

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

SCHEDULE 13G

Under the Securities Exchange Act of 1934  
(Amendment No. 2)

**Karyopharm Therapeutics Inc.**  
(Name of Issuer)

**Common Stock**  
(Title of Class of Securities)

**48576U106**  
(CUSIP Number)

**December 31, 2017**  
(Date of Event Which Requires Filing of this Statement)

Check the appropriate box to designate the rule pursuant to which this Schedule is filed:

Rule 13d-1(b)

Rule 13d-1(c)

Rule 13d-1(d)

The remainder of this cover page shall be filled out for a reporting person's initial filing on this form with respect to the subject class of securities, and for any subsequent amendment containing information which would alter the disclosures provided in a prior cover page.

The information required in the remainder of this cover page shall not be deemed to be "filed" for the purpose of Section 18 of the Securities Exchange Act of 1934 ("Act") or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act (however, see the Notes).

**Potential persons who are to respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB control number.**

1. Names of Reporting Persons.

**Patrick Lee, MD**

2. Check the Appropriate Box if a Member of a Group (See Instructions)

(a)

(b)  X

3. SEC Use Only

4. Citizenship or Place of Organization **U.S.A**

Number of	5. Sole Voting Power <b>0</b>
Shares	6. Shared Voting Power <b>3,544,439</b>
Beneficially	7. Sole Dispositive Power <b>0</b>
Owned by	8. Shared Dispositive Power <b>3,544,439</b>
Each Reporting	
Person With:	

9. Aggregate Amount Beneficially Owned by Each Reporting Person **3,544,439**

10. Check if the Aggregate Amount in Row (9) Excludes Certain Shares (See Instructions) \_\_\_\_\_

11. Percent of Class Represented by Amount in Row (9) **7.51%**

12. Type of Reporting Person (See Instructions) **IN, HC**

1. Names of Reporting Persons.

**Anthony Joonkyoo Yun, MD**

2. Check the Appropriate Box if a Member of a Group (See Instructions)

(a)

(b)  X

3. SEC Use Only

4. Citizenship or Place of Organization **U.S.A.**

Number of	<b>5. Sole Voting Power 0</b>
Shares	<b>6. Shared Voting Power 3,544,439</b>
Beneficially	<b>7. Sole Dispositive Power 0</b>
Owned by	<b>8. Shared Dispositive Power 3,544,439</b>
Each Reporting	
Person With:	

9. Aggregate Amount Beneficially Owned by Each Reporting Person **3,544,439**

10. Check if the Aggregate Amount in Row (9) Excludes Certain Shares (See Instructions) \_\_\_\_\_

11. Percent of Class Represented by Amount in Row (9) **7.51%**

12. Type of Reporting Person (See Instructions) **IN, HC**

1. Names of Reporting Persons.

**Palo Alto Investors, LLC**

2. Check the Appropriate Box if a Member of a Group (See Instructions)

(a)

(b)

3. SEC Use Only

4. Citizenship or Place of Organization **California**

Number of	5. Sole Voting Power <b>0</b>
Shares	6. Shared Voting Power <b>3,544,439</b>
Beneficially	
Owned by	7. Sole Dispositive Power <b>0</b>
Each Reporting	8. Shared Dispositive Power <b>3,544,439</b>
Person With:	

9. Aggregate Amount Beneficially Owned by Each Reporting Person **3,544,439**

10. Check if the Aggregate Amount in Row (9) Excludes Certain Shares (See Instructions) \_\_\_\_\_

11. Percent of Class Represented by Amount in Row (9) **7.51%**

12. Type of Reporting Person (See Instructions) **OO, IA**

1. Names of Reporting Persons.

**Palo Alto Healthcare Master Fund II, L.P.**

2. Check the Appropriate Box if a Member of a Group (See Instructions)

(a)

(b)

3. SEC Use Only

4. Citizenship or Place of Organization **Cayman Islands**

Number of	5. Sole Voting Power <b>0</b>
Shares	6. Shared Voting Power <b>2,429,762</b>
Beneficially	
Owned by	7. Sole Dispositive Power <b>0</b>
Each Reporting	8. Shared Dispositive Power <b>2,429,762</b>
Person With:	

9. Aggregate Amount Beneficially Owned by Each Reporting Person **2,429,762**

10. Check if the Aggregate Amount in Row (9) Excludes Certain Shares (See Instructions) \_\_\_\_\_

11. Percent of Class Represented by Amount in Row (9) **5.15%**

12. Type of Reporting Person (See Instructions) **PN**

**Item 1.**

(a) Name of Issuer

**Karyopharm Therapeutics Inc.**

(b) Address of Issuer's Principal Executive Offices

**85 Wells Avenue, 2nd Floor, Newton, MA 02459**

**Item 2.**

(a) The names of the persons filing this statement are:

**Palo Alto Investors, LLC ("PAI")**

**Patrick Lee, MD**

**Anthony Joonkyoo Yun, MD**

**Palo Alto Healthcare Master Fund II, L.P. ("Healthcare Master II")**

(collectively, the "Filers").

(b) The principal business office of the Filers except Healthcare Master II is located at:

**470 University Avenue, Palo Alto, CA 94301**

The principal business office of Healthcare Master II is located at:

**Cayman Corporate Centre, 27 Hospital Road**

**George Town, Grand Cayman KY1-9008**

**Cayman Islands**

(c) For citizenship of Filers, see Item 4 of the cover sheet for each Filer.

(d) This statement relates to shares of Common Stock of the Issuer (the "Stock").

(e) The CUSIP number of the Issuer is: **48576U106**

**Item 3. If this statement is filed pursuant to rule 240.13d-1(b) or 240.13d-2(b) or (c), check whether the person filing is a:**

- (a)  Broker or dealer registered under section 15 of the Act (15 U.S.C. 78o).
- (b)  Bank as defined in section 3(a)(6) of the Act (15 U.S.C. 78c).
- (c)  Insurance company as defined in section 3(a)(19) of the Act (15 U.S.C. 78c).
- (d)  Investment company registered under section 8 of the Investment Company Act of 1940 (15 U.S.C. 80a-8).
- (e)  An investment adviser in accordance with section 240.13d-1(b)(1)(ii)(E) (as to PAI).
- (f)  An employee benefit plan or endowment fund in accordance with section 240.13d-1(b)(1)(ii)(F).
- (g)  A parent holding company or control person in accordance with 240.13d-1(b)(1)(ii)(G) (as to Dr. Lee and Dr. Yun).
- (h)  A savings association as defined in section 3(b) of the Federal Deposit Insurance Act (12 U.S.C. 1813).
- (i)  A church plan that is excluded from the definition of an investment company under section 3(c)(14) of the Investment Company Act of 1940 (15 U.S.C. 80a-3).
- (j)  A non-U.S. institution in accordance with §240.13d-1(b)(ii)(J).
- (k)  Group, in accordance with Rule 13d-1(b)(1)(ii)(K).

If filing as a non-U.S. institution in accordance with §240.13d-1(b)(1)(ii)(J), please specify the type of institution

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**Item 4. Ownership.**

See Items 5-9 and 11 of the cover page for each Filer.

**Item 5. Ownership of Five Percent or Less of a Class**

If this statement is being filed to report the fact that as of the date hereof the reporting person has ceased to be the beneficial owner of more than five percent of the class of securities, check the following .

CUSIP 48576U106

**Item 6. Ownership of More than Five Percent on Behalf of Another Person.**

PAI is a registered investment adviser and is the general partner and investment adviser of Healthcare Master II and other investment limited partnerships and is the investment adviser to other investment funds. PAI's clients have the right to receive or the power to direct the receipt of dividends from, or the proceeds from the sale of, the Stock. No individual client, other than Healthcare Master II, separately holds more than five percent of the outstanding Stock.

**Item 7. Identification and Classification of the Subsidiary Which Acquired the Security Being Reported on By the Parent Holding Company.**

Not applicable.

**Item 8. Identification and Classification of Members of the Group.**

Dr. Lee and Dr. Yun co-manage PAI. The Filers are filing this Schedule 13G jointly, but not as members of a group, and each of them expressly disclaims membership in a group. Each Filer disclaims beneficial ownership of the Stock except to the extent of that Filer's pecuniary interest therein. In addition, the filing of this Schedule 13G on behalf of Healthcare Master II should not be construed as an admission that it is, and it disclaims that it is, a beneficial owner, as defined in Rule 13d-3 under the Securities Exchange Act of 1934, of any of the Stock covered by this Schedule 13G.

**Item 9. Notice of Dissolution of Group:**

Not applicable.

**Item 10. Certification of PAI, Dr. Lee and Dr Yun.**

By signing below I certify that, to the best of my knowledge and belief, the securities referred to above were acquired and are held in the ordinary course of business and were not acquired and are not held for the purpose of or with the effect of changing or influencing the control of the issuer of the securities and were not acquired and are not held in connection with or as a participant in any transaction having that purpose or effect.

**Certification of Healthcare Master II.**

By signing below I certify that, to the best of my knowledge and belief, the securities referred to above were not acquired and are not held for the purpose of or with the effect of changing or influencing the control of the issuer of the securities and were not acquired and are not held in connection with or as a participant in any transaction having that purpose or effect.

**Exhibits.**

Exhibit A Joint Filing Agreement.



CUSIP 48576U106

SIGNATURE

After reasonable inquiry and to the best of my knowledge and belief, I certify that the information set forth in this statement is true, complete and correct.

Dated: February 14, 2018

**PALO ALTO HEALTHCARE MASTER FUND II, L.P.**

**PALO ALTO INVESTORS, LLC**

By: Palo Alto Investors, LLC, General Partner

By: /s/ Angela Nguyen-Dinh, Chief Compliance Officer

By: /s/ Angela Nguyen-Dinh, Chief Compliance Officer

/s/ Patrick Lee, MD

/s/ Anthony Joonkyoo Yun, MD

EXHIBIT A  
AGREEMENT REGARDING JOINT FILING  
OF STATEMENT ON SCHEDULE 13D OR 13G

The undersigned agree to file jointly with the Securities and Exchange Commission (the "SEC") any and all statements on Schedule 13D or Schedule 13G (and any amendments or supplements thereto) required under section 13(d) of the Securities Exchange Act of 1934, as amended, in connection with purchases and sales by the undersigned of the securities of any issuer until such time as the undersigned file with the SEC a statement terminating this Agreement Regarding Joint Filing of Statement on Schedule 13D or 13G. For that purpose, the undersigned hereby constitute and appoint Palo Alto Investors, LLC, a California limited liability company, as their true and lawful agent and attorney-in-fact, with full power and authority for and on behalf of the undersigned to prepare or cause to be prepared, sign, file with the SEC and furnish to any other person all certificates, instruments, agreements and documents necessary to comply with section 13(d) and section 16(a) of the Securities Exchange Act of 1934, as amended, in connection with said purchases and sales, and to do and perform every act necessary and proper to be done incident to the exercise of the foregoing power, as fully as the undersigned might or could do if personally present, until such time as the undersigned file with the SEC a statement terminating this Agreement Regarding Joint Filing of Statement on Schedule 13D or 13G.

Dated: February 14, 2018

**PALO ALTO HEALTHCARE MASTER FUND II, L.P.**

**PALO ALTO INVESTORS, LLC**

By: Palo Alto Investors, LLC, General Partner

By: /s/ Angela Nguyen-Dinh, Chief Compliance Officer

By: /s/ Angela Nguyen-Dinh, Chief Compliance Officer

/s/ Patrick Lee, MD

/s/ Anthony Joonkyoo Yun, MD