

Harbor BioSciences, Inc.  
Form 10-K  
January 20, 2012

**UNITED STATES**  
**SECURITIES AND EXCHANGE COMMISSION**  
**WASHINGTON, D.C. 20549**

**FORM 10-K**

**ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the fiscal year ended December 31, 2011**

**OR**

**TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**FOR THE TRANSITION PERIOD FROM TO**

**Commission File Number 001-34584**

**HARBOR BIOSCIENCES, INC.**

(Exact name of Registrant as specified in its charter)

**Delaware**  
(State or other jurisdiction  
of incorporation or organization)

**13-3697002**  
(I.R.S. Employer  
Identification No.)

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9191 Towne Centre Drive, Suite 409

San Diego, CA  
(Address of principal executive offices)

92122  
(Zip Code)

Registrant's telephone number, including area code: (858) 587-9333

Securities registered pursuant to Section 12(b) of the Act: None

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, par value \$0.01 per share

Title of Class

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.

YES  NO

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act.

YES  NO

Indicate by check mark whether the Registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirement for the past 90 days. YES  NO

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).

YES  NO

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the Registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer or a smaller reporting company. See definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2. (Check One).

Large accelerated filer  Accelerated filer   
Non-accelerated filer  Smaller reporting company   
Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Act). YES  NO

The aggregate market value of the voting stock held by nonaffiliates of the Registrant as of June 30, 2011, the end of the Company's most recently completed second fiscal quarter, was approximately \$7,372,544 based on the closing stock price of \$0.21 for the Registrant's common stock as reported by the OTC Bulletin Board\*.

As of January 20, 2012, there were outstanding 35,422,140 shares of the Registrant's common stock, \$.01 par value per share.

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\*Excludes the common stock held by executive officers, directors and stockholders whose ownership exceeded 10% of the Registrant's common stock outstanding at June 30, 2011. This calculation does not reflect a determination that such persons are affiliates for any other purposes.

### **DOCUMENTS INCORPORATED BY REFERENCE**

None

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Harbor BioSciences, Inc.

Form 10-K

For the Fiscal Year Ended December 31, 2011

## INDEX

	<b>Page</b>
<b><u>PART I</u></b>	
<u>Item 1. Business</u>	1
<u>Item 1A. Risk Factors</u>	19
<u>Item 1B. Unresolved Staff Comments</u>	27
<u>Item 2. Properties</u>	27
<u>Item 3. Legal Proceedings</u>	28
<u>Item 4. Removed and Reserved</u>	28
<b><u>PART II</u></b>	
<u>Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</u>	28
<u>Item 6. Selected Financial Data</u>	29
<u>Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations</u>	29
<u>Item 7A. Quantitative and Qualitative Disclosures About Market Risk</u>	33
<u>Item 8. Financial Statements and Supplementary Data</u>	34
<u>Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure</u>	73
<u>Item 9A. Controls and Procedures</u>	73
<u>Item 9B. Other Information</u>	74
<b><u>PART III</u></b>	
<u>Item 10. Directors, Executive Officers and Corporate Governance</u>	74
<u>Item 11. Executive Compensation</u>	80
<u>Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholders Matters</u>	88
<u>Item 13. Certain Relationships and Related Transactions, and Director Independence</u>	89
<u>Item 14. Principal Accountant Fees and Services</u>	90
<b><u>PART IV</u></b>	
<u>Item 15. Exhibits and Financial Statement Schedules</u>	91

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## FORWARD-LOOKING STATEMENTS

*This Annual Report on Form 10-K, and the information incorporated herein, contains forward-looking statements that involve and are subject to risks and uncertainties. In particular, statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are contained or incorporated by reference in this Annual Report on Form 10-K. We have based these forward-looking statements on our current expectations about future events. While we believe these expectations reflected in this Annual Report on Form 10-K are reasonable, the inclusion of any forward-looking statements should not be regarded as a representation that any of our plans will be achieved and such forward-looking statements are inherently subject to risks and uncertainties, many of which are beyond our control. Such forward-looking statements include, but are not limited to, statements preceded by, followed by or that otherwise include the words, believe, may, might, can, could, will, would, should, estimate, continue, anticipate, intend, seek, plan, project, expect, or similar expressions. The actual future results for Harbor BioSciences, Inc. may differ materially from those discussed here for various reasons, including those discussed in this Annual Report in Part I, Item 1A under the heading Risk Factors, Part II, Item 7 entitled Management's Discussion and Analysis of Financial Condition and Results of Operations and elsewhere throughout this Annual Report on Form 10-K. Given these risks and uncertainties, you are cautioned not to place undue reliance on such forward-looking statements. The forward-looking statements included in this Annual Report are made only as of the date hereof. We do not undertake any obligation to update any such statements or to publicly announce the results of any revisions to any of such statements as a result of new information, to reflect future events or developments. When used in this Annual Report, unless otherwise indicated, we, our and us refers to Harbor BioSciences, Inc.*

### PART I

#### EXPLANATORY NOTE

On August 15, 2011, we filed a Form 15 (the Original Form 15) with the Securities and Exchange Commission (the SEC) certifying that, as of such date, there were fewer than 300 holders of record of our common stock. The Original Form 15 had the effect of terminating the registration of our common stock under the Securities Exchange Act of 1934, as amended (the Exchange Act), which was the first step in suspending our obligation to file current and periodic reports with the SEC. However, our duty to file current and periodic reports with the SEC was not suspended immediately upon filing the Original Form 15, due to the prior filing of certain registration statements under the Securities Act of 1933, as amended (the Securities Act) that were deemed to have been made effective during the fiscal year ended December 31, 2011 by the filing of our Annual Report on Form 10-K for the fiscal year ended December 31, 2010, which we filed with the SEC on March 30, 2011. As a result, following the filing of the Original Form 15, on October 28, 2011 we filed a Current Report on Form 8-K, and on November 7, 2011 we filed a Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2011. In addition, we are filing this Annual Report on Form 10-K for the fiscal year ended December 31, 2011. However, we have taken certain actions required by SEC rules to ensure that we are not required by the Exchange Act to file current or periodic reports with the SEC with respect to the fiscal year ending December 31, 2012, which actions have included the filing of post-effective amendments to each of our registration statements filed under the Securities Act to terminate such registration statements (which post-effective amendments have been declared effective by the SEC), and the filing, on January 12, 2012, of a Form 15 to notify the SEC that we had fewer than 300 holders of record of our common stock as of December 31, 2011. In addition, we do not expect that we will be required to file current or periodic reports with the SEC with respect to any fiscal year following the fiscal year ending December 31, 2012.

#### Item 1. Business

##### GENERAL OVERVIEW

Harbor BioSciences, Inc. ( Harbor BioSciences or the Company ), a clinical-stage pharmaceutical company, is engaged in the discovery and development of products for the treatment of diseases that typically onset with age. Our current development efforts are primarily focused on a novel series of hormone-related sterols that are derived from the human adrenal metabolome.

We are a development-stage company with two product candidates which recently completed Phase I/IIa clinical trials: Apoptone® (HE3235) in patients with late-stage prostate cancer, and Triolex® (HE3286) in obese type-2 diabetes mellitus patients. Apoptone and Triolex represent two of the lead candidates from Harbor BioSciences' technology platform based on endogenous human sterols and their metabolites.

Drawn from our unique and proprietary platform, our research program has identified additional lead candidates that are active in preclinical models of cancer, metabolic conditions, autoimmune conditions, lung, ocular and neuro-inflammation, bone degeneration and organ regeneration.

Our principal executive offices are located at 9191 Towne Centre Drive, Suite 409, San Diego, California 92122, and our telephone number is (858) 587-9333. We incorporated in Delaware in 1992.

On March 26, 1997, Hollis-Eden, Inc., a Delaware corporation, was merged with and into us, then known as Initial Acquisition Corp. (IAC), a Delaware corporation. Upon consummation of the merger of Hollis-Eden, Inc. with IAC, Hollis-Eden, Inc. ceased to exist and IAC changed its name to Hollis-Eden Pharmaceuticals, Inc.

Effective February 9, 2010, we changed our name from Hollis-Eden Pharmaceuticals, Inc. to Harbor BioSciences, Inc. The name change was effected pursuant to Section 253 of the General Corporation Law of the State of Delaware by the merger of our wholly owned subsidiary into us. We were the surviving corporation and, in connection with the merger, we amended our Amended and Restated Certificate of Incorporation to change our name to Harbor BioSciences, Inc.

Effective February 18, 2010, our common stock began trading under a new NASDAQ symbol, HRBR and CUSIP number 41150V 103. Our common stock was then delisted from the NASDAQ Stock Market at the opening of business on September 23, 2010. Our shares then traded on the OTC Bulletin Board (OTCBB), until August 17, 2011, when our common stock was delisted from the OTCBB as a result of our filing a Form 15 pursuant to SEC Rule 12g-4(a)(i), and subsequently became available for trading on the OTC Markets Group, Inc., informally known as the Pink Sheets under the trading symbol HRBR.PK and CUSIP number 41150V 202. On July 28, 2011, we sold an aggregate of 2,000,000 shares of our Series A Preferred Stock (the Redeemable Preferred Shares) to Amun, LLC, a Delaware limited liability company (the Investor) pursuant to the terms of a Stock Purchase Agreement (the Purchase Agreement) and related Stockholders Agreement (the Stockholders Agreement). The Redeemable Preferred Shares represent approximately a 28% of the economic interest in the Company and also entitle the Investor to a number of votes equal to 38.28% of the total number of votes entitled to be cast by holders of all shares of the Company's capital stock (including the Common Stock and Series A Preferred Stock) voting together as single class. Under the terms of these and other related agreements between us and the Investor, the Investor placed \$2.825 million in cash into an escrow account (Escrow), which amount is available under certain circumstances to pay certain Company related expenses and to fund our working capital needs. The Stockholder Agreement provides that the Investor will have the right to put the Redeemable Preferred Shares acquired pursuant to the Purchase Agreement back to us in return for the remaining cash held in Escrow at the time of the put, upon the occurrence of certain events.

As contemplated by the Purchase Agreement and the Stockholders Agreement, the Investor intends to bring an offer to us for us to acquire a controlling interest in a profitable entity, which transaction would provide to the Company at least \$5,000,000 in cash plus an amount equal to the costs and expenses incurred by the Company in connection with such transaction (not to exceed \$200,000), which amounts, together with any operating cash held by us immediately prior to closing such transaction, would be transferable, together with any and all (i) intellectual property and (ii) other assets of the Company related to our biotechnology business, to a newly formed subsidiary of the Company, Harbor Therapeutics Inc., which subsidiary will assume all liabilities of the Company as of immediately prior to such closing (a Qualifying Transaction). The Company expects that the closing of a Qualifying Transaction would provide access to capital and the continuation of its existing business. In addition, the acquisition of a controlling interest in a profitable entity would provide diversification for its shareholders.

On October 26, 2011, we completed the reverse and forward stock splits which were approved by our shareholders at our annual meeting. As a result, the Company purchased the 43,698 common shares that were cancelled, at the previous ten-day average closing price of \$0.142 for a total of \$6,205. In addition, as a result of the stock splits, the investors in our June 2010 registered direct offering of common stock and warrants became eligible to exercise a put right under the warrants, which entitled them to put the warrants back to us in return for a cash payment equal to the fair value of the warrants as determined by reference to a formula set forth in such warrants. All of the warrant holders exercised their put right and the Company purchased the warrants at a price of \$0.0955 for each underlying share for a total of \$337,679. An amount equals to the cost of the cancelled common shares and the warrants purchased was distributed to us from the Escrow account established with the funds from the sale of

Preferred Shares to Amun. Harbor BioSciences, Triolex, Apoptone, and the Harbor BioSciences stylized logo are trademarks of Harbor BioSciences, Inc. This filing also includes trademarks owned by other parties. All other trademarks mentioned are the property of their respective owners. Use or display by us of other parties' trademarks or products is not intended to and does not imply a relationship with, or endorsements or sponsorship of, us by the trademark or product owners.

Our periodic and current reports that we filed with the SEC are available free of charge, on our website. Our internet address is [www.harborbiosciences.com](http://www.harborbiosciences.com). The reference to our website does not constitute incorporation by reference of the information contained on our website.

### **Harbor BioSciences Approach**

Under conditions of stress, chronic infections or systemic inflammation, it is believed that changes in the profile of adrenal products, and the metabolism of these products, perturb signaling pathways in peripheral tissues to drive the growth of certain tumors and are causative to diseases of advancing age. These age-related diseases include metabolic syndrome, autoimmune diseases, immune-mediated inflammatory diseases and an impaired ability to fight infections. Our development strategy is based on the hypothesis that hormone-derived products are critical to the regulation of the body's complex biological systems. We believe that in young, healthy adults, adrenal products, such as cortisol, progesterone, dehydroepiandrosterone (DHEA), and its metabolome, which includes estrogen and testosterone, provide important signals for proper engagement and regulation of human biological processes.

Today, most drug developers take a *ground up* approach by first striving to intellectualize and identify critical components in the intricate functional biochemical cascades, and then attempting to design drugs that can successfully block or stimulate those specific pathways. This approach presumably results in validated molecular targets for specific diseases. While this approach has resulted in a number of successful drugs, uses of these drugs are often limited by serious side effects due to unanticipated off-target activities. In contrast, ours is a *top down* forward pharmacology approach that begins with the identification of previously unappreciated members of the human sterol metabolome. Then, by applying sophisticated drug development methodology, we develop novel compounds that modify critical endocrine pathways intrinsic to the activities of the native endogenous molecules. Our top-down methodology is based on a successful historical approach to drug discovery as applied to the early development of human hormones. We continue to apply this approach, which has the potential to produce new pharmaceutical product candidates to treat a myriad of diseases associated with advancing age, to our new discoveries in the vast, unexplored human metabolome. We believe that by reapplying this previously successful, but now neglected, top-down drug development principle the potential exists to produce pharmaceuticals that should address numerous important markets, including many with unmet medical needs.

## **TECHNOLOGY**

### **Platform**

Our primary technology is focused on developing novel series of hormone-related sterols that are useful for treating a wide variety of medical conditions. Many of these compounds are either depleted or elevated during advancing age, which are processes accelerated by infectious diseases and chronic inflammatory disorders. In certain indications, high plasma concentrations of these hormones are positively correlated with attenuated disease and the maintenance of good health.

The chemistry and biochemistry of steroids have been extensively studied and utilized in the development of various drugs, especially for treating hormonal imbalances, infections, and cancer, as well as inflammatory conditions. Harbor BioSciences' chemical inventory of greater than 700 sterol compounds represents a targeted chemical library derived from components of the mammalian metabolome. Many of the library compounds were previously unknown metabolome components. Other library members include compounds having novel structures based upon those metabolic products with potentially improved pharmaceutical properties. We believe this library contains many unique chemical structures with diverse biological properties and represents the largest sample of compounds associated with the DHEA metabolome.

Our targeted chemical library contains drug-like molecules since they were designed to have useful pharmaceutical properties, including improved oral bioavailability and metabolic and chemical stability. The library members further provide lead compounds for additional new chemical compositions that will expand our intellectual property portfolio. In addition, the library compounds are selected for facile and cost-effective syntheses of those newly derived chemical compositions by taking into consideration future commercialization.

## **OUR DRUG CANDIDATES IN DEVELOPMENT**

We are currently focused on the development of proprietary synthetic sterol derivatives derived from the human 19-carbon steroid scaffold of the mammalian sterol metabolome. We have conducted clinical trials with our lead drug development candidates: Apoptone (HE3235), for late-stage prostate cancer; Triolex (HE3286), for the treatment of obese type-2 diabetes, other metabolic disorders and autoimmune conditions; Neumune (HE2100), for the treatment of sepsis, which is a condition that arises with excess radiation exposure; and HE2000, for the prevention of opportunistic infections in immune-suppressed patients. Each of those compounds is described in more detail below. In addition, our research program focuses on the identification and characterization of new members of the sterol hormone metabolome that may result in future pharmaceutical candidates or nutraceutical products.

### ***Apoptone (HE3235)***

#### **Prostate Cancer**

Apoptone is a second-generation compound that we selected for clinical development in the area of hormone-associated cancers, such as prostate cancer. Approximately 234,000 patients are diagnosed with prostate cancer each year and global sales for leading prostate cancer drugs range approximately from \$500 million to \$1 billion annually. Apoptone was discovered by screening our proprietary chemical library against the LNCaP prostate cancer cell line. Its selection was based on a combination of its activity against tumor cells and desirable pharmaceutical properties. Apoptone has been tested in a number of preclinical cancer models and has shown indications of activity in controlling the incidence, growth and development of new tumors in these models. We believe that Apoptone is a disease-modifying agent that may directly induce apoptosis, or cell death, in tumor cells and differs from traditional hormone blockade therapies that interrupt the tumor cell growth signaling through direct androgen or estrogen receptor-mediated mechanisms. While hormone-blockade therapy can effectively control prostate cancer for a period of time, it often fails and the cancer growth resumes by spreading to other organs: usually the bone.

In 2008, we initiated a Phase I/IIa clinical trial with Apoptone in late-stage castrate resistant prostate cancer ( CRPC ) patients who have failed hormone therapy and at least one cycle of cytotoxic chemotherapy. In December 2009, the trial was amended to include a group of CRPC patients with progressive disease that have not been previously treated with chemotherapy. The open-label dose ranging clinical trial was conducted in various clinical sites including some within the Prostate Cancer Clinical Trial Consortium ( PCCTC ). The clinical trial is complete. Safety, tolerance, pharmacokinetics and potential activity of Apoptone was evaluated when the drug was administered twice daily in late-stage prostate cancer patients. The potential activity of the drug was measured by its effect on time to disease progression, as determined by prostate-specific antigen ( PSA ) blood tests, computerized tomography ( CT ), magnetic resonance imaging ( MRI ), or bone scintigraphy, and its effect on circulating tumor cells ( CTC ). Biological activity was found at the lowest dose studied (10 mg) and no dose-limiting toxicity was observed during a 70-fold dose-ranging study with the exception that at the highest dose tested (700 mg) a patient's concomitant medication produced a drug-drug interaction that presented safety concerns with the use of yet higher doses. Apoptone is now staged for Phase IIb clinical trials.

#### **Breast Cancer**

We are also exploring the potential for Apoptone to treat breast cancer. In the MNU-induced pre-clinical models of breast cancer, Apoptone successfully treated established tumors and prevented the formation of new tumors. It appeared to be synergistic when given in combination with concurrent taxane chemotherapy. A report on the pre-clinical activity in breast cancer recently published in the peer-reviewed scientific literature.



## Apoptone Development Status

Apoptone is manufactured starting from androsterone. The active pharmaceutical ingredient is formulated to an oral dosage form using standard excipients approved for oral dosage products. Non-clinical toxicology studies have been done that enable the use of Apoptone in clinical studies in late-stage prostate cancer and breast cancer patients using 28-day cycles of therapy. Encouraging data were first reported from the Phase I/IIa clinical trial in castration resistant prostate cancer – also referred to as hormone resistant prostate cancer – at the ASCO Genitourinary Cancers Symposium in San Francisco, March 6, 2010. Preliminary results from the study, conducted in part with participating member sites of the PCCTC, were first reported on November 16, 2009. The phase I/IIa trial was an open-label study with the primary objectives of assessing safety, tolerability, pharmacokinetics and activity of Apoptone in men with CRPC having an ECOG performance status score of less than or equal to 2 (ambulatory and capable of at least self-care). Patient cohorts are defined by oral daily doses of 10 mg, 20 mg, 30 mg, 50 mg, 100 mg, 200 mg, 350 mg and 700 mg. Subjects were treated until toxicity or disease progression, as assessed by CT and bone scans obtained every two cycles. Based on encouraging signs of activity, the PCCTC recommended an extension of the current trial into CRPC patients that had not been treated with cytotoxic chemotherapy. Accordingly, the subject eligibility criteria were amended to include earlier-stage, chemotherapy-naïve patients in 100 mg and 350 mg expansion cohorts. The clinical trial is now complete.

There were 68 patients enrolled in the trial on an intent-to-treat basis. There were 42 taxane-resistant prostate cancer patients entered into the clinical trial at 7 dose levels. Of these 28 (67%) reached their first reassessment (two 28-day cycles), 15 (58%) of these had stable disease on scans or imaging and have received up to 9 additional treatment cycles before disease progression. The Kaplan-Meier estimate for the median time to progression is 15.9 weeks (range 8-24) for this trial. Due to early signs of activity, the 20 mg dose group was expanded to include 14 taxane resistant patients. Eleven of these were evaluable with an actual median time to progression of 19.7 weeks (range 8-24).

In order to gain information on the healthier pre-chemotherapy patients and the tolerability of Apoptone at higher dose levels, twenty six chemotherapy naïve patients were enrolled to the protocol. The 100 mg and 350 mg dose groups were each expanded with 11 additional pre-chemotherapy patients and 4 were enrolled into the 700 mg group. Twenty two of the 26 chemotherapy naïve patients (85%) completed more than one 28-day treatment cycle. These patients all had a re-assessment at the completion of the second cycle. Sixteen (73%) had stable disease and received up to 12 additional cycles of therapy and 6 (27%) had progressive disease. The Kaplan-Meier estimate for the median time to progression (TTP) in the chemotherapy naïve cohort is > 24 weeks. In the individual 100 and 350 mg dose expansion cohorts, 10 of the 11 patients in each arm completed 2 or more 28-day treatment cycles. The Kaplan-Meier estimate for the median time to progression for the 10 patients that completed 2 or more cycles in each cohort was 24 weeks in the 100 mg cohort; (21, > 24) and 24 weeks (16, 35) in the 350 mg cohort. One patient in the 350 mg group achieved a sustained partial clinical response (100% decrease) of limited nodal (11 mm) disease. The non-target lesions were stable. The response was observed on the first re-evaluation and continued through study closure (8 completed treatment cycles).

Circulating tumor cells (CTC) were evaluated in fifty patients at baseline. Twenty nine (29) patients had < 5 cells per 7.5 mL ( favorable ) and 21 with  $\geq 5$  cells ( unfavorable ). After Apoptone treatment, 25 (86%) of those with favorable counts maintained those levels at 4 weeks, and 7 (33%) of those with  $\geq 5$  cells had a decrease to < 5 cells at 4 weeks. Twenty eight patients had CTC enumeration performed at 12 weeks. Of these 16 (84%) maintained < 5 cells and 6 (66%) patients with baseline CTC  $\geq 5$  cells converted to < 5 cells. These results indicate that the majority of patients either maintained a stable disease state or improved in disease status through the 12 week evaluation period. Although the number of patients is small, CTC count declines from  $\geq 5$  to < 5 have been previously associated with improved overall survival.

Changes in PSA levels were consistent with the properties of a tumor-differentiating agent. PSA declines were anticipated to be rare based on data from *in vitro* and pre-clinical studies, which demonstrated PSA expression generally increased concurrent with tumor growth suppression. In this study, Apoptone rarely induced PSA declines, with less than 10% of patients having a greater than 50% decline in PSA at some time during the course of their treatment. Therefore, PSA is not an appropriate surrogate marker for the evaluation of disease status in Apoptone treated patients.

In summary, Apoptone was well-tolerated and no overt dose-limiting toxicities were reported. The Kaplan-Meier estimate for the median time to progression is 15.9 weeks (range 8-24) for this trial. The Kaplan-Meier estimate for the median time to progression in the chemotherapy naïve cohort is > 24 weeks. The eleven evaluable taxane chemotherapy-resistant patients had a median time to progression of 19.7 weeks (range 8-24). There was one sustained partial response observed, and by CTC evaluation, a majority of the patients either maintained a stable disease state or improved in disease status through the 12 week evaluation period. The mechanism of action has been partially elucidated with biochemical molecular points of interaction identified.

Apoptone is a molecular entity that represents a new therapeutic approach for the treatment of hormone-associated cancers and is expected to have a more favorable side effect profile than found with presently approved treatments. Several patents have been obtained for pharmaceutical formulations of Apoptone and its use for the treatment of prostate cancer, breast cancer and benign prostate hypertrophy.

### **Competition**

Two forms of taxane chemotherapy are presently approved to treat castrate-resistant prostate cancer. Despite these and other current treatments, there is an ongoing need for novel oral agents that can control prostate cancer progression after conventional therapies or hormone treatments fail. Recently, PROVENGE®, produced by Dendreon, Inc., an autologous immune cell therapy that primes the patient's cells against prostate cancer, was approved. Many forms of prostate cancer are dependent on androgen receptor signaling and are responsive to low levels of androgens that remain after hormone ablation therapy. Abiraterone® produced by Cougar Biotechnology, Inc. (acquired by Johnson & Johnson), also a recently approved agent, impedes the synthesis of androgens by inhibition of an enzyme that transforms a precursor molecule into androgenic and estrogenic hormones. MDV-3100, produced by Medivation, Inc., is in clinical development and is an agent that strongly inhibits the action of androgens by interfering with the androgen receptor thereby inhibiting tumor growth. In addition, there are a number of companies with drug candidates in Phase III clinical trials that are targeting the late-stage castration-resistant prostate cancer patient.

Apoptone is believed to be a disease-modification agent with a novel mechanism of action that distinguishes it from competitive drug candidates. Unlike presently approved and in-development therapies, Apoptone is believed to induce apoptosis by forcing catastrophic differentiation of tumor cells using the same signaling pathways these cells have hijacked for proliferation and survival. Thus, emergence of resistance mechanism may be less likely.

### ***Triolex (HE3286)***

### **Inflammatory Processes in Chronic Diseases**

Another primary focus is on diseases that result from chronic inflammatory processes. Properly regulated, inflammation is a protective, life-saving response to invading pathogens. However, chronic and unproductive inflammation (also termed para-inflammation or sterile inflammation) can cause devastating tissue damage and loss of organ function. Chronic inflammation often arises from over-stimulation or dysregulation of the immune system, often resulting in the release of destructive products such as reactive oxygen species and proteolytic enzymes as well as additional pro-inflammatory mediators. The over-production of these dangerous biochemical products may be due to the presence of persistent low-grade infections that promote conditions in which the body's surveillance system is unable to differentiate between itself and invasion of foreign substances or to biochemical dysregulation. Chronic inflammation has been implicated in the pathogenesis of many diseases ranging from autoimmune conditions, such as arthritis and psoriasis, to infectious diseases, including human immunodeficiency virus (HIV), malaria and tuberculosis, lung inflammation conditions, such as asthma, chronic obstructive pulmonary disease and cystic fibrosis, macular degeneration, and neuroinflammatory conditions, such as Parkinson's and Alzheimer's disease, to metabolic diseases, including diabetes and cardiovascular diseases, as well as a number of different cancers.

### **Current Treatments for Chronic Inflammation**

Some of the most widely used drugs for reducing inflammation belong to the corticosteroid class of compounds, which are also derived from the mammalian metabolome. Market research indicates that U.S. physicians issue tens of millions of new prescriptions for corticosteroids each year for a wide range of conditions. While these drugs are highly effective, chronic use leads to immune suppression, bone loss, tissue necrosis, and other serious side effects including mental depression.

Over the last decade, a number of new drugs have been introduced that are focused on inhibiting specific components of the pro-inflammatory cascade, including agents that bind and neutralize specific inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , as well as drugs that inhibit specific enzymes, such as COX-2, that produce pro-inflammatory mediators. While these drugs have demonstrated significant activities in a number of clinical trials involving chronic inflammatory diseases, such as arthritis, inflammatory bowel disease and psoriasis, most have also demonstrated safety limitations. Many cause dangerous immune suppression and other serious side effects that limit their utility. Most focus on a specific inflammatory mediator, which means they may not remain perpetually effective due to redundancies and compensatory effects in biological pathways. Our goal has been to develop compounds that mediate homeostasis to regain control of the inflammatory process and restore homeostasis.

### **Obesity, Chronic Inflammation, Insulin Resistance and Diabetes**

Diabetes is a disease of aberrant insulin signaling that is comprised of a constellation of syndromes. Insulin is a hormone needed to regulate the transport of glucose from the blood into cells, where it can either be stored or converted to the energy needed to perform cellular processes. When insulin is insufficient or when insulin signaling functions improperly, the result is high blood glucose levels, which over time can lead to a host of severe medical conditions including nerve disease, blindness, limb amputation, heart attack, stroke and death. There are two forms of diabetes: type-1: a chronic condition in which little or no insulin is produced, and type-2 diabetes: a condition in which the body becomes resistant to the effects of insulin or the body produces some, but not enough, insulin to maintain a normal blood sugar level.

Epidemiological studies have clearly defined risk factors for the development or progression of type-2 diabetes, including genetics, and prenatal and postnatal environmental factors, including low birth weight, obesity, nutrient excess, inactivity, gestational diabetes, metabolic dysregulation with advancing age and obesity. Obesity in some individuals, through recently elucidated mechanisms, can lead to insulin resistance, hyper-glycemia, beta-cell dysfunction and ultimately overt diabetes. In turn, diabetes-related hyperglycemia and associated metabolic abnormalities can further alter signal transduction and gene-expression; thus contributing to a forward feeding cycle that results in disease progression.

The need for new classes of agents to treat type-2 diabetes is significant. There are over 25 million Americans with type-2 diabetes, 92 million in China and 220 million worldwide. Obese diabetes is a syndrome that is increasing rapidly as a result of advancing age and the rising incidence of obesity. Clinical data indicates only 36% of type-2 diabetics are currently able to maintain the American Diabetes Association maximum recommended HbA1c level of less than 7.0 % (a form of hemoglobin that is primarily used to identify the average plasma glucose concentration over a prolonged period of time). Large clinical studies have shown that failure to achieve these glucose targets, especially in obese patients, can progressively lead to severe health consequences including neuropathy, blindness, amputation, heart attack, stroke and death. Patients in large clinical trials consistently have a median BMI of 32 indicating that over half the population of type-2 diabetics is obese (BMI > 30).

Academic researchers have increasingly linked obesity-induced chronic inflammation with type-2 diabetes and elucidated its potential role in potentiating insulin resistance. In the setting of type-2 diabetes, evidence suggests that the pathology may arise through perturbations in NF $\kappa$ B signaling, particularly *via* the TLR4 and TNF $\alpha$  receptors. TLR4 is a receptor expressed on the surface of macrophages and other cells and is stimulated by dietary fatty acids as well as certain pathogens such as bacteria from the gut flora. Stimulation of the TLR4 receptor induces a cascade of pro-inflammatory signals including the production of TNF $\alpha$ . Elevated TNF $\alpha$  causes activation events that stimulate a complex network of signaling pathways culminating in the activation of NF $\kappa$ B and the expression of a number of genes under its control. Those gene products are involved in mediating inflammation and the cellular stress response. Persistent stimulation can lead to a chronic inflammatory state that produces the associated pathologies typifying the metabolic syndrome condition.

### **Current Treatments for Type-2 Diabetes**

There are several pharmaceutical approaches to treating obese type-2 diabetes. Metformin is usually the first intervention prescribed by physicians when an individual is diagnosed with type-2 diabetes. Often metformin control begins to fail and frequently clinicians will combine additional drugs that assert different metabolic effects in order to control the disease. These include drugs designed to increase insulin production by the pancreas and reduce glucose production by the liver, and drugs, referred to as insulin sensitizers which are designed to increase the body's sensitivity to insulin and thereby improve glucose disposal from the bloodstream.

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## Triolex to Treat Chronic Inflammation in Type-2 Diabetes

Triolex is a next-generation compound that we are developing for the treatment of individuals diagnosed with certain chronic inflammatory processes.

In the setting of obese type-2 diabetes, evidence suggests that the mechanism of action for Triolex may be through regulation of the MAPK and NF $\kappa$ B pathways, particularly when these pathways are stimulated through the TLR4 and TNF $\alpha$  receptors. These pathways are a major component of the type-2 diabetes syndrome that is characterized by the presence of a chronic inflammatory state. Triolex is believed to be the first in a new class of insulin sensitizers to target obesity-mediated dysregulated metabolism through re-regulation of these pathways. Our scientists believe that re-regulation by Triolex of the MAPK and NF $\kappa$ B pathways regains control over genes whose products, which includes TNF $\alpha$  and IL-6, are involved in the inflammatory signaling pathway. These cytokines are also thought to be critically involved in the pathogenesis of other metabolic diseases, such as non-alcoholic steatohepatitis, cardiovascular disorders, neuroinflammatory disease, certain autoimmune diseases, such as ulcerative colitis and rheumatoid arthritis, and are also implicated in the pathogenesis of cancer all of which are, in general, diseases associated with advancing age.

Based on biochemical experiments, Triolex has been shown to act on the NF $\kappa$ B pathway in a manner that is independent of the PPAR $\gamma$  pathway, which is targeted by other insulin sensitizers. Instead, the action of Triolex is associated with down-regulation of the pro-inflammatory JNK, IKK and p38 kinase pathways that cross-over into the NF $\kappa$ B pathway. Chronic activation of these kinase pathways leads to impairment of the insulin receptor substrate-1 protein (IRS-1) function, which is an important cellular mediator of insulin signaling and glucose transport.

A single-dose Phase I clinical trial conducted in healthy volunteers during 2007 demonstrates that Triolex is orally bioavailable in humans and provides significant drug concentrations in the blood at even the lowest dose tested. The findings also demonstrate that all doses of Triolex tested appear to be safe and well-tolerated with no reported drug-related serious adverse side effects.

A Phase I/II double-blind, placebo-controlled, multi-dose ranging clinical trial with Triolex in obese insulin-resistant subjects was initiated in 2007, and the safety, tolerance and pharmacokinetics of Triolex was evaluated when administered for 28 days. The potential for Triolex to decrease insulin resistance was also assessed. In addition, an open-label cohort of six patients with type-2 diabetes mellitus was studied.

Triolex was found to be safe and improved insulin sensitivity in insulin-resistant subjects. There was no trend in adverse events to differentiate between placebo- and treated-subjects, nor was there an increase in adverse events with dose escalation. Baseline and day 29 hyperinsulinemic-euglycemic clamp studies were performed on 36 subjects dosed twice daily. To test the hypothesis that Triolex would improve insulin sensitivity in insulin-resistant subjects, these subjects were stratified by the median baseline M value of 5 (a glucose disposal rate of 5 mg per minute per kg body weight): 21 subjects had M values < 5 (operationally defined as insulin-resistant); and 13 had M values of > 5 (operationally defined as insulin-sensitive). Pretreatment, insulin-resistant subjects had significantly higher fasting insulin levels, HOMA2 %B, HOMA2 IR values and LPS-stimulated PBMC MCP-1, TNF $\alpha$  and IL-6 protein levels, and trended for an increased IL-1 $\beta$  protein level confirming greater insulin resistance, inflammatory responses and beta cell function than insulin-sensitive subjects.

After 29 days of treatment there were significant differences in changes from baseline for M values and C-reactive protein levels between Triolex-treated subjects compared to placebo-treated subjects. To test the hypothesis that Triolex would benefit insulin-resistant but not insulin-sensitive subjects, the day 29 M-value changes from baseline were compared in the Triolex-treated subjects. In the insulin-resistant group, M values increased and in the insulin-sensitive group M values decreased. That difference was highly significant. When compared to placebo, insulin-resistant Triolex-treated subjects also showed significant improvement in M and trended for a decreased C-reactive protein level, whereas insulin-sensitive subjects did not show these changes. We concluded that Triolex was active in obese, insulin-resistant, pre-diabetic subjects but had no effect in insulin-sensitive, pre-diabetic subjects. That outcome is consistent with an insulin-sensitizing drug.

During 2008, a Phase IIa clinical trial was initiated with Triolex seeking early signs of activity in type-2 diabetes patients. The clinical trial proceeded in two stages. Stage 1 was a double-blinded, placebo controlled 12-week dosing trial that was exploratory in nature and enrolled 96 patients who were on a stable dose of metformin

with hemoglobin A1c (HbA1c) level in excess of 7.5 percent. The primary objectives of the study were to evaluate the change in HbA1c from baseline to week 12 and to evaluate the safety and tolerance of Triolex given 10 mg per day (5 mg BID) as compared to placebo. A final analysis for activity (HbA1c) in the clinical study of unaudited data was performed on all subjects that completed day 84 of the study (72 patients). There was no statistical difference between treatment and placebo for HbA1c in the overall patient population. However, a retrospective analysis of unaudited data was performed on the subpopulation of patients that represented the inflamed, obese, insulin-resistant, diabetic subgroup, in accordance with FDA guidance. That group is reflective of the impaired glucose tolerance subjects that responded to treatment in the company's Phase I pre-diabetes study. The analysis included patients divided into two strata with baseline values either less than or greater than (or equal to) the following criteria: BMI at least 27.3; fasting plasma insulin levels at least 3  $\mu\text{U/mL}$ ; and serum monocyte chemoattractant protein-1 (MCP-1) levels at least 400  $\text{pg/mL}$ . This phenotype represented 42% of all subjects (90 patients) with values for these parameters at baseline. Twenty-seven individuals in the high BMI strata completed 84 days of dosing. Those patients treated with Triolex (13) were showed improvements in their clinical parameters compared to the corresponding placebo patients (14). The improvements included significantly decreased HbA1c (-0.53 %,  $p = 0.01$ ) values and fasting plasma glucose (-26.80  $\text{mg/dL}$ ,  $p < 0.02$ ) levels, decreased body weight (-2.0  $\text{kg}$ ,  $p = 0.0005$ ) and significantly increased anhydroglucitol (+0.7  $\mu\text{g/mL}$ ,  $p = 0.03$ ) levels signifying decreased post-prandial glucose excursions. More Triolex subjects decreased weight (12/13 vs. 8/14, Fisher's Exact Test  $p < 0.08$ ) and increased 1,5 anhydroglucitol levels (8/9 vs. 4/10, Fisher's Exact Test  $p < 0.04$ ). The low BMI strata had a significant increase in HbA1c (+0.7%,  $p < 0.005$ ) levels but with no detectable changes in any other parameter. There were significant differences between the high BMI and low BMI patients in their response to Triolex. The strata differed significantly in HbA1c (1.15 %,  $p < 0.002$ ) and glucose (26.8  $\text{mg/dL}$ ,  $p < 0.02$ ) levels, body weight (2.2  $\text{kg}$ ,  $p < 0.0001$ ) and cholesterol (23.5  $\text{mg/dL}$ ,  $p < 0.006$ ) levels. Significant trends were detected for differences in LDL cholesterol (14.8  $\text{mg/dL}$ ,  $p = 0.08$ ), triglycerides (21.8  $\text{mg/dL}$ ,  $p < 0.09$ ) levels and HOMA2 %B (25 %,  $p < 0.06$ ) values. We conclude Triolex demonstrates signs of activity in chronically-inflamed, obese diabetes patients when this drug is taken in combination with metformin.

Stage 2 of the Phase IIa clinical trial was in treatment-naïve diabetic patients (no metformin) with inclusion criteria that restricted the lower limit of BMI to 28, insulin  $\geq 4 \mu\text{U/mL}$ , C-peptide  $\geq 2 \text{ ng/mL}$  and MCP-1  $\geq 400 \text{ pg/mL}$ . There was no significant overall treatment effect on day 84 HbA1c in Cohort 2 treatment-naïve subjects, despite restrictive inclusion criteria. Subjects were again stratified by BMI. Higher BMI subjects were defined as BMI  $\geq 31.3 \text{ kg/m}^2$ . At baseline, higher BMI subjects (32 of 69 subjects, 46%) had significantly higher resistin levels and statistical trends for higher CRP, C-peptide, HOMA2 %B, leptin and lower fructosamine levels when compared to the low BMI subjects. High BMI Triolex-treated subjects showed a statistically significant percent decrease in HbA1c levels at day 112 when compared to the corresponding placebo group (-1.1 %,  $p < 0.05$ ). In the placebo group there was a higher proportion of subjects with decreased HbA1c levels (8/9 vs. 6/13, Fisher's Exact Test  $p < 0.08$ ), and a higher portion with  $> 1\%$  decrease (5/9 vs. 2/13, Fisher's Exact Test  $p < 0.08$ ). The Triolex-treated subjects had a significantly greater frequency in decreased CRP levels (8/9 vs. 5/14, Fisher's Exact Test  $p < 0.03$ ), and a statistical trend for a day 84 decrease (-1.1  $\text{mg/L}$ , Fisher's Exact Test  $p = 0.08$ ). Post prandial glucose excursions were decreased as evidenced by the greater frequency of subjects with increased day 84 1,5-anhydroglucitol (median, + 1.4  $\mu\text{g/mL}$ ; 7/8 vs. 6/14 placebos, Fisher's Exact Test  $p < 0.03$ ). In contrast, low BMI patients (28  $\text{kg/m}^2$  - 31.3  $\text{kg/m}^2$ ) treated with Triolex had a significantly higher day 84 HbA1c percent change ( $p < 0.005$ ) from baseline (+0.18 %) when compared to the placebo group (-0.93 %) due to a large placebo effect in these patients. There was also a statistical trend for decreased day 84 fructosamine levels (-11.75  $\mu\text{mol}$ ,  $p < 0.08$ ) in the placebo but with an absence of a significant difference in day 84 fasting plasma glucose levels. We conclude Triolex demonstrates signs of activity in treatment naïve, chronically inflamed obese diabetes patients.

Triolex shows no consistent pattern of adverse events associated with its use. Actos and Avandia are two widely prescribed insulin sensitizers used in combination with metformin. Recently, Avandia was withdrawn after concerns were raised about an increased risk of cardiac events. The Actos cardiovascular safety profile compares favorably with Avandia and remains on the market with a black-box warning. Subsequently, it was found to be associated with bladder tumors and in some countries has also been withdrawn from the market. The side effects associated with the use of currently approved insulin sensitizers have not been observed with Triolex.

In summary, the Triolex studies have demonstrated a good safety profile for the drug with no consistent pattern of adverse events associated with its use. It is active in obese insulin-resistant, pre-diabetic subjects but has not demonstrated an effect in insulin-sensitive, pre-diabetic subjects, which is an outcome consistent with an insulin-sensitizing drug. We conclude Triolex demonstrates signs of activity in chronically inflamed obese diabetic patients as a single agent and in combination with metformin. The mechanism of action has been partially elucidated with biochemical molecular points of interaction identified.

## **Competition in Diabetes**

Given the large market opportunities for products that treat the indications for which we are currently developing our compounds, most major pharmaceutical companies and many biotechnology companies have programs directed toward finding drugs to treat the indications that we are exploring. In metabolism and type-2 diabetes, there are a number of drugs, such as Actos from Takeda Pharmaceuticals (already approved for improving insulin sensitivity), glucagon-like peptide-1 (such as Victoza<sup>®</sup> by Novo Nordisk), dipeptidyl peptidase-4 inhibitors (such as Januvia<sup>®</sup> by Merck & Co., Inc. and Onglyza<sup>®</sup> by Bristol Myers Squibb) and numerous other drugs in various stages of development. While Actos currently accounts for a significant share of the market for insulin sensitizers to treat type-2 diabetes, it is known to cause the unwanted side effects of weight gain and edema and was recently either removed from the market, as was the case for Avandia, or given a black-box warning (Actos) by the FDA because of increased treatment-related heart failure and bladder cancer risk associated with the use of the medication.

## **Autoimmune Disease and Chronic Inflammation**

### **Current Treatments for Autoimmune Diseases**

Immune modulators that correct immune dysregulation and chronic inflammatory conditions by inhibition or enhancement of single cytokine targets such as TNF $\alpha$  and IL-1 $\beta$  or their receptors have been developed by a number of companies. For example, Amgen's Enbrel targets TNF $\alpha$  as does Johnson & Johnson's Remicade. Other immune-modulating drugs such as Celebrex<sup>®</sup> from Pfizer target COX-2. While these targeted approaches have shown clinical benefit and have generated significant sales volumes, redundancy in the immune system can limit their effectiveness. In addition, side effects, health care costs and reimbursement issues are limiting their long-term global utility. We have shown our compounds affect cytokine cascades through direct interactions in the endocrine system. That may potentially make them more attractive drug candidates than those currently available as they directly interact through the endocrine system. Triolex may represent the first in a new class of agents to treat those diseases, assuming it is successfully developed and commercialized.

### **Rheumatoid Arthritis**

Rheumatoid arthritis is a type of chronic arthritis that occurs in joints on the extremities of the body (such as hands, wrists or knees). In rheumatoid arthritis, the immune system attacks the joints and sometimes other organs. According to the Centers for Disease Control and Prevention, or (CDCP), an estimated 50 million people were treated for some form of arthritis and other rheumatic conditions in 2009, 22% of the US adult population.

Based upon positive results with Triolex in published rodent models of collagen-induced and collagen antibody-induced arthritis, a Phase I clinical trial was initiated in rheumatoid arthritis patients in 2008. A 28-day oral dose-ranging study assessed the safety, pharmacokinetics and potential for drug-drug interactions in stable rheumatoid arthritis patients also receiving methotrexate. Triolex was found to be safe and well-tolerated. No drug-drug interaction with methotrexate was found. Triolex is now positioned to enter clinical studies in patients with active rheumatoid arthritis.

### **Ulcerative Colitis and Other Autoimmune Diseases**

Inflammatory bowel disease is comprised of ulcerative colitis, a chronic inflammation of the large intestine, or colon, and Crohn's disease, a condition of inflammation of the small intestines. Ulcerative colitis and Crohn's disease together affect approximately 500,000 to 2 million people in the United States.

Based upon published observations with Triolex in preclinical models widely used by both the pharmaceutical industry and academia to test agents as potential treatments for ulcerative colitis, we commenced a Phase I/II clinical trial in ulcerative colitis patients in 2008. This Phase I/II dose ranging study evaluated the safety, tolerance, pharmacokinetics and activity of Triolex when administered orally for 28 days to patients with active, mild-to-moderate ulcerative colitis. Triolex at the doses studied was found to be safe and well-tolerated but interpretation of the results was confounded by the high frequency of spontaneous colitis flare resolution. There was no indication of a treatment advantage in this acute inflammatory setting when compared to placebo. Triolex is staged for long-term clinical trials directed towards the control of the chronic inflammatory processes associated with this disease, a clinical setting believed to be consistent with the pharmacological properties of the compound.

Triolex has also shown activity in pre-clinical models of multiple sclerosis and lupus erythematosus, which represent additional candidate indications for clinical trials.

### **Neuroinflammation**

Neuroinflammation plays a major role in the pathophysiology of many of the most socially and economically significant diseases of first world nations. These diseases include Alzheimer's disease, Parkinson's disease, epilepsy, amyotrophic lateral sclerosis (ALS), autism, and multiple sclerosis. Recent scientific publications suggest these diseases share a common inflammatory mediator, the ubiquitous intranuclear protein, high mobility group box 1 protein (HMGB1), which is released to the extracellular environment from necrotic cells. HMGB1 acts through at least one pathway known to be regulated by Triolex. Because Triolex readily penetrates the blood-brain-barrier, it has the potential to treat a broad spectrum of diseases with a neuroinflammatory etiology. The Company is investigating the use of Triolex as a treatment for Parkinson's disease with funding from The Michael J. Fox Foundation. The terms of the collaboration call for MJFF to fund up to approximately \$150,000 toward pre-clinical development of Triolex in rodents. Our work with MJFF has shown that in a rodent model of MPTP induced neuronal excitotoxicity (a model that closely mimics Parkinson's disease in humans), Triolex significantly reduced motor impairment and production of inflammatory cytokines, which was associated with significantly greater numbers of surviving neurons in the brains of Triolex treated animals. Further funding of preclinical and clinical development is pending a decision by The MJFF. Similarities between the molecular pathophysiology of Parkinson's disease and epilepsy suggest that Triolex may also be active against epilepsy, which affects approximately 5 million people in the U.S. and Europe and 10 million in China, one-third of which are refractory to currently approved anti-seizure drugs. The company intends to initiate Triolex product development activities for neuroinflammation through corporate partners or investment financing.

### **Ophthalmology**

Diseases of the eye are common and frequently have an inflammatory etiology. The associated temporary or permanent loss of vision is socially and economically important. The most common treatments for ocular inflammation are glucocorticoids and cyclosporins, which are associated with serious side effects that include glaucoma, cataract, and increased susceptibility to infection. The development of ophthalmic pharmaceuticals is increasingly popular because cost of clinical trials and product approval for certain ocular conditions can be substantially less than most systemic indications because of the acute nature of many ocular diseases, and the limited systemic drug exposure from topical administration. Inflammatory ocular diseases should be amenable to Triolex treatment based on Triolex's mechanism of action and disease molecular pathophysiology. Importantly, Triolex's mechanism of action cannot cause any of the deleterious side effects of currently approved medications. The results of recent preclinical studies of Triolex in rodent models of uveitis indicate potent anti-inflammatory activity. The Company intends to continue investigating the potential breadth of this opportunity, and to initiate ophthalmic product development through corporate partners or investment financing. Ocular conditions of interest include anterior and posterior uveitis, idiopathic dry eye, Sjogren's dry eye disease (an autoimmune condition related SLE), conjunctivitis, blepharitis, and post surgical inflammation.

### **Pulmonary Diseases and other Autoimmune Diseases**

Triolex has shown signs of activity in pre-clinical models of lung inflammation. Accordingly, the Company is exploring the potential for Triolex in a variety of pulmonary diseases with academic collaborators. These conditions include cystic fibrosis, chronic pulmonary disease and asthma.

### **Triolex Development Status**

Triolex is manufactured economically using a multi-step organic synthesis from the widely abundant and inexpensive starting material, DHEA. It is formulated for oral administration with excipients approved for oral dosage products. Diseases associated with chronic inflammation are thought to require drug exposures of extended duration to observe definitive treatment effects. Long term toxicology studies have been completed that qualify Triolex for use in clinical studies of 6 month's duration or longer. There were no untoward side effects detected. Allowed and issued patents claim the compound itself, pharmaceutical formulations and methods of use to treat a variety of inflammatory diseases including type-2 diabetes and autoimmune conditions such as rheumatoid arthritis and ulcerative colitis in the United States, Europe and elsewhere. Applications with pending claims filed to extend patent coverage in additional regions of economic interest including China, Japan and Korea.

### **NEUMUNE (HE2100)**

#### **Neumune as treatment for acute radiation exposure; an ERβ selective agonist.**

In December 2010, The Company reported on the safety, tolerability and signs of hematologic activity in four double-blinded, randomized, placebo-controlled studies of NEUMUNE in healthy human subjects, published in *The Journal of Radiological Protection*. Those studies demonstrated that Neumune has the potential to directly enhance innate immunity in humans and defined the compound as a highly selective ERβ ligand. ERβ ligand treatment has been suggested as a potentially safe anti-inflammatory and neuroprotective strategy in multiple sclerosis and other neurodegenerative diseases. In May of 2010, the Company reported that Neumune could ameliorate neuroinflammation in mice and has the potential to limit relapses in patients with multiple sclerosis. The Company is actively soliciting partnerships to develop an orally bioavailable, metabolically stable second generation derivative.

### **HE2000**

#### **HE2000 in Infectious Disease**

The Company conducted clinical trials in HIV, AIDS and malaria from the late 1990 s until early 2002. While the primary market opportunities for pharmaceuticals have traditionally been in the U.S., Europe and Japan, our adrenal hormones have a number of attributes that make them potentially globally useful. Included are the potential broad-spectrum activity in multiple infectious diseases, an attractive safety profile to date, a low likelihood of resistance and the relative ease of manufacture. Increasing focus on the infectious disease crises around the world such as those represented by HIV, malaria and tuberculosis has led to a number of recent third party initiatives designed to provide funding for effective approaches to these diseases.

HE2000 has been tested in a series of Phase I/II and Phase II clinical trials in HIV/AIDS patients in the U.S. and South Africa. In all of these studies, HE2000 treatment appeared to be generally well-tolerated with mild to moderate pain at the injection site as the most common adverse event. In addition to assessing the safety profile of HE2000 in clinical trials, we have also assessed the effect of HE2000 on a wide variety of immune and inflammatory markers that are associated with HIV disease progression.

In a South Africa study, HE2000 treatment of HIV patients that received no other therapy resulted in long-lasting, statistically significant declines in a number of key inflammatory mediators including TNFα, IL-1β and IL-6. In this placebo-controlled study, we also observed significant durable increases in a wide variety of immune cell subsets associated with innate and cell-mediated immunity following treatment with HE2000. In addition, patients that received HE2000 in this trial experienced a significant decline in blood virus levels over the course of the study, which correlated with an increase in HIV specific T-cell mediated immunity. HE2000 was then tested as a monotherapy in late-stage AIDS patients. During this study, patients experienced a statistically significant reduction in the number of opportunistic infections compared to those treated with placebo and the life-threatening tuberculosis infections were completely quelled after 4-months of treatment.

The ability of HE2000 to reduce pro-inflammatory mediators while stimulating innate and cell-mediated immunity has potential implications for the treatment of a number of other infectious diseases, including parasitic infections such as malaria. Based on multiple pre-clinical studies performed by collaborators at the Walter Reid Naval Hospital and the University of Vermont, we performed two Phase II clinical studies in malaria patients at Mahidol University in Bangkok, Thailand. Results indicated that HE2000 was effective in reducing malarial parasite count and cleared blood-borne malarial parasites in most patients within seven days.

A series of tuberculosis animal model studies have also shown that HE2000 is effective when given as a monotherapy in either the acute or chronic phase of this bacterial infection and it appears to have a synergistic effect when combined with the current three-drug regimen considered the standard of care for antibiotic treatment of tuberculosis.



## Government Regulation

### General

The manufacturing and marketing of our proposed drug candidates and our research and development activities are, and will continue to be, subject to regulation by federal, state and local governmental authorities in the U.S. and other countries. In the U.S., pharmaceuticals are subject to rigorous regulation by the Food and Drug Administration, ( FDA ), which reviews and approves the marketing of drugs. The Federal Food, Drug and Cosmetic Act, the regulations promulgated thereunder, and other federal and state statutes and regulations govern, among other things, the testing, manufacturing, labeling, storage, record keeping, advertising and promotion of our potential products.

### Approval Process

*The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ( ICH )*. Since its inception in 1990, ICH has evolved, through its ICH Global Cooperation Group, to respond to the increasingly global face of drug development, so that the benefits of international harmonization for better global health can be realized. Harmonization ensures that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner worldwide. Specifically, China has been steadily improving its regulatory regime governing food and pharmaceutical industries in recent years, aligning the country with international standards of practice. Regional Harmonization Initiatives ( RHI ) include Asia-Pacific Economic Cooperation ( APEC ), Association of Southeast Asian Nations ( ASEAN ), Gulf Cooperation Council ( GCC ), Pan American Network on Drug Regulatory Harmonization ( PANDRH ) and the Southern African Development Community ( SADC ). Development in each of these regions may or may not require bridge studies, depending on the genetic diversity within each population, but in any event, costs for such studies would be borne by each regional partner.

The process of obtaining FDA approval for a new drug may take many years and generally involves the expenditure of substantial resources. The steps required before a new drug can be produced and marketed for human use include clinical trials and the approval of a New Drug Application.

*Preclinical Testing:* In the preclinical phase of development, the promising compound is subjected to extensive laboratory and animal testing to determine if the compound is biologically active and safe.

*Investigational New Drug or IND:* Before human tests can start, the drug sponsor must file an IND application with the FDA, showing how the drug is made and the results of animal testing. An IND becomes effective 30 days following receipt by the FDA.

*Human Clinical Testing:* The human clinical testing program usually involves three phases which generally are conducted sequentially, but which, particularly in the case of anti-cancer and other life-saving drugs, may overlap or be combined. Clinical trials are conducted in accordance with protocols that detail the objectives of the study, the parameters to be used to monitor safety and the efficacy criteria to be evaluated. Each protocol is submitted to the FDA as part of the IND filing. Each clinical study is conducted under the auspices of an independent Institutional Review Board, or IRB, for each institution at which the study will be conducted. The IRB will consider, among other things, the design of the clinical trial, ethical factors, the risk to human subjects and the potential benefits of therapy relative to the risk.

*Phase I clinical trials:* Studies usually are conducted on healthy volunteers or, in the case of certain terminal illnesses such as AIDS or cancer patients with disease that have failed to respond to other treatment, to determine the maximum tolerated dose, side effects and pharmacokinetics of a product.

*Phase II clinical studies:* These are conducted on a small number of patients having a specific disease to determine initial efficacy in humans for that specific disease, the most effective doses and schedules of administration, and possible adverse effects and safety risks. Phase II/III differs from Phase II in that the trials involved may include more patients and, at the sole discretion of the FDA, be considered the pivotal trials, or trials that will form the basis for FDA approval.

*Phase III clinical studies:* These are normally the pivotal drug trials consisting of broad scope of studies on diseased patients, in order to evaluate the overall benefits and risks of the drug for the treated disease compared with other available therapies. The FDA continually reviews the clinical trial plans and results and may suggest design changes or may discontinue the trials at any time if significant safety or other issues arise.

*New Drug Application or NDA:* Upon successful completion of Phase III clinical trials, the drug sponsor files an NDA with the FDA for approval containing details of the chemistry, manufacture and quality control information that has been developed, nonclinical data, results of human tests, and proposed labeling.

*Post Approval.* If the FDA approves an NDA, the drug sponsor is required to submit reports periodically to the FDA containing adverse reactions, production, and quality control and distribution records. The FDA may also require post-marketing testing to support the conclusion of efficacy and safety of the product, which can involve significant expense. After FDA approval is obtained for initial indications, further clinical trials may be necessary to gain approval for the use of the product for additional indications.

The testing and approval process is likely to require substantial time, from several months to years, and there can be no assurance that any FDA approval will be granted on a timely basis, if at all. The approval process is affected by a number of factors, primarily the side effects of the drug (safety) and its therapeutic benefits (efficacy). Additional preclinical or clinical trials may be required during the FDA review period and may delay marketing approval. The FDA may also deny an NDA if applicable regulatory criteria are not met.

Outside the U.S., we will be subject to foreign regulatory requirements governing human clinical trials and marketing approval for our products. The requirements governing human clinical trials ex-US usually follow International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ( ICH ) Good Clinical Practices ( GCP ) or country-specific GCPs which are based on the ICH GCPs. Regulatory approval outside the U.S. typically includes the risks and costs associated with obtaining FDA approval but may also include additional risks and costs.

## **Manufacturing**

We do not have plans to establish manufacturing facilities to produce our drug candidates or any future products. We plan to control our capital expenditures by using contract manufacturers to make our products. We believe that there are a sufficient number of high-quality FDA-approved contract manufacturers available, and we have had discussions, and in some cases established relationships, to fulfill our near-term production needs for both clinical and commercial applications.

The manufacture of our drug candidates or any future products will be subject to rigorous regulations, including the need to comply with the FDA's current Good Manufacturing Practice regulations. As part of obtaining FDA approval for each product, each of the manufacturing facilities must be inspected, approved by and registered with the FDA. In addition to obtaining FDA approval of the prospective manufacturer's manufacturing and quality control procedures, domestic and foreign manufacturing facilities are subject to periodic inspection by the FDA and/or foreign regulatory authorities.

## **Patents**

We currently own or have obtained licenses to a large estate of U.S. and foreign patents and patent applications. We consider the protection of our technology, whether owned or licensed, to the exclusion of use by others, to be vital to our business. While we intend to focus primarily on patented or patentable technology, we may also rely on trade secrets, unpatented property, know-how, regulatory exclusivity, patent extensions and continuing technological innovation to develop our competitive position. In the U.S. and certain foreign countries, the exclusivity period provided by patents covering pharmaceutical products may be extended by a portion of the time required to obtain regulatory approval for a product.

In certain countries, some pharmaceutical-related technology such as disease treatment methods are not patentable or only recently have become patentable and enforcement of intellectual property rights in many countries has been limited or non-existent. Future enforcement of patents and proprietary rights in many countries can be expected to be problematic or unpredictable. We cannot guarantee that any patents issued or licensed to us will provide us with competitive advantages or will not be challenged by others. Furthermore, we cannot be certain that others will not independently develop similar products or will not design around patents issued or licensed to us.

In most cases, patent applications in the U.S. are maintained in secrecy until 18 months after the earliest filing or priority date. Publication of discoveries in the scientific or patent literature, if made, tends to lag behind actual discoveries by at least several months. U.S. patent applicants can elect to prevent publication until the application issues by agreeing not to file the application outside the U.S. This option is rarely used for pharmaceutical patent applications. Consequently, we cannot be certain that a patent owner or licensor of its intellectual property was the first to invent the technology or compounds covered by pending patent applications or issued patents or that it was the first to file patent applications for such inventions. In addition, the patent positions of biotechnology and pharmaceutical companies, including our own, are generally uncertain, partly because they involve complex legal and factual questions.

In addition to the considerations discussed above, companies that obtain patents claiming products, uses or processes that are necessary for, or useful to, the development of our drug candidates or future products could bring legal actions against us claiming infringement. Patent litigation is typically costly and time consuming, and if such an action were brought against us, it could result in significant cost and diversion of our attention. We may be required to obtain licenses to other patents or proprietary rights, and we cannot guarantee that licenses would be made available on terms acceptable to us. If we do not obtain such licenses, we could encounter delays in product market introductions while we attempt to develop or license technology designed around such patents, or we could find that the development, manufacture or sale of products requiring such licenses is foreclosed.

Further, we cannot guarantee that patents that are issued will not be challenged, invalidated or infringed upon or designed around by others, or that the claims contained in such patents will not interfere with the patent claims of others, or provide us with significant protection against competitive products, or otherwise be commercially valuable. To the extent that we are unable to obtain patent protection for our products or technology, our business may be materially adversely affected by competitors who develop substantially equivalent technology.