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

FORM 8-K

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

Date of Report (Date of earliest event reported): October 13, 2023

LIXTE BIOTECHNOLOGY HOLDINGS, INC.

DELAWARE	001-39717	20-2903526
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

680 East Colorado Blvd. Suite 180
Pasadena, California 91101
(Address of principal executive offices)

(631) 830-7092
(Registrant's telephone number, including area code)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (See General Instruction A.2. below):

□ Written communications pursuant to Rule 425 under the Securities Act of 1933 (17 CFR 230.425)

□ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

□ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

□ Pre-commencement communications pursuant to Rule 13e-4(e) under the Exchange Act (17 CFR 240.13e-4(c))

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

Title of Each Class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	LIXT	The Nasdaq Stock Market LLC
Warrant to Purchase Common Stock	LIXTW	The Nasdaq Stock Market LLC

Item 1.01 Entry into a Material Definitive Agreement.

Amendment to Development Collaboration Agreement

On October 8, 2021, Lixte Biotechnology Holdings, Inc. (the "Company") entered into a Development Collaboration Agreement (the "Collaboration Agreement") with the Netherlands Cancer Institute, Amsterdam (NKI), one of the world's leading comprehensive cancer centers, and Oncode Institute, Utrecht, a major independent cancer research center, to identify the most promising drugs to be combined with LB-100, and potentially LB-100 analogues, to be used to treat a range of cancers, as well as to identify the specific molecular mechanisms underlying the identified combinations. On October 13, 2023, the parties signed an amendment ("Amendment 2") to expand the collaboration to study drug synergies of the Company's lead compound, LB-100, with immunotherapy in various cancers. Under Amendment 2, the parties will seek to find synthetic lethal combinations in additional cancer types. Amendment 2 also extends the Collaboration Agreement for an additional two years. The foregoing description of Amendment 2 does not purport to be complete and is subject to and qualified in its entirety by the full text of Amendment 2, a copy of which is filed hereto as Exhibit 10.1.

Item 8.01 Other Events.

On October 16, 2023, the Company issued a press release with respect to Amendment 2 of the Development Collaboration Agreement.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Filed as part of this Current Report on Form 8-K are the exhibits listed on the accompanying Index to Exhibits, which information is incorporated herein by reference.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: October 17, 2023

LIXTE BIOTECHNOLOGY HOLDINGS, INC.

By: */s/ BASTIAAN VAN DER BAAN*
Bastiaan van der Baan,
President and Chief Executive Officer

INDEX TO EXHIBITS

Exhibit No.	Description
10.1	Amendment 2 to Development Collaboration Agreement (certain portions of this Exhibit have been omitted)
99.1	Press Release Announcing the Amendment to the Development Collaboration Agreement
104	Cover Page Interactive Data File (embedded within the Inline XBRL Document)

Exhibit 10.1

CERTAIN IDENTIFIED INFORMATION HAS BEEN EXCLUDED FROM THIS EXHIBIT BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED

AMENDMENT 2 TO DEVELOPMENT COLLABORATION AGREEMENT

THIS AMENDMENT IS MADE ON October 3, 2023 AND ENTERED INTO BY AND BETWEEN:

1. **LIXTE BIOTECHNOLOGY HOLDINGS, INC. ("Lixte"), with its office and place of business at 680 E Colorado Blvd., Suite 180, Pasadena, CA 91101 and**

2. **STICHTING HET NEDERLANDS KANKER INSTITUUT – ANTONI VAN LEEUWENHOEK ZIEKENHUIS, a foundation incorporated under the laws of The Netherlands, with its registered office at Plesmanlaan 121, 1066 CX Amsterdam ("NKI-AVL" or "Institution") and**

3. **STICHTING ONCODE INSTITUTE, a foundation incorporated under the laws of The Netherlands, with its registered office at Jaarbeursplein 6, 3521AL, Utrecht, and registered with the chamber of commerce with number 69303010 ("Oncode").**

Each of Lixte, NKI-AVL and Oncode are referred to as a "Party" and together as, the "Parties." each a **"Party"** and together the **"Parties"**.

WHEREAS

1. Parties have entered into a Development Collaboration Agreement with effective date of 8 October 2021 (the "**Agreement**");

2. Parties wish to amend the Agreement by adding language to cover an extension of the Study, as set forth in this amendment (the "**Amendment**");

NOW, THEREFORE, IT IS AGREED AS FOLLOWS:

1 In Section 9, the 'third anniversary' as a termination date shall be replaced by 'fifth anniversary'.

2 The Exhibit A shall be amended with the following additional research activities and budget and shall read as follows:

EXHIBIT A

THE STUDY

It is proposed to focus the research collaboration on 5 topics, as described below.

1. Further study of drug synergies of LB-100 in different cancers.

Our data indicate that LB-100 shows strong synergy with specific stress-targeted drugs. In colon cancer, the best synergy was seen with the WEE1 inhibitor adavosertib. It is well possible that in other cancer types the optimal synergy will be with perturbation of other stress response pathways. We will test one additional rare cancer type: cholangiocarcinoma for the stress-targeted drugs that show the best synergy with LB-100. Such studies may reveal novel potent drug combinations in a rare cancer type for which Lixte could apply for an orphan drug designation, which could provide certain regulatory incentives to Lixte.

2. Further studies on understanding synergy between LB-100 and checkpoint immunotherapies.

There is ample data in the literature that LB-100 shows synergy with immune checkpoint therapies in pre-clinical models. Our own contribution to this is the finding that LB-100 massively perturbs proper mRNA splicing, which could be a source of cancer neo-antigens. We will study this in more detail in the next period. We will perform immunopeptidomic analyses, in which we ask whether specific neo-antigens are presented by the MHC class I antigens of tumor cells following exposure to LB-100. We will then search for the same neo-antigens in LB-100 treated patient samples of the LB-100 trials we plan to initiate at NKI in the coming two years (see point 5 below).

3. Testing of novel PP2A inhibitory compounds for potency in vitro and in vivo.

Lixte has access to novel PP2A inhibitory compounds through a collaboration with Biopharmaworks. So far, NKI has received two compounds from this collaboration (compounds 1 and 2). We will test these compounds in vitro and in vivo in different models to assess their utility as PP2A inhibitory drugs in comparison to LB-100.

4. Identification of biomarkers of response to LB-100 ([_____] studies).

A genome-scale CRISPR screen has identified [_____] as a gene whose knockout confers resistance to LB-100. Our initial data indicate that [_____] is a hydrolase required for the conversion of LB-100 in the active drug endothall. We will study in detail whether [_____] can convert LB-100 into endothall in vitro and study how the [_____] enzyme catalyzes this reaction. Since [_____] has variable expression in cancers, [_____] is a potential biomarker of response to LB-100 in the clinic. We will measure [_____] protein levels in the NKI clinical studies with LB-100 (see below) to address this.

5. Translational studies on patient material derived from upcoming clinical trials at NKI testing combinations of LB-100 with PDL1 or ZN-C3.

Our pre-clinical studies have identified several new aspects of LB-100 biology, including misregulation of mRNA splicing, generation of neo-antigens and a form of acquired drug resistance associated with reduced levels of tumor aneuploidy. Moreover, our data indicate that [_____] can be a potential biomarker of response to LB-100 (combination) therapies.

The potential performance of two clinical trials at NKI, combining LB-100 with either PDL1 or ZN-C3 provides an opportunity to ask if these aspects of LB-100 biology are also seen in patient tumor samples during LB-100 therapy.

To address this, we will use biopsies from patients in NKI trials before and during LB-100 therapy for several translational studies.

1. We will perform RNAseq on RNA isolated from tumor biopasies before therapy and on treatment to ask if mRNA missplicing is also induced in patients.
2. If we see evidence for missplicing, we will perform immunopeptidomic analyses to ask if neo-antigens are presented by the MHC class I antigens on the tumor cells during LB-100 treatment.
3. We will perform low coverage Next Generation Sequencing to assess changes in aneuploidy during LB-100 treatment.
4. We will measure protein levels of [_____] using immunohistochemistry to ask if tumors with low [_____] are less responsive to LB-100 based therapies.

Budget:

Duration of the extension of the Study is two (2) years and starts at October 3, 2023.

Annual project cost of €250.000, which includes salary cost, consumable costs, infrastructure support and overhead. This amount shall be invoiced at the start of each year of the extended Study.

3 The Parties agree that the terms of this Amendment are intended to be supplemental to the terms of the Agreement. Except as specifically set forth in this Amendment, all provisions of the Agreement shall remain in full force and effect and shall apply to this Amendment as well. Capitalized terms used but not defined in this Amendment shall have the respective meaning defined in the Agreement.

4 This Amendment shall enter into force on the date of the last signature to this Amendment.

-signature page follows-

IN WITNESS WHEREOF the Parties have caused this Amendment to be executed by their duly authorised representatives.

LIXTE BIOTECHNOLOGY HOLDINGS, INC

Name(s):
Title(s):
Date(s):
Signature(s):

STICHTING HET NEDERLANDS KANKER INSTITUUT – ANTONI VAN LEEUWENHOEK ZIEKENHUIS

Name:
Date:
Title:
Signature:

Stichting Oncode Institute

Name:
Title:
Date:
Signature:

Exhibit 99.1

LIXTE, Netherlands Cancer Institute, and Oncode Institute to Expand Collaboration

Extension Agreement Follows Successful Two-Year Collaboration in Colon Cancer

PASADENA, CA, October 16, 2023 — LIXTE Biotechnology Holdings, Inc. (Nasdaq: LIXT and LIXTW) announced that it has signed an agreement to expand its collaboration with the Netherlands Cancer Institute (NKI) and Oncode Institute to study drug synergies of LIXTE's lead clinical compound, LB-100, with immunotherapy in various cancers. The new agreement also will seek to find synthetic lethal combinations in additional cancer types.

The two-year extension agreement follows successful collaboration during the past two years to identify the most promising drugs to be combined with LB-100 for treating colon cancer, as well as to identify the specific molecular mechanisms underlying the identified combinations in order to provide a rationale to test these combinations in clinical trials.

NKI, based in Amsterdam, Netherlands, is among the world's leading comprehensive cancer centers. Oncode Institute, headquartered in Utrecht, Netherlands, is a major independent cancer research center dedicated to translating research into practice and bringing discoveries into a clinic setting more quickly.

NKI's René Bernards, Ph.D., and his group – using genome-wide functional genetic techniques to identify effective drug combinations, new drug targets and mechanisms of resistance to cancer drugs – have identified a number of drug combinations that are now approved for patients or in advanced clinical development. Prof. Bernards is a professor of molecular carcinogenesis and has been a member of LIXTE's board of directors since June 2022.

"We are excited to continue and extend our work with LIXTE on additional types of cancer, as we look to identify the most powerful drug combinations of LB-100 for various cancer therapies," Prof. Bernards said. "In addition, we look forward to working with LIXTE to investigate the molecular mechanism of synergy of LB-100 with immune checkpoint therapy and testing of novel PP2A inhibitor molecules in cancer models."

Bas van der Baan, the recently appointed Chief Executive Officer and President of LIXTE, added, "The collaboration with Prof. Bernards and his team provides us with unique insights in our efforts to identify promising therapy combinations for LB-100 and a more targeted approach to cancer treatment."

About LIXTE Biotechnology Holdings, Inc.

LIXTE Biotechnology Holdings, Inc. is a clinical-stage pharmaceutical company developing a new class of cancer therapy called PP2A inhibitors. The Company's innovative approach enhances the efficacy of both chemotherapy and immunotherapy, potentially providing new treatment options for patients. At the core of the Company's therapy is LB-100, the Company's proprietary compound that acts as an inhibitor of the PP2A phosphatase with a favorable toxicity profile. LB-100 promotes the production of neoantigens and cytokines, boosts T-cell proliferation, and disrupts the DNA repair mechanisms of cancer cells, potentially improving treatment outcomes. The Company is conducting multiple clinical trials for solid tumors with unmet medical needs. LIXTE's unique approach has no known competitors and is covered by a comprehensive patent portfolio.

Additional information about LIXTE can be obtained at www.lixte.com and by reviewing the Company's filings with the United States Securities and Exchange Commission at https://www.sec.gov.

About Netherlands Cancer Institute, Amsterdam

Netherlands Cancer Institute, founded in 1913, is among the world's best comprehensive cancer centers, combining world-class fundamental, translational, and clinical research with dedicated patient care. Initiatives to promote excellent translational research have been recognized by the European Academy of Cancer Sciences, when they designated NKI as a 'Comprehensive Cancer Center of Excellence in Translational Research.' For more information, visit www.nki.nl.

About the Oncode Institute, Utrecht

Oncode Institute is an independent research organization dedicated to understanding cancer and translating research into practice. The Institute strives for a future in which everyone can survive cancer with the best possible quality of life. With this vision in mind, it joins forces with 12 research institutes across the Netherlands, bringing together some of the leading fundamental cancer researchers in the country, supporting them in developing and translating breakthrough discoveries into new diagnostics and treatments for cancer patients. Oncode Institute sits at the interface between academic research, clinicians, and industry, and includes the active participation of patients - taking an integrated approach focused on three fundamental pillars: scientific excellence, collaboration and valorization. For more information, visit www.oncodeinstitute.nl.

Forward-Looking Statements

This announcement contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, and Section 21E of the Securities Exchange Act of 1934. For example, statements regarding the Company's financial position, business strategy and other plans and objectives for future operations, and assumptions and predictions about future activities, including the continuing development of proprietary compounds, the planning, funding, coordination and potential results of clinical trials, and the patent and legal costs to protect and maintain the Company's intellectual property worldwide, are all forward-looking statements. These statements are generally accompanied by words such as "intend," anticipate," "believe," "estimate," "potential(ly)," "continue," "forecast," "predict," "plan," "may," "will," "could," "would," "should," "expect" or the negative of such terms or other comparable terminology. The Company believes that the assumptions and expectations reflected in such forward-looking statements are reasonable, based on information available to it on the date hereof, but the Company cannot provide assurances that these assumptions and expectations will prove to have been correct or that the Company will take any action that the Company may presently be planning. However, these forward-looking statements are inherently subject to known and unknown risks and uncertainties. Actual results or experience may differ materially from those expected or anticipated in the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, regulatory policies, available cash, research results, competition from other similar businesses, and market and general economic factors. This discussion should be read in conjunction with the Company's filings with the United States Securities and Exchange Commission at https://www.sec.gov.

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