

BIO-INVESTIGATIONS LTD.

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For more information, please contact:

Stewart B. Rosenberg, President

OPINION LETTER ON

IMMUNOSCIENCES INC.

505 JACKSON AVE.

NEW HYDE PARK, NY 11040

TELEPHONE: (516) 746-5005

SCIENTIFIC DIRECTOR: DR. ARIE BARTAL, M.D./D.Sc.

OVERVIEW

ImmunoSciences Inc. (ISI), established in 1988, is a biopharmaceutical company focusing on the research and development of monoclonal antibodies for application towards diagnosis and therapy of cancer. Monoclonal antibody technology is over twenty years old and is reaching a mature phase. Antibodies are being used for in vitro diagnostic kits, for in vivo diagnostic imaging and are under development for therapeutic applications in unconjugated and conjugated forms. ImmunoSciences has identified and carved out a unique niche in the field of monoclonal antibodies and genetically engineered products. The company has established itself as one of the leading international centers for the evaluation and characterization of monoclonal antibodies. ISI performs services for biotechnology and pharmaceutical companies including: tumor tissue reactivity, normal tissue crossreactivity, GLP/GMP production, safety/toxicology, hybridoma generation, immunohistochemical reference laboratory, clinical trial support, conjugation, marketing antibodies for research and evaluation of new antibodies. One of the most valuable assets of the company is its extensive frozen tissue bank. Characterization of tumor reactivity, determination of normal tissue crossreactivity, safety and toxicology testing, and standardized immunocytochemistry controls require fresh human frozen tissues. ISI most likely has accumulated one of the largest frozen tissue banks in the world. It appears that this resource has not been duplicated by other biotechnology or pharmaceutical companies. ISI receives monoclonal antibodies for characterization from commercial and academic institutions from around the world including the United States, Canada, Australia, Japan, Israel and Europe. The company has executed contract agreements for antibody characterization with leading pharmaceutical and biotechnology companies including Bristol-Myers Squibb, Eli Lilly, IDEC, Advanced Tissue Sciences, Biotechnology Research Institute, Biomira, CellPro, Hybritech, Neoprobe, Cancer Diagnostics, NeoRx, Biogen, Coulter, Medarex and Hygeia. Data and reports generated by ImmunoSciences are used by client companies for preclinical evaluation, product development and FDA applications for product approval. ISI has participated in meetings between client companies and the FDA.

32 COUNTRY WAY

MADISON, CT 06443 U.S.A.

(203) 421-3697

As progress is made in the development of monoclonal antibody and genetically engineered products, FDA regulatory issues have dramatically increased. FDA requirements for the characterization of antibodies are becoming more rigorous. Regulations are increasingly more stringent for entry of antibodies into clinical trials and for the manufacturing of antibody products. In the past few months, the FDA's Hematological and Pathological Devices Classification Panel has recommended that immunohistochemicals including monoclonal antibodies should be regulated as class II medical devices (Genetic Engineering News vol 14 No. 20 1994). Therefore, as the commercialization of antibodies for research, diagnostic and therapeutic applications increases, there will most likely be a significant increase in demand for ISI's unique antibody characterization services.

ISI has developed state-of-the-art technology called the colloidal gold-silver enhancement system (CGSS) for application in a new line of immunodiagnostic kits that will detect micrometastatic cancer and minimal residual disease in bone marrow and blood. Currently, there are no in vitro diagnostic kits available that accurately detect tumor cells in bone marrow and blood. The company plans to incorporate the CGSS immunogold technology in diagnostic kits that can be used for diagnosis, staging, and monitoring of patients undergoing anti-cancer therapies. The company will utilize CGSS technology along with proprietary and established antibodies to develop novel immunodiagnostic kits for the most prevalent cancers including breast, lung, colon, ovarian and prostatic cancer.

After six years of operation, the company is now in an excellent position to move to the next level which includes - expansion of its core antibody characterization service business, establishment of an immunopathology service to local hospitals and institutions, and development of a new line of immunodiagnostic test kits for cancer. The company has developed a strategy to reduce the high research and development costs usually associated with identifying new monoclonal antibodies that can be incorporated into diagnostic kits. ImmunoSciences will use its in-house antibody testing service as a pipeline for identifying proprietary and useful antibodies that have been isolated by others. Through exclusive licensing agreements the company plans to obtain rights to use outside antibodies for its diagnostic kits. This strategy has already proved to be successful. ImmunoSciences has obtained exclusive marketing rights to anti-sarcoma (OS-TP1 and OS-TP3) and anti-colon carcinoma (PCA) monoclonal antibodies. One of the company's objectives is to obtain licenses to anti-cytokeratin, anti-CEA, anti-prostate specific antigen and anti-fibronectin antibodies for use in immunodiagnostic kits. ImmunoSciences will incorporate its proprietary CGSS immunogold detection system in its kits which will enable use in applications where standard immunoperoxidase diagnostic kits cannot be used. Immunogold assay technology was developed under the auspices of a Phase I federal government Small Business Innovation Research (SBIR) grant and the company has submitted an application for a Phase II SBIR grant to further develop the technology. ImmunoSciences' immunodiagnostic kits will contain the most highly characterized antibodies available and an improved assay technology. Long range goals call for the company to generate new murine and human monoclonal antibodies through an in-house research program.

In our classification of companies, ImmunoSciences is well past the startup phase and is poised to emerge as a major biopharmaceutical company in the management of oncological diseases. ImmunoSciences is unique for the biotechnology industry in that during the difficult startup phase it was able to establish a revenue generating arm in its earliest stage of development. Additionally, the company has a well-conceived strategic plan that utilizes its established business reputation and core technologies to its highest advantage to move to the next stage of development. It is our recommendation that potential investors give ImmunoSciences a high priority in their review process. Similarly, we view ImmunoSciences as highly appropriate for participation by government funding agencies and a prime candidate for strategic alliances with multiconglomerate organizations.

Methodology.

ImmunoSciences was brought to the attention of BIO-INVESTIGATIONS LTD. by Dr. Robert Greenfield, Ph.D., of Wallingford, CT. Dr. Greenfield was a senior research scientist for twelve years in the Bristol-Myers Squibb Pharmaceutical Research Institute and is a recognized leader in the field of monoclonal antibodies. He currently is working as a consultant in the biotechnology industry and has worked with BIO-INVESTIGATIONS LTD. in other projects. Our review of ImmunoSciences has been extremely in-depth and has been accomplished by a number of interrelated activities. A detailed review of the master business plan was done followed by a review of supplemental documentation. A meeting was held with Dr. Arie Bartal and Dr. Robert Greenfield to further discuss the technology, business directions and financial requirements. A visit to ImmunoSciences facilities in New Hyde Park, NY was accomplished and in-depth discussions were held with Dr. Yashar Hirshaut (President), Dr. Bartal (Scientific Director) and Dr. Greenfield.

The purpose of this review is to raise key issues relating to ImmunoSciences as opposed to summarizing the business plan. It is expected that response to this opinion letter will generate an interest to formally request additional details and information directly from ImmunoSciences. While the scientific staff of ImmunoSciences is highly qualified, it is not our intent to review each contributor's publication record. Rather, it is our intent to raise key issues critical to existing strengths and weaknesses of ImmunoSciences as it is presently positioned. We will present the issues point-by-point for clarity and brevity.

Management.

Dr. Arie Bartal is a medical oncologist and was a former medical researcher in hybridoma technologies at Memorial Sloan-Kettering Cancer Center (MSKCC). Dr. Bartal has served as the Scientific Director of ImmunoSciences from its inception in 1988. Dr. Bartal has been key to the success of the company and has many accomplishments including establishing a modern 4,000 sq.ft. research facility, hiring an excellent technical staff, accumulation of an extensive frozen tissue bank and development of a revenue producing immunodiagnostic

service for evaluation of commercial and academic antibodies. ImmunoSciences has developed an excellent reputation in the Biotechnology and Pharmaceutical industries as a leading company in the evaluation and characterization of monoclonal antibodies. Dr. Bartal has also directed business development aspects of the company and has established an extensive international network of collaborations with academic laboratories as well as biotechnology and pharmaceutical companies. Additionally, Dr. Bartal has been instrumental in ImmunoSciences being awarded two Phase I SBIR grants totaling over \$130,000. Dr. Bartal has recently submitted a Phase II SBIR based upon successful completion of the work in the Phase I grant on immunogold technologies and is submitting an STTR grant in conjunction with SUNY Downstate Health Center in Brooklyn N.Y. Dr. Bartal has experience with government regulatory procedures and has worked directly with FDA departments which regulate the use of antibodies both as medical devices and as pharmaceuticals. Dr. Yashar Hirshaut (MD, FACP) is a co-founder of ImmunoSciences and is currently serving as President of ImmunoSciences. He has been instrumental in raising over \$850,000 in private investments. Dr. Hirshaut is formerly Head of the Immunodiagnosis Laboratory and Tumor Procurement Center at MSKCC (18 years), editor of *Cancer Investigations* (Marcel and Dekker Publisher) and co-editor with Dr. Bartal of Methods of Hybridoma Formation (Humana Press, 1987). He is a leading medical oncologist and researcher who is devoted to bringing new immunodiagnostic products to the marketplace for the improved management of treatment and care of cancer patients. Previously, Dr. Hirshaut was co-founder of Dianon Inc., Stratford, CT, (NASDQ, DIAN) which specializes in cancer test services for physicians.

Dr. Robert Greenfield is currently a consultant for ImmunoSciences and intends to join the senior management team upon successful procurement of capital for the Phase II growth of ImmunoSciences. He has co-authored over thirty research publications and articles and is an inventor on seven patents in antibody technologies at BMS. Dr. Greenfield discovered and developed BR96-DOX, BMS's first monoclonal antibody-drug conjugate being tested in Phase I/II clinical trials for the treatment of cancer. Dr. Greenfield brings to ImmunoSciences outstanding technical and managerial experience, in addition to knowledge of the pharmaceutical industry.

Technology.

ImmunoSciences was formed to operate in five areas: monoclonal antibody characterization and services; clinical pathology; immunodiagnostic kits; antibody development; and cancer research. In the first six years, ImmunoSciences has successfully developed a broad-based business to serve the biotechnology industry in various aspects of antibody characterization and has established a reputation for excellence within the scientific, biotechnology and pharmaceutical industries. In Phase II, the company plans to increase the marketing of its antibody characterization services including - immunohistochemical reference laboratory, compliance to FDA regulations for antibody products, tissue crossreactivity analysis for safety and toxicology testing, and new antibody evaluation. The company will also expand operations into the areas of commercialization of immunodiagnostic kits for cancer,

establishment of a clinical immunopathology laboratory service for local hospitals and research and development of novel antibodies. New antibodies will be incorporated into immunodiagnostic kits that the company will manufacture and market.

The most critical tests that antibodies must pass to be considered useful for applications as diagnostic and therapeutic antibodies are reactivity, specificity and sensitivity towards human tissues. One of ImmunoSciences' greatest assets is having collected over the last six years one of the largest commercial normal and tumor frozen tissue banks. Tissue procurement at ImmunoSciences is an on-going program and the tissue bank continues to expand on a weekly basis through the company's network of clinical pathologists and oncologists at local hospitals. Through the development of the tissue bank, ImmunoSciences has uniquely positioned itself to be the leading company for screening and evaluating antibodies. This resource has allowed ImmunoSciences to establish its successful revenue producing Antibody Characterization Service.

ImmunoSciences plans to develop new immunodiagnostic kits for applications in cancer. The company will obtain antibodies for the immunodiagnostic kits through two means: licensing outside antibodies and in-house research and development. Over the past six years, ImmunoSciences has established many contacts in the commercial and academic sectors that are generating new monoclonal antibodies. The company will expand its contract antibody testing capability to evaluate outside antibodies on its proprietary tissue bank and license the most promising antibodies. ImmunoSciences already has successfully utilized this approach to obtain exclusive licenses to monoclonal antibodies for the immunohistochemical detection of colon cancer and osteosarcomas.

ImmunoSciences also has developed under the auspices of an SBIR grant a proprietary CGSS immunogold tissue staining assay that provides increased sensitivity and specificity in immunohistochemical applications. The CGSS immunogold detection system has significant advantages over standard immunohistochemical assays kits that utilize peroxidase enzyme systems. Immunoperoxidase assays frequently suffer from high non-specific reactions on normal tissues. It is especially difficult to detect cancer cells in hematological specimens such as bone marrow and blood specimens using immunoperoxidase staining. CGSS immunogold technology eliminates the non-specific reactions with normal hematological tissues and therefore can be used to detect cancer cells in bone marrow and blood specimens. There is a very large need for immunodiagnostic kits that can detect tumor cells in bone marrow and blood. The ability to detect residual tumor cells and micrometastases in bone marrow and blood will lead to improved management of cancer patient care in the areas of diagnosis, staging and monitoring the progress of cancer patients undergoing therapy. CGSS immunogold assay technology will allow ImmunoSciences to capture a large market which other companies cannot enter with immunoperoxidase assay formats. Autologous bone marrow transplantation is increasingly becoming a standard procedure in cancer treatment regimens. The success of the transplantation procedure relies on the determination that no tumor cells are present in the transplanted bone marrow. ImmunoSciences' kits will be important new products in clinical diagnostic laboratories at cancer centers which perform

bone marrow transplantation procedures. ImmunoSciences has the ability and experience to manufacture diagnostic kits under GLP conditions and to satisfy all FDA regulatory issues. The company has in place an international network of expert pathologists to field test its diagnostic kits.

Long range plans call for an in-house research program to develop human monoclonal antibodies. Human tumors are known to be immunogenic in man. Human B-cells of the immune system are designed to defend the body against a tumor by making antibodies that bind to the tumor. Hybridoma technology which was originally developed to isolate murine derived antibodies now has been made applicable to isolate human monoclonal antibodies. Reports have shown human antibodies identify unique antigens not previously identified using murine hybridoma technology. Human monoclonal antibodies are obtained by fusion of human B-lymphocytes from cancer patients with immortalized human fusion partners to obtain hybridomas producing human monoclonal antibodies. The two major problems encountered by many laboratories generating human hybridomas are the ability to obtain fresh human lymph nodes from cancer patients and to rapidly and accurately analyze the specificity and sensitivity of human antibodies that have been isolated. These are major strengths of ImmunoSciences. ImmunoSciences has the technology, know-how and experience over other companies and academic laboratories to rapidly identify unique antibodies that will be useful for the diagnosis, staging and monitoring of cancer patients.

ImmunoSciences is uniquely positioned to identify human antibodies that will be important for diagnosis and therapy because the company:

1. has a professional and technical staff trained in all areas required for research and development including immunohistology, immunochemistry, immunology, tissue culture and pathology;
2. possesses a large bank of tumors and normal tissues required for screening new antibodies;
3. has developed expertise in evaluating and testing human antibodies;
4. has direct access to fresh, sterile human lymph nodes from cancer patients through the company's in-house tissue procurement program.

Market Opportunity.

The in vitro laboratory immunodiagnostic market is the general market into which ImmunoSciences services and products are targeted. This market is estimated to be

approximately \$4.7 billion for 1994. ISI's immunodiagnostic test kits for cancer will be targeted to pathology and hematology laboratories. It is estimated that kits for colon, breast, lung, prostate and ovarian cancer can each generate \$10-20 million per year based upon the number of newly diagnosed cancer patients per year and the number of patients undergoing cancer therapies. Major companies in immunodiagnostics are Abbott Laboratories, DaKo, Syva, Vector, Baxter, Sigma, Zymed and Shandon among others. None of these companies are marketing diagnostic kits targeted for detection of residual cancer cells in bone marrow and blood. There appear to be no major competitors to the Antibody Characterization Service division of ISI. Impath (NY) mainly conducts immunopathological services for hospitals and commercial organizations. However, Impath is not a fully integrated immunodiagnostic company with research and development capabilities. ImmunoSciences should be able to increase revenues of its antibody characterization service through an aggressive marketing campaign. It is estimated that revenues can reach \$1-2 million per year. Establishment of a licensed Immunopathology laboratory is estimated to generate \$2.5 million per year based upon evaluating 5000 specimens per year.

Strategic Alliances.

Further support of the classification of ImmunoSciences as an emerging company can be obtained through an assessment of collaborative arrangements already in place. Goldmark Biologics, a marketing arm of Biocell (UK), and ImmunoSciences have formed a consortium for the development of immunogold nanoparticle technology. This has led to successful development of the proprietary CGSS immunogold assay that has improved sensitivity and specificity over presently available tissue staining tests. The company plans to establish with Biocell through Goldmark Biologics an exclusive marketing arrangement for colloidal gold immunologic reagents.

ImmunoSciences has a strategic alliance with International Bioimmune Science (IBS). ISI serves as an incubator facility and marketing arm for IBS antibodies. ISI has collaborated with IBS on the development of PCA 33.28 and PCA 31.1 anti-colon monoclonal antibodies and has obtained an exclusive licensing agreement from IBS for immunohistochemical use of PCA 33.28 and 31.1. Dr. Louis Pertchuck (SUNY Downstate Medical Center, Brooklyn, NY) a world renown pathologist and researcher on the estrogen receptor has been retained as a consultant and in-house pathologist. ISI will license the hybrid spheroid tumor technology from Downstate Medical Center. A U.S. government STTR research grant on this technology with Dr. Bozidar Djordjevic has been filed (Nov. 1994). The company has established working relations and collaborations with many of the major hospitals, academic and research institutions in the New York metropolitan area.

ImmunoSciences has an international focus. ISI has secured rights to antibodies from laboratories in Norway and Israel and has established many research collaborations with foreign academic and clinical researchers.

Valuation.

Traditional valuation methods including discounted cash flow analysis and price/earnings ratio analysis have all been taken into account in our final valuation of ImmunoSciences. We strongly believe the valuation of the company should take into consideration the following: accomplishments over the first six years of operation, successful development of the Antibody Characterization Service, collaborations and alliances, industry reputation, technology, executed licensing agreements, potential of future research, and position to rapidly develop and market 3 - 5 in vitro diagnostic kits within the coming year. One must also recognize the invaluable asset of the frozen tissue bank. To date, the company has expended almost \$850,000 of funds secured from private investors. Operations have also been supported by \$1 million in revenues from the Antibody Characterization Service. The future success of the company lies in its ability to expand its current contract service, identify new applications of its core antibody characterization service to the biotechnology and pharmaceutical industries and production and sales of diagnostic kits. We believe the company is well focused on these goals. ImmunoSciences is not a startup, and is not focused on raising 40 - 50 million dollars of investment capital for expensive long term research programs that are high risk. The company is presently poised to enter into the product development phase with short term profitability projections and returns on investment. ImmunoSciences' products will have an immediate impact in the industry. Our valuation of the company at the present time is between fifteen and twenty million dollars.

Critical Issues.

We consider the following to be key for ImmunoSciences' continued success. ImmunoSciences recently moved into new facilities and requires upgrading of the laboratory facilities and additional capital equipment. ImmunoSciences needs to increase its visibility within the biotechnology and pharmaceutical industries through an aggressive marketing campaign and increased attendance at medical and scientific meetings. The technology behind ImmunoSciences is sound and needs to be backed up by highly qualified individuals and leaders in their field. The company will benefit from the talents and capabilities of individuals of Dr. Greenfield's stature and ability. The company should aggressively recruit individuals of this caliber as future employees. The company also needs to gain experience and expertise in the commercialization of diagnostic kits.

Rating: A

The recommendations and opinions provided in this letter are those of BIO-INVESTIGATIONS LTD. Reasonable efforts have been made to collect accurate factual information from ImmunoSciences' company headquarters, by conducting site visits, and performing face-to-face interviews with management on technical and business issues. Corporate investors, strategic alliance partners and venture capital firms, however, are all encouraged to do their own due diligence. BIO-INVESTIGATIONS LTD. assumes no responsibility for actions taken as a result of this Opinion Letter.

BIO-INVESTIGATIONS LTD. is a venture capital consultancy headquartered in the United States, having commenced operations in September 1987. With an international client base, BIO-INVESTIGATIONS LTD. is heavily focused on identifying technologies for acquisition or investment.

We welcome your comments and questions related to ImmunoSciences Inc.