Advaxis, Inc.
Form S-3
February 18, 2014

As filed with the Securities and Exchange Commission on February 18, 2014

Registration No. 333-

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-3

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

ADVAXIS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**02-0563870**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

305 College Road East
Princeton, New Jersey 08540
(609) 452-9813

(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant's Principal Executive Offices)

Mr. Daniel J. O'Connor
Chief Executive Officer
305 College Road East
Princeton, New Jersey 08540
(609) 452-9813

(Name, Address, Including Zip Code, and Telephone Number, Including Area Code, of Agent For Service)

The Commission is requested to send copies of all communications to:

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Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this registration statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. ¨

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest

reinvestment plans, check the following box. x

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨ _____

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨ _____

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box. ¨

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box. ¨

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 definition of “large accelerated filer,” “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Exchange Act.

Large accelerated filer ¨	Accelerated filer ¨
Non-accelerated filer ¨ (Do not check if smaller reporting company)	Smaller reporting company x

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered[1]	Amount to be registered	Proposed maximum aggregate offering price per unit	Proposed maximum aggregate offering price	**Amount of registration fee**[3]
Common Stock, $0.001 par value per share	N/A	[2] N/A	[2] $ 50,000,000	$ 6,440

(1) Such indeterminate number of shares of Common Stock of Advaxis, Inc. as may from time to time be issued at indeterminate prices. Pursuant to Rule 416 under the Securities Act of 1933, as amended, such number of shares of Common Stock registered hereby shall include an indeterminate number of shares of Common Stock that may be issued in connection with a stock split, stock dividend, recapitalization or similar event.

(2) Omitted pursuant to General Instruction II.D of Form S-3 under the Securities Act of 1933, as amended.

(3) The registration fee has been calculated in accordance with Rule 457(o) under the Securities Act of 1933, as amended.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the registration statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion—Dated February 18, 2014

PROSPECTUS

$50,000,000

Common Stock

We may offer and sell an indeterminate number of shares of our common stock from time to time under this prospectus. You should read this prospectus and any prospectus supplement carefully before you invest.

This prospectus provides a general description of the securities we may offer. Each time we sell securities, we will provide specific terms of the securities offered in a supplement to this prospectus. The prospectus supplement may also add, update or change information contained in this prospectus. You should carefully read this prospectus and the applicable prospectus supplement carefully before you invest in any securities. This prospectus may not be used to consummate a sale of securities unless accompanied by the applicable prospectus supplement.

Our common stock is traded on the NASDAQ Capital Market, under the symbol ADXS. On February 13, 2014, the last reported sale price for our common stock on the NASDAQ Capital Market was $5.29 per share.

As of February 13, 2014, the aggregate market value of the voting and non-voting common equity held by non-affiliates, computed by reference to the price at which the common equity was last sold or the average bid and

asked price of such common equity on that date, was approximately $70,386,676, based on 13,903,885 shares of outstanding common stock, of which 13,305,610 were held by non-affiliates. Pursuant to General Instruction I.B.6 of Form S-3, in no event will we sell securities in a public primary offering with a value exceeding more than one-third of our public float in any 12-month period so long as our public float remains below $75.0 million. We have not offered any securities pursuant to General Instruction I.B.6 of Form S-3 during the 12 calendar months prior to and including the date of this prospectus.

INVESTING IN OUR SECURITIES INVOLVES RISKS. YOU SHOULD REVIEW CAREFULLY THE RISKS AND UNCERTAINTIES DESCRIBED UNDER THE HEADING "RISK FACTORS" ON PAGE 4 AND CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT AND UNDER SIMILAR HEADINGS IN THE OTHER DOCUMENTS THAT ARE INCORPORATED BY REFERENCE INTO THIS PROSPECTUS.

We may offer our common stock in one or more offerings in amounts, at prices, and on terms determined at the time of the offering. We may sell our common stock through agents we select or through underwriters and dealers we select. If we use agents, underwriters or dealers, we will name them and describe their compensation in a prospectus supplement.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR DETERMINED IF THIS PROSPECTUS IS TRUTHFUL OR COMPLETE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

The date of this prospectus is , 2014.

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ABOUT THIS PROSPECTUS

This prospectus is a part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a “shelf” registration process. Under this shelf process, we may sell the securities described in this prospectus in one or more offerings. This prospectus provides you with a general description of the securities we may offer. Each time we sell securities under this shelf registration, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus or in any documents that we have incorporated by reference into this prospectus. You should read this prospectus and any applicable prospectus supplement, together with the information incorporated herein by reference as described under the heading “Where You Can Find More Information.”

You should rely only on the information that we have provided or incorporated by reference in this prospectus and any applicable prospectus supplement. We have not authorized any dealer, salesman or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus or any applicable prospectus supplement. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus or the accompanying prospectus supplement. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you.

This prospectus and the accompanying supplement to this prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and the accompanying supplement to this prospectus constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus or any applicable

prospectus supplement is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus or any applicable prospectus supplement is delivered or securities sold on a later date.

(i)

SUMMARY

Prospectus Summary

This summary highlights selected information from this prospectus and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, including the risks of investing discussed under “Risk Factors” on page 4, the information incorporated by reference, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part. Unless otherwise stated or the context requires otherwise, references in this prospectus to “Advaxis,” “we,” “us,” or “our” refer to Advaxis, Inc.

Our Company

Business Overview

We are a clinical development stage biotechnology company focused on the discovery, development and commercialization of our proprietary Lm-LLO immunotherapy product candidates to treat cancers and infectious diseases. These immunotherapies are based on a platform technology that utilizes live attenuated Listeria monocytogenes, which we refer to as Listeria or Lm, that have been bioengineered to secrete antigen/adjuvant fusion proteins. We believe that these Lm-LLO strains are a significant advancement in immunotherapy as they integrate multiple functions into a single immunotherapy because they access and direct antigen presenting cells, or APC, to stimulate anti-tumor T-cell immunity, stimulate and activate the immune system with the equivalent of multiple adjuvants, and simultaneously reduce tumor protection in the tumor microenvironment to enable the T-cells to eliminate tumors. Other immunotherapies may employ individual elements of our comprehensive approach, but, to our knowledge, none combine all of these elements together in a single, easily administered, well-tolerated yet comprehensive immunotherapy.

The effectiveness of our approach has been validated by numerous publications in multiple models of human disease. In the clinic, ADXS-HPV, our lead Lm- LLO immunotherapy for the treatment of HPV-associated cancers, is well-tolerated and has been administered to both young patients with pre-malignant dysplasia, as well as patients with advanced disease. Clinical efficacy has been demonstrated by apparent prolonged survival, complete and partial tumor responses, and the prolonged stabilization of advanced cancer. The preliminary data from our completed Phase 2 clinical trial of ADXS-HPV in patients with recurrent cervical cancer demonstrate that ADXS-HPV is an active agent in this disease setting with a manageable safety profile. We achieved proof of concept with this Phase 2 study, and over the next two to five years, we plan to advance ADXS-HPV through registrational Phase 3 trials and regulatory approval(s) in the United States and relevant markets for the treatment of women with cervical cancer. We are currently evaluating this same Lm -LLO immunotherapy in Phase 1/2 clinical trials for two other HPV-associated

cancers: head and neck cancer and anal cancer. In addition, we plan to advance ADXS-PSA, our second Lm -LLO immunotherapy, into a Phase 1 dose escalation trial to determine the maximum tolerated dose for the treatment of prostate cancer in the first half of 2014. A third Lm -LLO immunotherapy, ADXS-cHER2, is being evaluated for safety and efficacy in the treatment of companion dogs with HER2 over-expressing osteosarcoma. We plan to advance ADXS-cHER2 into a Phase 1 dose escalation trial to determine the maximum tolerated dose for the treatment of breast cancer.

We have a robust and extensive patent portfolio relating to our core Lm-LLO immunotherapy technology. Our current patent portfolio includes 42 issued patents and 38 pending patent applications. To develop our technology, we may enter into commercial partnerships, joint ventures, or other arrangements with competitive or complementary companies, including pharmaceutical or biotechnology companies or universities during the preclinical or clinical stages. Our current collaborations include the preclinical development of Lm-LLO immunotherapies for a number of indications. We currently have over 15 distinct immunotherapies in various stages of development, developed directly by us and through strategic collaborations with recognized centers of excellence. These include but are not limited to the following Advaxis immunotherapy and corresponding tumor antigen: ADXS11-001/HPV16-E7, ADXS31-142/Prostate Specific Antigen, ADXS31-164/HER2/neu Chimera, Lm-LLO-HMW-MAA/HMW-MAA, C-terminus fragment, Lm-LLO-ISG15/ISG15, Lm-LLO CD105/Endoglin, Lm-LLO-flk/VEGF and Bivalent Therapy, HER-2-Chimera/HMW-MAA-C. We will continue to conduct preclinical research to develop additional Lm-LLO constructs to expand our platform technology and may develop additional distinct immunotherapies in the future. We are exploring potential development and commercialization collaborations for certain product candidates in our development pipeline.

We have sustained losses from operations in each fiscal year since our inception, and we expect these losses to continue for the indefinite future, due to the substantial investment in research and development. As of October 31, 2013, we had an accumulated deficit of $70,465,823, and stockholders’ equity of $18,002,142.

Our *Lm*-LLO Immunotherapy Platform Technology

Our Lm -LLO immunotherapies are based on a platform technology under exclusive license from the Trustees of the University of Pennsylvania, or Penn, that utilizes live attenuated Lm bioengineered to secrete antigen/adjuvant fusion proteins. These Lm strains use a fragment of the protein listeriolysin, or LLO, fused to a tumor associated antigen, or TAA, or other antigen of interest and we refer to these as Lm -LLO immunotherapies. Regardless of which antigen(s) is fused to LLO, the proposed mechanism of action is basically the same. We believe these Lm -LLO immunotherapies redirect the potent immune response to Lm that is inherent in humans, to the TAA or other antigen of interest. Lm -LLO immunotherapies stimulate the immune system to induce antigen-specific anti-tumor immune responses involving both innate and adaptive arms of the immune system. In addition, our technology facilitates the immune response by altering the tumor microenvironment to reduce immunologic tolerance in the tumors but leaves normal tissues unchanged. This makes the tumor more susceptible to immune attack by inhibiting the T-cells, or Tregs, and myeloid-derived suppressor cells, or MDSC, that we believe promote immunologic tolerance of cancer cells in the tumor.

The field of immunotherapy is a relatively new area of cancer treatment development that holds tremendous promise to generate more effective and better tolerated treatments for cancer than the more traditional, high dose chemotherapy and radiation therapies that have been the mainstay of cancer treatment thus far. There are many approaches toward immunotherapy that have been recently approved or are in development. We believe *Lm*-LLO immunotherapies will offer a more comprehensive immunotherapy in a single, well-tolerated, easy to administer treatment than other alternative immunotherapy treatments.

Our Preclinical and Clinical Development Pipeline

Our most advanced product candidates in clinical development are ADXS-HPV, ADXS-PSA and ADXS-cHER2:

- ***ADXS-HPV***. ADXS-HPV is an Lm -LLO immunotherapy directed against HPV. ADXS-HPV is designed to target cells expressing the HPV gene E7. Expression of the E7 gene from high-risk HPV strains is responsible for the transformation of infected cells into dysplastic and malignant tissues and in the laboratory, was more effective than ADXS vectors targeting HPV E6. Eliminating these cells can eliminate the dysplasia or malignancy. ADXS-HPV is designed to direct antigen-presenting cells to generate powerful innate and cellular immune responses to HPV transformed cells resulting in the infiltration of cytotoxic T cells and attack on tumors. At the same time, we believe ADXS-HPV treatment may cause a reduction in the number and function of immunosuppressive regulatory Tregs and MDSC in the tumors that are protecting tumors from immune attack. ADXS-HPV is being evaluated in four ongoing clinical trials for HPV-associated diseases: locally advanced cervical cancer (with the GOG, largely underwritten by the NCI, U.S.); head and neck cancer (underwritten by the CRUK, U.K.); head and neck cancer (ISMMS, U.S.) and anal cancer (BrUOG, U.S.). Our next goal is to conduct Phase 1/2 trials to optimize the dose and schedule of ADXS-HPV, which we believe may further increase efficacy with respect to both clinical response and

survival. Additional studies will investigate how best to combine ADXS-HPV with existing cytotoxic treatments. We plan to advance ADXS-HPV through registrational Phase 3 trials and regulatory approval in the United States and relevant markets for the treatment of cervical cancer. We also plan to evaluate ADXS-HPV in Phase 1/2 clinical trials for the treatment of patients with HPV-positive head and neck cancer and HPV-positive anal cancer. Future plans for the ADXS-HPV franchise are contingent upon a number of variables including available resources, types and number of studies, study initiation, patient enrollment, clinical and safety data generated, regulatory interactions and changing competitive landscape.

- ***ADXS-PSA***. ADXS-PSA is an *Lm*-LLO immunotherapy directed against PSA. ADXS-PSA is designed to target cells expressing PSA. ADXS-PSA secretes the PSA antigen, fused to LLO, directly inside the APC, that are cable of driving a cellular immune response to PSA expressing cells. In preclinical analysis, the localized effect is the inhibition of the Treg and MDSC cells that we believe may promote immunologic tolerance of the PSA cancer cells of the tumor. We have conducted a pre-Investigational New Drug application, or IND, meeting with the FDA to discuss the chemistry, manufacturing and controls, pharmacology, toxicity and clinical plans for ADXS-PSA. We will finalize the toxicology and good manufacturing practice, or GMP, documentation required for the IND we plan to submit to the FDA and advance ADXS-PSA into a Phase 1 dose escalation trial to determine the maximum tolerated dose for the treatment of prostate cancer. Future plans for the ADXS-PSA clinical program are contingent upon a number of variables including available resources, types and number of studies, study initiation, patient enrollment, clinical and safety data generated, regulatory interactions and changing competitive landscape.

ADXS-cHER2. ADXS-cHER2 is an *Lm*-LLO immunotherapy for HER2 overexpressing cancers (such as breast, gastric and other cancers in humans and for osteosarcoma in canines). ADXS-cHER2 secretes the cHER2 antigen, fused to LLO, directly inside APC that are capable of driving a cellular immune response to cHER2 overexpressing cells. In preclinical analysis, localized effect is the inhibition of the Treg and MDSC cells that we believe may promote immunologic tolerance of the HER2 overexpressing cancer cells of the tumor. We currently are conducting a Phase 1 study in companion dogs evaluating the safety and efficacy of ADXS-cHER2 in the treatment of canine osteosarcoma. Preliminary data has shown encouraging survival in 9 dogs treated with ADXS-cHER2, as compared to 11 untreated dogs, appearing to validate the activity of the platform. We plan to meet with the U.S. Department of Agriculture, to discuss the requirements to proceed forward with our first immunotherapy in the veterinary market. Future plans for the ADXS-cHER2 program are contingent upon a number of variables including available resources, types and number of studies, study initiation, patient enrollment, clinical and safety data generated, regulatory interactions and changing competitive landscape.

Corporate Information

We were originally incorporated in the State of Colorado on June 5, 1987 under the name Great Expectations, Inc. We were a publicly-traded “shell” company without any business until November 12, 2004 when we acquired Advaxis, Inc., a Delaware corporation, through a Share Exchange and Reorganization Agreement, dated as of August 25, 2004, which we refer to as the Share Exchange, by and among Advaxis, the stockholders of Advaxis and us. As a result of the Share Exchange, Advaxis became our wholly-owned subsidiary and our sole operating company. On December 23, 2004, we amended and restated our articles of incorporation and changed our name to Advaxis, Inc. On June 6, 2006, our stockholders approved the reincorporation of our company from Colorado to Delaware by merging the Colorado entity into our wholly-owned Delaware subsidiary. Our date of inception, for financial statement purposes, is March 1, 2002.

Our principal executive offices are located at 305 College Road East, Princeton, New Jersey 08540 and our telephone number is (609) 452-9813. We maintain a website at www.advaxis.com which contains descriptions of our technology, our drugs and the trial status of each drug. The information on our website is not incorporated into this prospectus.

The Securities We May Offer

We may offer shares of our common stock, from time to time under this prospectus, together with any applicable prospectus supplement, at prices and on terms to be determined by market conditions at the time of offering. This prospectus provides you with a general description of the securities we may offer. Holders of our common stock are entitled to one vote for each share held of record on each matter submitted to a vote of stockholders. Each time we offer our common stock, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities. A prospectus supplement to be provided to you may also add, update or change information contained in this prospectus or in documents we have incorporated by reference. However, no prospectus

supplement will offer a security that is not registered and described in this prospectus at the time of the effectiveness of the registration statement of which this prospectus is a part.

We may sell the securities directly to or through underwriters, dealers or agents. We, and our underwriters or agents, reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities through underwriters or agents, we will include in the applicable prospectus supplement:

- the names of those underwriters or agents;
- applicable fees, discounts and commissions to be paid to them;
- details regarding over-allotment options, if any; and
- the net proceeds to us.

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider and evaluate all of the information included and incorporated by reference or deemed to be incorporated by reference in this prospectus or the applicable prospectus supplement, including the risk factors contained herein and those incorporated by reference herein from our Annual Report on Form 10-K for the fiscal year ended October 31, 2013, as updated by annual, quarterly and other reports and documents we file with the SEC after the date of this prospectus and that are incorporated by reference herein or contained in the applicable prospectus supplement. Our business, results of operations or financial condition could be adversely affected by any of these risks or by additional risks and uncertainties not currently known to us or that we currently consider immaterial.

Risks Related to our Business and Industry

We are a development stage company.

We are an early development stage biotechnology company with a history of losses and can provide no assurance as to future operating results. As a result of losses that will continue throughout our development stage, we may exhaust our financial resources and be unable to complete the development of our products. We anticipate that our ongoing operational costs will increase significantly as we continue conducting our clinical development program. Our deficit will continue to grow during our drug development period. Since our inception, we have had no revenue, and do not expect to have any revenue for another three to five years, depending on when we can commercialize our immunotherapies, if at all.

We have sustained losses from operations in each fiscal year since our inception, and we expect losses to continue for the indefinite future due to the substantial investment in research and development. As of October 31, 2013, we had an accumulated deficit of $70,465,823 and shareholders' equity of $18,002,142. We expect to spend substantial additional sums on the continued administration and research and development of proprietary products and technologies with no certainty that our immunotherapies will become commercially viable or profitable as a result of these expenditures. If we fail to raise a significant amount of capital, we may need to significantly curtail operations or cease operations in the near future. If any of our product candidates fails in clinical trials or does not gain regulatory approval, we may never become profitable. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods.

Our limited operating history does not afford investors a sufficient history on which to base an investment decision.

We commenced our *Lm* -LLO based immunotherapy development business in February 2002 and have existed as a development stage company since such time. Prior thereto we conducted no business. Accordingly, we have a limited operating history. We have no approved products or products pending approval and therefore have not derived any revenue from the sales of products and have not yet demonstrated ability to obtain regulatory approval, formulate and manufacture commercial scale products, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, there is limited information for investors to use as a basis for assessing our future viability. Investors must consider the risks and difficulties we have encountered in the rapidly evolving vaccine and immunotherapy industry. Such risks include the following:

- difficulties, complications, delays and other unanticipated factors in connection with the development of new drugs;
- competition from companies that have substantially greater assets and financial resources than we have;
- need for acceptance of our immunotherapies;
- ability to anticipate and adapt to a competitive market and rapid technological developments;
- need to rely on multiple levels of complex financing agreements with outside funding due to the length of drug development cycles and governmental approved protocols associated with the pharmaceutical industry; and
- dependence upon key personnel including key independent consultants and advisors.

We cannot be certain that our strategy will be successful or that we will successfully address these risks. In the event that we do not successfully address these risks, our business, prospects, financial condition and results of operations could be materially and adversely affected. We may be required to reduce our staff, discontinue certain research or development programs of our future products and cease to operate.

We may face legal claims; Litigation is expensive and we may not be able to afford the costs.

We may face legal claims involving stockholders, consumers, competitors, and other issues. As described in "Legal Proceedings" in Part I Item 3 of this prospectus, we are engaged in a number of legal proceedings. Litigation and other legal proceedings are inherently uncertain, and adverse rulings could occur, including monetary damages, or an injunction stopping us from engaging in business practices, or requiring other remedies, such as compulsory licensing of patents.

The costs of litigation or any proceeding relating to our intellectual property or contractual rights could be substantial even if resolved in our favor. Some of our competitors or financial funding sources have far greater resources than we do and may be better able to afford the costs of complex litigation. Also, in a law suit for infringement or contractual breaches, even if frivolous, will require considerable time commitments on the part of management, its attorneys and consultants. Defending these types of proceedings or legal actions involve considerable expense and could negatively affect our financial results.

We can provide no assurance of the successful and timely development of new products.

Our immunotherapies are at various stages of research and development. Further development and extensive testing will be required to determine their technical feasibility and commercial viability. We will need to complete significant additional clinical trials demonstrating that our product candidates are safe and effective to the satisfaction of the FDA and other non-U.S. regulatory authorities. The drug approval process is time-consuming, involves substantial expenditures of resources, and depends upon a number of factors, including the severity of the illness in question, the availability of alternative treatments, and the risks and benefits demonstrated in the clinical trials. Our success will depend on our ability to achieve scientific and technological advances and to translate such advances into licensable, FDA-approvable, commercially competitive products on a timely basis. Failure can occur at any stage of the process. If such programs are not successful, we may invest substantial amounts of time and money without developing revenue-producing products. As we enter a more extensive clinical program for our product candidates, the data generated in these studies may not be as compelling as the earlier results.

Immunotherapies and vaccines that we may develop are not likely to be commercially available until five to ten or more years. The proposed development schedules for our immunotherapies may be affected by a variety of factors, including technological difficulties, clinical trial failures, regulatory hurdles, competitive products, intellectual property challenges and/or changes in governmental regulation, many of which will not be within our control. Any delay in the development, introduction or marketing of our products could result either in such products being marketed at a time when their cost and performance characteristics would not be competitive in the marketplace or in the shortening of their commercial lives. In light of the long-term nature of our projects, the unproven technology involved and the other factors described elsewhere in this section, there can be no assurance that we will be able to successfully complete the development or marketing of any new products.

Our research and development expenses are subject to uncertainty.

Factors affecting our research and development expenses include, but are not limited to:

- competition from companies that have substantially greater assets and financial resources than we have;
- need for acceptance of our immunotherapies;
- ability to anticipate and adapt to a competitive market and rapid technological developments;
- amount and timing of operating costs and capital expenditures relating to expansion of our business, operations and infrastructure;
- need to rely on multiple levels of outside funding due to the length of drug development cycles and governmental approved protocols associated with the pharmaceutical industry; and
- dependence upon key personnel including key independent consultants and advisors.

There can be no guarantee that our research and development expenses will be consistent from period to period. We may be required to accelerate or delay incurring certain expenses depending on the results of our studies and the availability of adequate funding.

We are subject to numerous risks inherent in conducting clinical trials.

We outsource the management of our clinical trials to third parties. Agreements with clinical investigators and medical institutions for clinical testing and with other third parties for data management services, place substantial responsibilities on these parties that, if unmet, could result in delays in, or termination of, our clinical trials. For example, if any of our clinical trial sites fail to comply with FDA-approved good clinical practices, we may be unable to use the data gathered at those sites. If these clinical investigators, medical institutions or other third parties do not carry out their contractual duties or obligations or fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to their failure to adhere to our clinical protocols or for other reasons, our clinical trials may be extended, delayed or terminated, and we may be unable to obtain regulatory approval for, or successfully commercialize, agents such as ADXS-HPV. We are not certain that we will successfully recruit enough patients to complete our clinical trials nor that we will reach our primary endpoints. Delays in recruitment, lack of clinical benefit or unacceptable side effects would delay or prevent the initiation of the Phase 3 trials of ADXS-HPV.

We or our regulators may suspend or terminate our clinical trials for a number of reasons. We may voluntarily suspend or terminate our clinical trials if at any time we believe they present an unacceptable risk to the patients enrolled in our clinical trials or do not demonstrate clinical benefit. In addition, regulatory agencies may order the temporary or permanent discontinuation of our clinical trials at any time if they believe that the clinical trials are not being conducted in accordance with applicable regulatory requirements or that they present an unacceptable safety risk to the patients enrolled in our clinical trials.

Our clinical trial operations are subject to regulatory inspections at any time. If regulatory inspectors conclude that we or our clinical trial sites are not in compliance with applicable regulatory requirements for conducting clinical trials, we may receive reports of observations or warning letters detailing deficiencies, and we will be required to implement corrective actions. If regulatory agencies deem our responses to be inadequate, or are dissatisfied with the corrective actions we or our clinical trial sites have implemented, our clinical trials may be temporarily or permanently discontinued, we may be fined, we or our investigators may be precluded from conducting any ongoing or any future clinical trials, the government may refuse to approve our marketing applications or allow us to manufacture or market our products, and we may be criminally prosecuted.

The lengthy approval process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval for ADXS-HPV or our other product candidates, which would materially harm our business, results of operations and prospects.

The successful development of immunotherapies is highly uncertain.

Successful development of biopharmaceuticals is highly uncertain and is dependent on numerous factors, many of which are beyond our control. Immunotherapies that appear promising in the early phases of development may fail to reach the market for several reasons including:

- preclinical study results that may show the immunotherapy to be less effective than desired (e.g., the study failed to meet its primary objectives) or to have harmful or problematic side effects;
- clinical study results that may show the immunotherapy to be less effective than expected (e.g., the study failed to meet its primary endpoint) or to have unacceptable side effects;
- failure to receive the necessary regulatory approvals or a delay in receiving such approvals. Among other things, such delays may be caused by slow enrollment in clinical studies, length of time to achieve study endpoints, additional time requirements for data analysis, or Biologics License Application preparation, discussions with the FDA, an FDA request for additional preclinical or clinical data, or unexpected safety or manufacturing issues;
- manufacturing costs, formulation issues, pricing or reimbursement issues, or other factors that make the immunotherapy uneconomical; and

- the proprietary rights of others and their competing products and technologies that may prevent the immunotherapy from being commercialized.

Success in preclinical and early clinical studies does not ensure that large-scale clinical studies will be successful. Clinical results are frequently susceptible to varying interpretations that may delay, limit or prevent regulatory approvals. The length of time necessary to complete clinical studies and to submit an application for marketing approval for a final decision by a regulatory authority varies significantly from one immunotherapy to the next, and may be difficult to predict.

Even if we are successful in getting market approval, commercial success of any of our product candidates will also depend in large part on the availability of coverage and adequate reimbursement from third-party payers, including government payers such as the Medicare and Medicaid programs and managed care organizations, which may be affected by existing and future health care reform measures designed to reduce the cost of health care. Third-party payers could require us to conduct additional studies, including post-marketing studies related to the cost effectiveness of a product, to qualify for reimbursement, which could be costly and divert our resources. If government and other health care payers were not to provide adequate coverage and reimbursement levels for one any of our products once approved, market acceptance and commercial success would be reduced.

In addition, if one of our products is approved for marketing, we will be subject to significant regulatory obligations regarding the submission of safety and other post-marketing information and reports and registration, and will need to continue to comply (or ensure that our third party providers) comply with cGMPs, and GCPs, for any clinical trials that we conduct post-approval. In addition, there is always the risk that we or a regulatory authority might identify previously unknown problems with a product post-approval, such as adverse events of unanticipated severity or frequency. Compliance with these requirements is costly, and any failure to comply or other issues with our product candidates post-market approval could have a material adverse effect on our business, financial condition and results of operations.

We must comply with significant government regulations.

The research and development, manufacture and marketing of human therapeutic and diagnostic products are subject to regulation, primarily by the FDA in the United States and by comparable authorities in other countries. These national agencies and other federal, state, local and foreign entities regulate, among other things, research and development activities (including testing in animals and in humans) and the testing, manufacturing, handling, labeling, storage, record keeping, approval, advertising and promotion of the products that we are developing. If we obtain approval for any of our product candidates, our operations will be directly or indirectly through our customers, subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statue and the federal False Claims Act, and privacy laws. Noncompliance with applicable laws and requirements can result in various adverse consequences, including delay in approving or refusal to approve product licenses or other applications, suspension or termination of clinical investigations, revocation of approvals previously granted, fines,

criminal prosecution, civil and criminal penalties, recall or seizure of products, exclusion from having our products reimbursed by federal health care programs, the curtailment or restructuring of our operations, injunctions against shipping products and total or partial suspension of production and/or refusal to allow a company to enter into governmental supply contracts.

The process of obtaining requisite FDA approval has historically been costly and time-consuming. Current FDA requirements for a new human biological product to be marketed in the United States include: (1) the successful conclusion of preclinical laboratory and animal tests, if appropriate, to gain preliminary information on the product's safety; (2) filing with the FDA of an IND to conduct human clinical trials for drugs or biologics; (3) the successful completion of adequate and well-controlled human clinical trials to establish the safety and efficacy of the investigational new drug for its recommended use; and (4) filing by a company and acceptance and approval by the FDA of a Biologic License Application, or BLA, for a biological investigational new drug, to allow commercial distribution of a biologic product. The FDA also requires that any drug or formulation to be tested in humans be manufactured in accordance with its Good Manufacturing Practices, or GMP, regulations. This has been extended to include any drug that will be tested for safety in animals in support of human testing. The GMPs set certain minimum requirements for procedures, record-keeping and the physical characteristics of the laboratories used in the production of these drugs. A delay in one or more of the procedural steps outlined above could be harmful to us in terms of getting our immunotherapies through clinical testing and to market.

We can provide no assurance that our clinical product candidates will obtain regulatory approval or that the results of clinical studies will be favorable.

We are currently evaluating the safety and efficacy of ADXS-HPV in a number of ongoing clinical trials. However, even though the initiation and conduct of these trials is in accordance with the governing regulatory authorities in each country, as with any investigational new drug (under an IND in the United States, or the equivalent in countries outside of the United States), we are at risk of a clinical hold at any time based on the evaluation of the data and information submitted to the governing regulatory authorities.

There can be delays in obtaining FDA (U.S.) and/or other necessary regulatory approvals in the United States and in countries outside the United States for any investigational new drug and failure to receive such approvals would have an adverse effect on the investigational new drug's potential commercial success and on our business, prospects, financial condition and results of operations. The time required to obtain approval by the FDA and non-U.S. regulatory authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. For example, the FDA or non-U.S. regulatory authorities may disagree with the design or implementation of our clinical trials or study endpoints; or we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks. In addition, the FDA or non-U.S. regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials or the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an NDA or other submission or to obtain regulatory approval in the United States or elsewhere. The FDA or non-U.S. regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and the approval policies or regulations of the FDA or non-U.S. regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

In addition to the foregoing, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not submitted for nor obtained regulatory approval for any product candidate and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval.

We may not obtain or maintain the benefits associated with orphan drug designation, including market exclusivity.

Although we have submitted a new request for orphan drug designation for ADXS-HPV for use in the treatment of invasive cervical cancer our original request was denied and there can be no assurance that our new request will be granted. Although, we have been granted orphan drug designation for ADXS-HPV for use in the treatment of HPV-associated anal cancer and for HPV-associated head and neck cancer in the United States, and intend to request a similar designation for these uses in the European Union, we may not be granted orphan drug designation, or even if granted, we may not receive the benefits associated with orphan drug designation. This may result from a failure to maintain orphan drug status, or result from a competing product reaching the market that has an orphan designation for the same disease indication. Under U.S. rules for orphan drugs, if such a competing product reaches the market before ours does, the competing product could potentially obtain a scope of market exclusivity that limits or precludes our product from being sold in the United States for seven years. Even if we obtain exclusivity, the FDA could subsequently approve the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. A competitor also may receive approval of different products for the same indication for which our orphan product has exclusivity, or obtain approval for the same product but for a different indication for which the orphan product has exclusivity.

In addition, if and when we request orphan drug designation in Europe, the European exclusivity period is ten years but can be reduced to six years if the drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMEA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

We may not obtain or maintain the benefits associated with breakthrough therapy designation.

On October 7, 2013, we submitted a request for breakthrough therapy designation (BTD) to the IND for ADXS-HPV in the treatment of invasive cervical cancer in the United States. The FDA denied the request in December 2013, but stated that a new request may be submitted if we obtain new clinical evidence that supports BTD.

If we resubmit, we may not be granted breakthrough therapy designation, or even if granted, we may not receive the benefits associated with breakthrough therapy designation. This may result from a failure to maintain breakthrough therapy status if ADXS11-001 is no longer considered to be a breakthrough therapy. For example, a drug's development program may be granted breakthrough therapy designation using early clinical testing that shows a much higher response rate than available therapies. However, subsequent interim data derived from a larger study may show a response that is substantially smaller than the response seen in early clinical testing. Another example is where breakthrough therapy designation is granted to two drugs that are being developed for the same use. If one of the two drugs gains traditional approval, the other would not retain its designation unless its sponsor provided evidence that the drug may demonstrate substantial improvement over the recently approved drug. When breakthrough therapy designation is no longer supported by emerging data or the designated drug development program is no longer being pursued, the FDA may choose to send a letter notifying the sponsor that the program is no longer designated as a breakthrough therapy development program.

We rely upon patents to protect our technology. We may be unable to protect our intellectual property rights and we may be liable for infringing the intellectual property rights of others.

Our ability to compete effectively will depend on our ability to maintain the proprietary nature of our technologies, including the *Lm* -LLO based immunotherapy platform technology, and the proprietary technology of others with whom we have entered into collaboration and licensing agreements.

We have 42 patents that have been issued and 38 patent applications that are pending. We have licensed all of these patents and 25 of the pending patent applications from Penn. We have obtained the rights to all future patent applications in this field originating in the laboratories of Dr. Yvonne Paterson and Dr. Fred Frankel.

We own or hold licenses to a number of issued patents and U.S. pending patent applications, as well as foreign patents and foreign counterparts. Our success depends in part on our ability to obtain patent protection both in the United States and in other countries for our product candidates, as well as the methods for treating patients in the product indications using these product candidates. Such patent protection is costly to obtain and maintain, and we cannot guarantee that sufficient funds will be available. Our ability to protect our product candidates from unauthorized or infringing use by third parties depends in substantial part on our ability to obtain and maintain valid and enforceable patents. Due to evolving legal standards relating to the patentability, validity and enforceability of patents covering pharmaceutical inventions and the scope of claims made under these patents, our ability to obtain, maintain and enforce patents is uncertain and involves complex legal and factual questions. Even if our product candidates, as well as methods for treating patients for prescribed indications using these product candidates are covered by valid and enforceable patents and have claims with sufficient scope, disclosure and support in the specification, the patents will provide protection only for a limited amount of time. Accordingly, rights under any issued patents may not provide us with sufficient protection for our product candidates or provide sufficient protection to afford us a commercial advantage against competitive products or processes.

In addition, we cannot guarantee that any patents will issue from any pending or future patent applications owned by or licensed to us. Even if patents have issued or will issue, we cannot guarantee that the claims of these patents are or will be valid or enforceable or will provide us with any significant protection against competitive products or otherwise be commercially valuable to us. The laws of some foreign jurisdictions do not protect intellectual property rights to the same extent as in the United States and many companies have encountered significant difficulties in protecting and defending such rights in foreign jurisdictions. Furthermore, different countries have different procedures for obtaining patents, and patents issued in different countries offer different degrees of protection against use of the patented invention by others. If we encounter such difficulties in protecting or are otherwise precluded from effectively protecting our intellectual property rights in foreign jurisdictions, our business prospects could be substantially harmed.

The patent positions of biotechnology and pharmaceutical companies, including our patent position, involve complex legal and factual questions, and, therefore, validity and enforceability cannot be predicted with certainty. Patents may be challenged, deemed unenforceable, invalidated, or circumvented. Our patents can be challenged by our competitors who can argue that our patents are invalid, unenforceable, lack sufficient written description or enablement, or that the claims of the issued patents should be limited or narrowly construed. Patents also will not protect our product candidates if competitors devise ways of making or using these product candidates without infringing our patents.

We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that our technologies, methods of treatment, product candidates, and any future products are covered by valid and enforceable patents or are effectively maintained as trade secrets and we have the funds to enforce our rights, if necessary.

The expiration of our owned or licensed patents before completing the research and development of our product candidates and receiving all required approvals in order to sell and distribute the products on a commercial scale can adversely affect our business and results of operations.

Litigation regarding patents, patent applications and other proprietary rights may be expensive and time consuming. If we are involved in such litigation, it could cause delays in bringing product candidates to market and harm our ability to operate.

Our success will depend in part on our ability to operate without infringing the proprietary rights of third parties. The pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may obtain patents in the future and allege that the products or use of our technologies infringe these patent claims or that we are employing their proprietary technology without authorization.

In addition, third parties may challenge or infringe upon our existing or future patents. Proceedings involving our patents or patent applications or those of others could result in adverse decisions regarding:

- the patentability of our inventions relating to our product candidates; and/or
- the enforceability, validity or scope of protection offered by our patents relating to our product candidates.

Even if we are successful in these proceedings, we may incur substantial costs and divert management time and attention in pursuing these proceedings, which could have a material adverse effect on us. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court. Patent litigation is costly and time consuming. We may not have sufficient resources to bring these actions to a successful conclusion. In addition, if we do not obtain a license, develop or obtain non-infringing technology, fail to defend an infringement action successfully or have infringed patents declared invalid, we may:

- incur substantial monetary damages;
- encounter significant delays in bringing our product candidates to market; and/or
- be precluded from participating in the manufacture, use or sale of our product candidates or methods of treatment requiring licenses.

We may be unable to adequately prevent disclosure of trade secrets and other proprietary information.

We also rely on trade secrets to protect our proprietary technologies, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, outside scientific collaborators, sponsored researchers, and other advisors to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover our trade secrets and proprietary information. Costly and time-consuming