

| OMB APPROVAL                                 |           |
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**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934 or Section 30(h) of the Investment Company Act of 1940

|   |   |   |
|---|---|---|
| 1. Name and Address of Reporting Person*<br><u>Keutzer Timothy</u><br><br>(Last) (First) (Middle)<br>C/O SPERO THERAPEUTICS, INC.<br>675 MASSACHUSETTS AVENUE, 14TH FLOOR<br><br>(Street)<br>CAMBRIDGE MA 02139<br><br>(City) (State) (Zip) | 2. Issuer Name and Ticker or Trading Symbol<br><u>Spero Therapeutics, Inc. [ SPRO ]</u> | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable)<br>Director 10% Owner<br><input checked="" type="checkbox"/> Officer (give title below) Other (specify below)<br><u>Chief Development Officer</u> |
|   | 3. Date of Earliest Transaction (Month/Day/Year)<br><u>08/26/2021</u>                   |   |
|   | 4. If Amendment, Date of Original Filed (Month/Day/Year)                                |   |

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

| 1. Title of Security (Instr. 3) | 2. Transaction Date (Month/Day/Year) | 2A. Deemed Execution Date, if any (Month/Day/Year) | 3. Transaction Code (Instr. 8) |   | 4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5) |            |        | 5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4) | 6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4) | 7. Nature of Indirect Beneficial Ownership (Instr. 4) |
|---------------------------------|--------------------------------------|--|--------------------------------|---|---|------------|--------|---|--|---|
|                                 |                                      |  | Code                           | V | Amount  | (A) or (D) | Price  |   |  |   |
| Common Stock                    | 08/26/2021                           |  | A                              |   | 24,067 <sup>(1)</sup>   | A          | \$0.00 | 26,567  | D  |   |

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

| 1. Title of Derivative Security (Instr. 3) | 2. Conversion or Exercise Price of Derivative Security | 3. Transaction Date (Month/Day/Year) | 3A. Deemed Execution Date, if any (Month/Day/Year) | 4. Transaction Code (Instr. 8) | 5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5) | 6. Date Exercisable and Expiration Date (Month/Day/Year) |                 | 7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4) | 8. Price of Derivative Security (Instr. 5) | 9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4) | 10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4) | 11. Nature of Indirect Beneficial Ownership (Instr. 4) |
|--|--|--------------------------------------|--|--------------------------------|--|--|-----------------|---|--|--|---|--|
|  |  |                                      |  |                                |  | Date Exercisable   | Expiration Date |   |  |  |   |  |

**Explanation of Responses:**

1. Consists of restricted stock units ("RSUs"). Each RSU represents the right to receive one share of common stock upon vesting. The RSUs vest in four equal annual installments beginning on August 26, 2022, subject to the Reporting Person's continued service through the applicable vesting date.

**Remarks:**

/s/ Matthew J. Gardella,  
Attorney-in-Fact for Timothy Keutzer 08/30/2021

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.