene's power that is found in public discourse (Nelkin and Lindee 1995). Nelkin also provided a troubling analysis of the emergence of the body and body parts as commodities in the marketplace. A recent attempt to regulate this market was discussed by Rogier Holla (European Union, Brussels), who introduced the new directive of the European Commission for legalizing and restricting the patenting of biological materials and processes.

### Epistemological critiques and reconstructions

Turning to the conceptual development of molecular biology, Kay argued that historically contingent interlocking informational and linguistic representations of DNA, which emerged because of the impact of communication sciences in the 1950s (Judson 1979, Keller 1995, Sarkar 1996), have led to a reification of a genetic "code." She questioned

the existence of a "Book of Life" encoded by DNA sequences but endorsed no alternative conceptual scheme for genetics. Sarkar argued that classical genetics has consistently failed to explicate how nature–nurture interactions cause phenogenesis and wondered whether genomics could do any better. It is possible that, by providing a powerful alternative, genomics will finally displace

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discredited classical techniques, such as heritability analysis, that were used to navigate the nature–nurture problem. But Lehrach defended the gene-centered point of view, arguing for the centrality of genetics and genomics for all biological research.

Talk of genetic information and codes leads to the theoretical idea of a "genetic program" driving phenotypic expression. But Richard Strohman (University of California–Berkeley) asked: "Where is the program?" His answer was that the notion of a genetic program, at least in the usual sense of a set of sequentially activated routines, is illusory (see also Strohman 1993). He distinguishes five overlapping phases of genomics, which he suggested evolved partly from technological developments and discoveries emerging from the Human Genome Project. The first and second phases correspond to monogenic and polygenic determinisms; the third consists of a shift of emphasis from DNA to protein (e.g., Alberts 1998); the fourth focuses on the functional role of genes in model organisms, for example, transgenic or knockout mice (also discussed by Michel Morange, Université de Paris; see also Miklos and Rubin 1996); and the fifth consists of an awareness of nonlinear, adaptive properties of complex dynamical systems. At this last phase (postgenomics?), unjustified recourse to linear genetic causality will be replaced by the

analysis of rules governing environmentally open networks of agents, including, but not limited to, genes.

Strohman also distinguishes four levels of regulation of biological activity: genetic, epigenetic, morphogenetic, and organismal. The mainstream genome projects are mainly restricted to the first level, for which agents (DNA sequences), processes (replication, transcription, and translation), and rules (base pairing and the genetic code) are well characterized. Although agents (gene–protein networks, morphogenetic fields) and processes (DNA modifications, epigenetic regulation) can be identified at the three other levels, specific structural or dynamical rules have not yet been characterized thoroughly. These gaps in our biological knowledge might explain the ubiquity and hegemony of epistemological reductionism in contemporary molecular biology.

### Toward postgenomics?

One of the most striking characteristics of genomic projects is the development of new modes of production, exchange, and organization of biological data. For example, the conference brought together the experiences of scientists involved in genome projects in France, Germany, and the United States. There was also some discussion of genomic projects in which the scientists were not personally involved. It became clear that important differences exist between the various projects. For example, Dujon discussed the differences between the centralized single-laboratory strategy of The Institute for Genomic Research (Rockville, Maryland) for bacterial genome sequencing, which emphasizes increasing technological sophistication, and the network-based approach of the initial European *S. cerevisiae* genome project, which relied on locally existing expertise and technologies.

The general tendency has been toward improving and scaling up sequencing performance. The rapid adoption of "shotgun" sequencing testifies to the precedence of rapid and efficient sequencing over functional analysis. At the same time, genome projects rely increasingly on sophisticated informatics, both hardware and software, to drive auto-

mated sequencers and to assemble, store, and analyze DNA sequences. Many software packages for sequence analysis are already available, for example, to localize putative genes, predict their structure and function, and look for promoters and putative regulatory sites. However, the main public DNA databases (GenBank in the United States and the European Molecular Biology Laboratory in Europe) are not yet prepared to deal with basic functional information (for a recent review of molecular databases, see Ashburner and Goodman 1997).

Functional analysis of the putative genes uncovered by the genome projects is still largely in its infancy, as attested to by the fact that attempts to anticipate the results of gene mutations in metazoans (e.g., knockout mice) usually fail. Similarly, many of the so-called genetic diseases have turned out to be far more complex than initially expected. Redundancy, functional complementation, and complex epigenetic regulation seem to be the rule rather than the exception. Many regulatory mechanisms have proved to be context sensitive, and the dynamics of gene expression often depend on both the past history and the environment of organisms. As a result, genomes are increasingly conceptualized as complex dynamical systems that are even able to engineer themselves to some extent. There is thus an increasing need for formal techniques to deal with these open, dynamic gene-metabolism networks. This need goes beyond efficient sequencing, and even beyond the mere identification of functions of individual sequenced loci. Without the development of such formal techniques, postgenomics will remain little more than a beguiling name.

What was most interesting during the meeting was the confrontation of

a broad variety of opinions about both social and epistemological issues, including those such as the estimation of the predictive power of DNA sequences. Strikingly, as the conference progressed, it became clear that disagreement on such fundamental issues was as broad among scientists themselves as between scientists and historians, philosophers, and other social scientists and humanists. These discussions underscored the extent to which scientific issues about genomics remain unresolved. Unfortunately, little from these debates has reached the public, even though, in the case of so "human" a science as genomics, these disputes concern issues of immediate and general public interest. Scientists are left to wonder how to address this problem.

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