Specifically inhibit DNA repair in these resistant cells by targeting the key enzymes. Genetic polymorphisms in relevant repair genes will be identified and efforts made to correlate them with effects on activity of the respective proteins, with response to particular therapies and with clinical outcomes. Although a number of polymorphisms in DNA repair genes are being reported, there is presently little functional information on the consequences of the attendant amino acid changes. It will be important to find out which polymorphisms actually affect protein function and then concentrate on these in epidemiological and clinical studies. For example, homozygosity for a particular polymorphism in the DNA ligase subunit XRCC1 is associated with higher sister chromatid exchange frequencies in smokers, suggesting an association of this allele with a higher risk for tobacco- and age-related DNA damage (19). Larger studies and comparison with other polymorphisms having known biochemical effects will be needed to further validate and extend these findings.

Furthermore, with the use of gene and protein array techniques, it should be possible to compare expression profiles of DNA repair genes in normal and tumor cells—information that could eventually lead to individually tailored therapies with chemicals and radiation. Although a number of polymorphisms in DNA repair genes are being reported, there is presently little functional information on the consequences of the attendant amino acid changes. It will be important to find out which polymorphisms actually affect protein function and then concentrate on these in epidemiological and clinical studies. For example, homozygosity for a particular polymorphism in the DNA ligase subunit XRCC1 is associated with higher sister chromatid exchange frequencies in smokers, suggesting an association of this allele with a higher risk for tobacco- and age-related DNA damage (19). Larger studies and comparison with other polymorphisms having known biochemical effects will be needed to further validate and extend these findings.

The chromosomal position of human genes is rapidly being established. We integrated these mapping data with genome-wide messenger RNA expression profiles as provided by SAGE (serial analysis of gene expression). Over 2.45 million SAGE transcript tags, including 160,000 tags of neuroblastomas, are presently known for 12 tissue types. We developed algorithms to assign these tags to UniGene clusters and their chromosomal position. The resulting Human Transcriptome Map generates gene expression profiles for each chromosome region in 12 normal and pathologic tissue types. The map reveals a clustering of highly expressed genes to specific chromosomal regions. It provides a tool to search for genes that are overexpressed or silenced in cancer.
Fig. 1. Whole chromosome view of expression levels of the 1208 UniGene clusters mapped to chromosome 11 on the GB4 radiation hybrid map of GeneMap’99. Each unit on the vertical axis represents one UniGene cluster. UniGene clusters mapped by several markers are only shown once, at the position of the highest lod score (the logarithm of the odds ratio for linkage). Only clusters for which we could extract a tag with our algorithms are included. Expression is shown for SAGE libraries of 8 out of the 12 available tissue types. Expression levels in the libraries are normalized per 100,000 tags. Expression levels from 0 to 15 tags are shown by horizontal blue bars. Tag frequencies over 15 are shown by red bars. The blue-only section to the right represents a moving median with a window size of 39 UniGene clusters generated from the expression levels in “all tissues.” Green bars indicate RIDGEs. The boxed region shows the tissue-specific expression of a cluster of five metalloproteinases and two apoptosis inhibitors in normal breast tissue and breast cancer tissue.

The Human Transcriptome Map [for Web site, see (4)] uses these tag assignments to relate 2.31 million tags in public SAGE libraries (NCBI SAGEmap database) (5) and 160,000 tags in our neuroblastoma SAGE libraries to the UniGene clusters mapped in GeneMap’99. The Human Transcriptome Map shows expression profiles for any chromosomal region in 12 tissue types. SAGE libraries of a specific tissue (e.g., normal colon) were included tissues for which 100,000 or more tags were available, as most transcripts in a tissue are represented in a library of this size (6). Five libraries represent normal tissues (colon epithelium, brain, mammary gland, ovary, and prostate), and seven libraries represent tumor tissues (neuroblastoma, glioblastoma, medulloblastoma, and carcinomas of colon, ovary, breast, and prostate). The Human Transcriptome Map has three levels of resolution. The “whole chromosome view” shows gene expression per chromosome (Fig. 1). Each horizontal blue or red bar represents the expression level of a UniGene cluster. UniGene clusters mapped by several markers are shown only once, at the position of the highest reliability (7). The identity, map position, and precise expression of the genes are shown in the “concise interval view.” The highest resolution is given by the “extended interval view,” where expression levels are shown for all individual tags of a gene (Fig. 2).

The whole chromosome views reveal a higher order organization of the genome, as there is a strong clustering of highly expressed genes. Chromosome 11 has several large regions of high gene expression, interspersed with regions where gene expression is low (Fig. 1). This pattern is observed in all 12 tissues. An application of a moving median with a window size of 39 genes to the chromosome 11 map even more clearly visualizes the expression differences (Fig. 1, blue graph to the right). Most chromosomes show these clusters of highly expressed genes, which we call RIDGEs (regions of increased gene expression) (Fig. 3). A quantitative definition of RIDGEs is not straightforward, as there is a continuum from small to very large clusters. We analyzed whether RIDGEs can be explained by a random variation in the distribution of highly expressed genes among the 18,954 genes of the Human Transcriptome Map. When defined as regions in which 10 consecutive moving medians have a lower limit of four times the genomic median, we identify 27 RIDGEs (green bars in Figs. 1 and 3). The probability of observing this number of RIDGEs under a random permutation of the order of the 18,954 genes is very low [P = 10^-12; see supplementary information (3)]. In addition, Bayesian statistical model-
ing without prior cluster definition showed that a model of nonrandom distribution provided the best fit with the observed clustering. These analyses show that RIDGEs most likely represent a higher order structure in the genome.

Analysis of RIDGEs for physical characteristics suggests that many of them have a high gene density. Chromosome 18 is, on average, weakly expressed, and only 385 genes have been mapped to it on GeneMap’99. The equally large chromosome 19...
consists of a succession of RIDGES and harbors 937 mapped genes (Fig. 3). Although many human genes are still unmapped, the difference in gene density of chromosomes 18 and 19 is supported by CpG island density analyses (7). The correlation between RIDGES and gene density is even more suggestive for chromosomes 3 and 6 (Fig. 4). The RIDGE on chromosome 6 corresponds to the major histocompatibility complex (MHC) region. A correlation between gene expression and density of mapped genes is found for 50 to 60% of the RIDGES [Web fig. 1 (3)]. Typical RIDGES count 6 to 30 mapped genes per centiray, compared to 1 to 2 mapped genes per centiray for weakly transcribed regions. In RIDGES, average expression levels per gene are up to seven times that of the genomic average. This suggests that in RIDGES, transcription per unit length of DNA is 20 to 200 times that in weakly expressed regions. About 40 to 50% of the RIDGES are not gene dense. These RIDGES preferentially map to telomeres, which is remarkable in light of the observed telomeric silencing in yeast (8, 9). Chromosomes 4, 13, 18, and 21 show an overall low gene expression and are devoid of RIDGES (Fig. 3). The latter three chromosomes are responsible for most constitutional trisomies, suggesting that the low expression and low gene density could limit the lethality of an extra copy of them.

The Human Transcriptome Map provides a tool to identify candidate genes that are overexpressed or silenced in cancer tissue. Neuroblastomas frequently show amplification of the distal chromosome 2p region, which targets the N-myc oncogene (10). Comparison of the whole chromosome views of chromosome 2p shows overexpression of two adjacent genes in neuroblastoma SAGE libraries. The extended interval view identifies these genes as N-myc and the often coamplified neighboring gene DDX-1 (Fig. 2). Therefore, global positional information of chromosomal defects is sufficient to identify candidate oncogenes (11). Also, tumor-specific down-regulation can be detected. Examples are a cluster of five matrix metalloproteinases on chromosome 11 [348 to 353 centirays (cR)] that are down-regulated in breast cancer tissue (Fig. 1, box); the E-cadherin tumor suppressor gene on chromosome 16 (406 cR) that is down-regulated in breast cancer tissue, as compared to normal breast tissue; and five carcinoembryonic antigen–related cell adhesion molecule genes on chromosome 19 (238 to 244 cR) that are down-regulated in colon carcinoma tissue, as compared to normal colon tissue (4).

Potential error sources in the Human Transcriptome Map are clustering errors in UniGene and the assignment of wrong tags to UniGene clusters. Our algorithms assign ~6.2% erroneous tags to UniGene clusters. The influence of these errors is probably attenuated. Assuming a total of 100,000 genes with 2 tags each, 200,000 tags would represent all human genes. Because there are >1 million variants of a 10-bp tag sequence, ~80% of the erroneously extracted tags will not match tags present in SAGE libraries and therefore will not influence overall expression profiles. However, individual tags and expression levels of UniGene clusters may harbor errors and require experimental confirmation. To test whether errors in UniGene clustering and mapping to GeneMap’99 may influence our observation of RIDGES, we constructed a sequence-based expression map for the annotated chromosome 21 sequence and for a 4.3-Mb annotated contig of the MHC region on chromosome 6 (12, 13). Also, these maps showed that the MHC region is a pronounced RIDGE, whereas chromosome 21 is devoid of RIDGES and has an overall weak gene expression [see Web fig. 4 for maps (3)]. Therefore, the higher order structure of the genome observed with the Human Transcriptome Map will largely be correct. The existence of RIDGES is unanticipated, as a comparable SAGE-based transcriptome map for yeast showed an even distribution over the genome of highly and weakly expressed genes (8). Because the Human Transcriptome Map identifies different types of transcription domains, it can now be analyzed as to how they relate to known nuclear substructures, such as nuclear speckles, PML bodies, and coiled bodies (14–16). Definition of the position of tags to the full chromosomal sequence will further increase the resolution of the transcriptome map. Incorporation of the growing number of SAGE libraries from different tissues and various developmental stages will extend the overview of gene expression profiles in the human body.

References and Notes
3. Supplemental Web material is available at www. scientificmag.org/cgi/content/full/291/5507/1289/ DC1.
4. The Human Transcriptome Map is available at http:// bioinfo.amc.ou.nl/HTM/.
5. A. Lal et al., Cancer Res. 59, 5403 (1999).
11. N. Speier et al., Genomics, in press.
17. We thank A. Luyl and A. Sha Sawari for their help in computational analyses, A. Lash for use of the SAGEmap database and help in tag analyses, and E. Roos for expert digital imaging. Supported by grants from the Stichting Kindergeneeskundig Kankeronderzoek, the A. Meelmeijer Fund, and the Dutch Cancer Society. H.C. is a fellow of the Dutch Royal Academy of Sciences.

23 October 2000; accepted 11 January 2001
The Human Transcriptome Map: Clustering of Highly Expressed Genes in Chromosomal Domains

Huib Caron, Barbera van Schaik, Merlijn van der Mee, Frank Baas, Gregory Riggins, Peter van Sluis, Marie-Christine Hermus, Ronald van Asperen, Kathy Boon, P. A. Voûte, Siem Heisterkamp, Antoine van Kampen and Rogier Versteeg

Science 291 (5507), 1289-1292
DOI: 10.1126/science.1056794

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