### ***Cancer Therapeutics (Telomerase Inhibition)***

While most normal cells in our body can divide only a finite number of times (cell mortality), cancer cells are abnormal in that they can divide without limit (cell immortality). Normal cells have the potential to become cancerous when a series of random mutations activate various oncogenes and deactivate tumor suppressor genes. With each mutation, pre-cancerous cells become increasingly aberrant and uncontrolled, and may begin to generate a tumor mass. The Company believes, however, that most cells which undergo such changes are eliminated when telomere shortening leads to either cell senescence or chromosomal instability and cell death. Geron's and its collaborators' research indicates that for most cancerous tumors to attain life threatening size, or for cancer to metastasize throughout the body, some cancer cells must become immortal, which occurs through the activation of telomerase. Telomerase enables cancer cells to maintain telomere length, providing them with indefinite replicative capacity, or cellular "immortality." While not sufficient in itself to transform a normal cell into cancer cell, telomerase is believed to be necessary for the cancer cell to grow without limit. Geron's intention is to discover and develop a small molecule telomerase inhibitor, which, by blocking the activity of telomerase, will allow cancer cell telomeres to resume shortening, ultimately leading to cancer cell death. The uniqueness of Geron's strategy resides in the universality and specificity of telomerase as a target for cancer. Historically speaking, telomerase is an unusually attractive target for drug discovery because there may have never been a molecule discovered that was present in nearly all cancers, required for the tumor cells to continue growing without limit, and a molecule that if eliminated by a drug, would not have serious side effects. In regard to universality, research has shown that telomerase is present in all of the over 20 different cancer types that Geron and its collaborators have studied, including the 10 most prevalent cancers of prostate, breast, lung, colon, bladder, uterus, and ovary, along with lymphomas and leukemias, melanomas and pancreatic cancer. In all of these cancers, nearly all tumor samples contain telomerase. Because telomerase is present in all cancer types evaluated and is not biologically active in most normal cells, telomerase appears to be the first universal marker for cancer. In regard to specificity, telomerase is not present in most normal cells and tissues in levels sufficient to confer replicative immortality with the exception of the reproductive cells. *Therapeutics.* Geron's research has demonstrated that a telomerase inhibitor can block cancer cells from using telomerase to maintain telomere length. As a result, the telomeres in the cancer cells shorten as the cells continue to divide, until reaching a critically short length, at which point the cancer cells die. Geron scientists have blocked human telomerase in tumor cell lines *in vitro* using an antisense compound to the human telomerase RNA component. In this experiment, blocking telomerase led to telomere shortening and cancer cell death. Based on these results, Geron is aggressively pursuing the identification of telomerase inhibitors as potential lead compounds for preclinical development. While it has identified several strategies for inhibiting telomerase activity, Geron is primarily focused on developing a small molecule inhibitor. The Company believes the small molecule approach will produce a development candidate with a more favorable commercial profile - oral bioavailability, compound stability and low manufacturing cost. Geron and its collaborators are using proprietary screening technologies to identify small molecule compounds that selectively inhibit telomerase. Traditional medicinal chemistry and combinatorial chemistry are being used to optimize these compounds and animal models of human tumor growth have been developed to test appropriateness for preclinical development. Geron has established corporate alliances with Pharmacia and Upjohn, and Kyowa Hakko for the development and marketing of these compounds (see press release of 3/24/97).

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### ***Proprietary Screening Technology Leads to New Inhibitors***

To advance this program, Geron has developed proprietary screening technology, assembled a structurally diverse library of over 100,000 small molecules and established medicinal and combinatorial chemistry capabilities. For telomerase, Geron has developed a substantial automated high throughput screening effort for the identification of telomerase inhibitors using proprietary assays. Geron is using this proprietary screening capability to screen diverse small molecule compounds that we have either acquired or created through our internal combinatorial chemistry capabilities. As a result of its screening efforts, Geron and its collaborators have identified several classes of compounds that demonstrate telomerase inhibition and are actively pursuing structure/activity relationship studies to develop lead compounds. Geron believes that these screens provide a strong competitive advantage in view of the extreme difficulty and specialized skills required for their development and use. Importantly, the United States Patent and Trademark Office has recently issued patents on two of Geron's telomerase inhibitor screens. Geron believes that blocking telomerase activity will cause the affected cancer cells to resume telomere shortening during cell division and thus lose their immortality. When telomeres reach a critically short length, cancer cells will die. Telomerase inhibition is therefore expected to have delayed efficacy as cancer cell telomeres resume normal shortening. Although Geron envisions that a telomerase inhibitor could be effective as a stand-alone treatment in certain cases, it is expected that in many cases a telomerase inhibitor will be used in conjunction with other therapeutic modalities to debulk the tumor mass. Geron believes that a telomerase inhibitor will be an effective therapeutic for a broad range of cancers, although there may be certain limitations to its use. Because telomerase is present in reproductive cells, a telomerase inhibitor, like almost all current cancer agents in current use, may have a negative impact on such cells. Accepted practices exist to address this issue. Telomerase is also transiently expressed in certain cells in hematopoietic (blood) cells, skin and the gastrointestinal tract. However, Geron scientists and others have demonstrated that these tissues age and show gradual telomere shortening during the course of cell division. The Company believes that this is a result of transient or low levels of telomerase expression and therefore means that telomerase is unlikely to be biologically important for these tissues. Consequently, telomerase inhibitors are unlikely to have significant negative effect on them. Thus, a telomerase inhibitor is expected to have a side effect profile that is superior to current cancer therapies that target all dividing cells. Geron has established a global strategic alliance with Pharmacia and Upjohn and Kyowa Hakko, a leading oncology company in Japan, for the development of a telomerase inhibitor for the treatment of cancer.

### ***Cancer Diagnostics***

The Company believes that telomerase is also a universal and highly specific marker of cancer and, therefore, the detection and quantification of telomerase could have significant clinical utility for cancer diagnosis, prognosis, patient monitoring and screening. While cancer diagnostics usually apply to a single or limited number of cancer types, telomerase-based diagnostics can potentially address a broad range of cancer types. The Company also believes that the availability of telomerase-based diagnostics for cancer, which are likely to reach the market before telomerase-based therapeutics, will enhance the commercial opportunity for a telomerase inhibitor by increasing the understanding of clinicians of the biological significance of telomerase activity in cancer. The Company has developed several proprietary assays for the detection of telomerase based on its activity or components. The first generation assay is the Telomeric Repeat Amplification Protocol ("TRAP") assay which can be used to detect telomerase activity in malignant tumor tissue. The United States Patent and Trademark Office recently issued Geron a patent for the TRAP assay. The second generation assay detects the RNA component of human telomerase, which was first cloned by Geron scientists. This enables the Company to use proprietary *in situ* hybridization and other detection methods to detect the presence of telomerase. The United States Patent and Trademark Office has issued Geron a patent relating to the RNA component of human telomerase and issued a patent exclusively licensed to Geron for methods related to prognosis and detection of specific types of cancer based on telomerase activity. Geron is overseeing preclinical studies to assess the diagnostic and prognostic potential of its telomerase detection technology. Data from initial studies indicate telomerase levels correlate with clinical outcome in breast, leukemia, prostate, gastric, and neuroblastoma cancer patients. The Company intends to proceed with development of its telomerase detection technology as a novel and important diagnostic and prognostic for numerous other cancers. Telomerase assays should also have utility in screening for cancer, since telomerase can be detected in cancer cells in blood, urine, oral rinses, and PAP smears. Oncor Inc. ("Oncor"), Boehringer Mannheim GmBH ("Boehringer Mannheim") and Kyowa Medex Co., Ltd. ("Kyowa Medex") have licensed the Company's TRAP assay technology; Dako Corporation ("Dako") has licensed the Company's RNA detection technology; and Pharmingen (a Becton Dickinson subsidiary) has licensed the TRAP assay and telomere length measurement technology, each on a non-exclusive basis for sale to the research-use-only market. Oncor commenced commercial sale of the TRAP-eze(TM) kit in May 1996, followed by Boehringer Mannheim and Kyowa Medex in late 1996. Although the Company does not expect royalties from the sale of these kits to be significant, their use is expected to stimulate additional studies of telomerase activity by academic laboratories. The Company recently formed a worldwide collaboration with Boehringer Mannheim to develop and market clinical diagnostic products based on its telomerase technology. The Company will receive funding and milestone payments as well as royalties on marketed products. The Company has also established research collaborations for the study of telomerase detection with The Cleveland Clinic, the University of Texas, San Antonio, Johns Hopkins University, Children's Hospital of Los Angeles and the University of Texas Southwestern Medical Center at Dallas.

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### ***Genomics of Aging***

Our bodies are composed of billions of cells many of which divide during the course of our lifetimes. With the exception of our reproductive cells, most body cells possess a clock of aging at the telomere limiting the number of times they can divide. Geron has demonstrated that once telomeres reach a certain short length, cell division halts, and the cell enters a state known as cell senescence. Although senescent cells have stopped dividing, they remain metabolically active and, importantly, demonstrate an altered pattern of gene expression. In senescent cells, certain genes normally expressed by young and healthy cells are turned off or down-regulated while other genes are turned on or up-regulated, creating an imbalance of proteins and other gene products that Geron believes has a direct and destructive effect on the surrounding tissue. Geron believes that this dysfunction at the cellular level, which occurs in numerous tissues throughout the body, causes or contributes to age-related diseases and conditions. Since telomerase activity correlates with cellular immortality, the Company believes that the recent cloning of the telomerase protein gene (see press release dated 8/14/97) may facilitate the immortalization of human cells. Geron had earlier cloned, and has received an issued United States patent relating to the RNA component of human telomerase. The Company announced on 12/1/97 that the recently-cloned hTRT gene product, when combined with the RNA component was sufficient to give telomerase activity. This suggests that these two components together make active enzyme. The paper of 12/1/97 also showed that the hTRT gene alone when transferred into normal human cells conferred telomerase activity. This could allow the Company to immortalize cells without inducing malignant characteristics to the cells. Such technology would have many important applications in medicine and drug discovery, ranging from techniques to rejuvenate human cells to treat human age-related diseases, to technologies of use to the biotechnology industry that are currently limited by the mortality of normal human cells. The complete cloning of the telomerase enzyme and its regulators may also provide the Company with the next generation of telomerase inhibitor screens, new reagents for telomerase detection, and other markers useful in cancer diagnosis. Geron seeks to develop therapeutics to modulate the biological processes leading to and regulating cell aging or senescence. The Company is applying proprietary genomics techniques to target the destructive genetic changes that occur in senescent cells. Geron has entered into research collaborations with several research institutions to support its Genomics of Aging program, including the Lawrence Berkeley Laboratory, Stanford University, and Memorial Sloan-Kettering Institute for Cancer Research. The goal of the program is to treat age-related diseases and conditions by small molecule drugs which modulate the destructive pattern of gene expression that occurs in cells as they exhaust their replicative capacity. Geron's approach to genomics is unique in that it focuses on the differences in gene expression between replicatively young versus senescent cells. Geron believes there is a significant advantage in defining differences in gene expression between young and senescent cells and then utilizing senescent cells in drug discovery screens. Many genomics companies use diseased tissue for research and drug discovery, but diseased tissue is complex in structure and varies from patient to patient. By comparison, Geron believes that senescent cells are more representative of the disease process and provide a homogeneous and reproducible population of cells for both gene and drug discovery. Geron has developed proprietary high throughput genetic analysis techniques called "Enhanced Differential Display" and "Subtractive Differential Display". These technologies have enabled the Company to identify genes, including those which express products at low levels, and gene products that are differentially expressed by replicatively young versus senescent cells. The Company intends to use these genes and their products in automated screens for discovering small molecule drugs that counteract the destructive effects that may be caused by the altered patterns of gene expression associated with cell senescence. The Company's Genomics of Aging program is targeted at a wide range of age-related diseases and conditions. Geron's initial focus is on skin aging, atherosclerosis and macular degeneration. Geron and collaborators have established that when dermal fibroblasts age, or senesce, they undergo numerous changes in gene expression. Geron and its collaborators have discovered over 100 gene markers that are differentially expressed in replicatively young versus senescent dermal fibroblasts. Some of these gene markers appear to be associated with gene products destructive to the extracellular matrix. The Company believes that these and other changes in gene expression contribute to the characteristic age-related atrophy of skin. Reversing or offsetting the effects of such altered gene expression in senescent fibroblasts by targeted and cell-based drug discovery could provide an effective treatment for dermal atrophy and problems with wound healing in aging adults. The United States Patent and Trademark Office recently issued Geron a patent for methods to extend the replicative capacity of fibroblasts for the treatment of skin aging using specific types of small organic molecules known as PARP inhibitors. Atherosclerotic plaques frequently form in blood vessels at areas of turbulent blood flow, such as the vessels in the heart. Geron and its collaborators have shown that endothelial cells lining arteries with turbulent blood flow, where cell turnover and thus cell division is high, have shorter telomeres than cells in regions with less blood turbulence and cell turnover. Further, some gene products differentially expressed in senescent endothelial cells have been shown to play a role in atherosclerosis. The Company believes that altering expression of the senescence-associated genes and their products in the vascular endothelium could provide a unique and effective therapy for atherosclerosis.

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