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Compugen's mission is to be the world leader in the discovery and licensing of product candidates to the drug and diagnostic industry. The Company's powerful discovery engines enable the predictive discovery of numerous potential therapeutics and diagnostic biomarkers. This capability results from the Company's decade-long pioneering efforts in the deeper understanding of important biological phenomena at the molecular level through the incorporation of ideas and methods from mathematics, computer science and physics into biology, chemistry and medicine. To date, Compugen's product discovery efforts and its initial discovery engines have focused mainly on the areas of cancer, immune-related and cardiovascular diseases. The Company's primary commercialization pathway for its product candidates is to enter into milestone and revenue sharing out-licensing and joint development agreements with leading therapeutic and diagnostic companies.

Founded in 1993, Compugen initially developed a computer hardware system and software applications to accelerate homology searches of biological sequences. In 1997, we directed a significant portion of our activities to the development of computational biology platforms and technologies that allow molecular biologists to obtain significantly more valuable information from genomic and related databases. The technologies that we developed solve quantitative and qualitative problems inherent in the analysis of genomic and expressed sequence data. Our first major technology platform was our LEADS computational biology platform, which, among other functions, analyzes and rearranges – also known as clustering and assembly – genomic and expressed sequence data. With the use of our computational platforms, we have been able to discover novel genes and gene-based products, including novel transcripts and proteins. In past years, we licensed out use of this technology for specific purposes or time periods to a number of pharmaceutical and biotechnology companies, including Abbott Laboratories (IL, USA), Novartis Pharma AG and Pfizer, Inc. (NY, USA).

In 1998, we established our biology laboratory, the initial purpose of which was to validate our computationally generated predictions. Subsequently, we expanded the use of the laboratory to support our efforts towards discovering and developing therapeutic and diagnostic product candidates.

Since 2002, we have been focusing on the discovery of novel therapeutic proteins and peptides, diagnostic targets, and biomarker candidates

through the use of the intellectual property, scientific know-how and computational biology capabilities that we continue to develop.

Compugen has been publicly traded on Nasdaq (NASDAQ: CGEN) since August 2000 and on the Tel Aviv Stock Exchange since January 2002. The company has approximately 80 employees, of which approximately 75% are in R&D, and is headquartered in Tel Aviv, Israel.

Discovery programs

Compugen's main discovery programs are:

- Large-scale genetic variations: we have identified many thousands of novel non-SNP variations in the human genome and have statistically confirmed their existence with individual human DNA samples. We are in the process of studying specific phenotypic implications of those variations, and are also developing a practical experimental process to assay large numbers of such variations in parallel. Potential applications include novel biomarkers for drug development, drug response and toxicity or disease predisposition prediction. This program is further described in the section of this article below, entitled genomic markers discovery platform.
- Diagnostic biomarkers: in current collaborations with Siemens Medical Solutions (NY, USA) (Diagnostic Products Corporation), Johnson & Johnson (Ortho-Clinical Diagnostics, NJ, USA) and Biosite (CA, USA), more than ten specific Compugen candidates are

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being studied for utility in cancer and cardiovascular disease screening through immunoassay-based tests. Over 30 mRNA candidates are being initially evaluated by Compugen as nucleic acid testing markers.

- Therapeutic proteins: three novel therapeutic protein candidates have passed *in vitro* and initial *in vivo* studies in the fields of cancer (splice variant of *c-Met*), inflammatory disease (splice variant of *MCP-1*) and cardiovascular disorders (splice variant of *ANP*).
- G-protein coupled receptor (GPCR) ligands: in a recently concluded first use of our GPCR ligand platform, we identified eight novel peptide ligands that activated six GPCRs, the most ubiquitous drug-target family. The ligands' activity was confirmed *in vitro* with standard functional GPCR assays. Novel ligands for two of these receptors were chosen for further development as drug candidates by Compugen.
- Antibody targets: we recently signed an agreement with Medarex (NJ, USA), a therapeutic monoclonal antibody company, to jointly develop antibody therapies. The targets will be selected utilizing a Compugen discovery engine for identifying novel targets for monoclonal antibody-based therapies.
- Toxicity predictors: Compugen has developed discovery engines for identifying tissue-specific transcripts and proteins that may be used for the early detection of tissue damage induced by drugs. These methods are the basis for a recently signed agreement with Teva focusing on the early detection of tissue damage in the preclinical setting (initially targeting nephrotoxicity).
- EGFR-MAP kinase pathway: Compugen is leading a simulation of the map-kinase pathway, SIMAP – an EU consortium of companies and academic organizations seeking to develop a comprehensive simulation of the EGFR-MAP kinase pathway, using and correlating biochemical and clinical data.
- New indications for existing drug molecules: Compugen has developed a new discovery engine for the identification of novel therapeutic indications for existing drug molecules. We have already selected nine new therapeutic candidates from the initial use of this engine.

Genomic markers discovery platform

The GeneVa™ genomic markers discovery platform is based on genotyping of genomic insertions and deletions (INDELs) ranging from 15 to 50,000 bases. Those structural variations may be studied in relation to phenotypic

phenomena, and we believe they will facilitate drug response and disease predisposition studies with a higher degree of success than current SNP-only approaches.

In SNP experiments, selected genomic regions are scanned or a whole-genome scan is performed. The purpose of this scan is to discover SNPs that correlate with the studied phenotype. The GeneVa platform, which allows fine-scale INDEL genetic study, completes this research scheme by directing the efforts towards variations larger than SNPs that are believed to have a more direct influence on genes' phenotypes and be the final causative variations rather than intermediate correlated SNPs. Thus, a fine-scale INDEL-based study opens a new route that increases the probability of success and shortens the way to the final marker discovery.

The discovery platform

The platform contains three main components:

- A large database of insertions and deletions in the human genome
- A system linking structural genomic variations, genes, diseases and drugs
- A novel sequencing-based genotyping method for insertions and deletions

The database platform consists of two sets of variations: over 100,000 fine-scale variations (15–500 bp) and over 60,000 intermediate-scale variations (5–50 kbp). More than 40% of the fine-scale variations are located within known genes and thousands are located in drug-target genes and in drug-target interacting genes.

The database was created by analyzing all human genome sequencing fragments (over 130 million sequences) and public and proprietary expressed sequence tags (EST) databases. A specialized computational biology analysis platform was developed to handle and integrate those disparate data sources, identify possible genomic structural variations and, in many cases, predict their association with specific disease pathways, such as those associated with breast and colon cancer, congestive heart failure, Type 2 diabetes, hypertension, lipid disorders, rheumatoid arthritis and stroke.

The key to genotyping INDELs by sequencing is having an accurate method to analyze chromatograms in the heterozygote state. Our novel mixed chromatogram decomposition algorithm handles complicated cases including alleles appearing only in the heterozygote state, complex chromatograms representing unpredicted

allele combinations and multi-allelic sites. This method is used to genotype fine-scale variations where a method for genotyping of intermediate-scale variations is based upon dense SNP arrays and comparative genomic hybridization arrays (under development).

The GeneVa platform was used during 2006 to design, perform and analyze predisposition studies on Type 2 diabetes and Parkinson's disease. In these studies, more than 200 fine-scale variations were tested on hundreds of DNA samples. A novel 15-bp genomic deletion, associated with the risk of having Type 2 diabetes, has been identified in the *PFKP* gene. PFKP is a key regulatory enzyme in glycolysis. Further validation of this discovery is required.

Compugen proposes to utilize this unique platform to find novel markers by correlating patients' genetic profiles with clinical data such as drug response or toxicity and disease predisposition.

Outlook

Compugen in 2007 possesses a unique, powerful, widely applicable and constantly improving life science discovery capability. This capability exists as the result of our decade-long commitment to seek deeper understandings of important life processes at the molecular level while, in parallel, creating a world-class biology infrastructure. With the pharmaceutical industry suffering from increasing difficulty in discovering and developing new drugs, new sources of innovation are critical for the continuing health of the industry.

Based on our accomplishments to date, we feel confident that our highly efficient and broadly applicable discovery capabilities will result in a rapidly increasing number of products

in a wide range of fields in the development pipelines of major pharmaceutical and diagnostic companies worldwide under licensing arrangements with us. Since we expect additional discoveries and, therefore, product candidates each year, this should result in exponentially increasing future profit opportunities for Compugen, but without the risks and costs typically associated with drug and diagnostic research and development. This potentially very high-profit and low-risk business model can only be pursued by a company that has a predictable, continuing and improving product candidate discovery capability – a unique capability that is the core of Compugen's mission.

In addition, we anticipate that our unique multidisciplinary team will continue to develop new discovery engines to tackle the next decade's discovery challenges. Compugen's GeneVa platform, which identifies markers to predict drug response, toxicity and disease predisposition, among other utilities, and future descendants of this project, may pave the way for the discovery of a multitude of markers that will make the term 'personalized medicine' a reality. In this way, Compugen will achieve its mission to be the world leader in the discovery and licensing of product candidates to the drug and diagnostic industry.

Financial & competing interests disclosure

EZ works for Compugen, Ltd. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Highlights

- Compugen's discovery engines enable predictive discovery of numerous potential therapeutics and diagnostic biomarkers.
- Capabilities result of incorporating ideas and methods from mathematics, computer science and physics into biology, chemistry and medicine.
- Proprietary GeneVa platform identified many thousands of novel non-SNP variations in the human genome; platform used to find novel drug response and other markers by correlating patients' genetic profiles with clinical data.
- More than ten specific biomarker candidates being studied for utility in cancer and cardiovascular disease screening through immunoassay-based tests; another 30 mRNA candidates being initially evaluated as nucleic acid testing markers.
- Three novel therapeutic protein candidates identified and passed *in vitro* and initial *in vivo* studies.
- Eight novel peptide ligands identified that activate six G-protein coupled receptors.
- Joint development of antibody therapies with Medarex.
- Discovery engine developed for identifying tissue-specific transcripts and proteins that may be used for early detection of tissue damage induced by drugs.
- Discovery engine developed for identifying existing drug molecules predicted to have important new therapeutic indications.