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**SECURITIES AND EXCHANGE COMMISSION**  
WASHINGTON, DC 20549

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**SCHEDULE 13D**

**Under the Securities Exchange Act of 1934**

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**SPRUCE BIOSCIENCES, INC.**

(Name of Issuer)

**Common Stock, par value \$0.001 per share**  
(Title of Class of Securities)

**85209E109**  
(CUSIP Number)

**Jay W. Schmelter**  
**101 S. Hanley Road, Suite 1850**  
**St. Louis, MO 63105**  
**(314) 726-6700**

*With copy to:*

**Gloria M. Skigen, Esq.**  
**Holland & Knight LLP**  
**One Stamford Plaza 263 Tresser Boulevard Suite 1400**  
**Stamford, CT 06901**  
**(203) 905-4526**

(Name, Address and Telephone Number of Person Authorized to Receive Notices and Communications)

**October 14, 2020**  
(Date of Event which Requires Filing of this Statement)

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If the filing person has previously filed a statement on Schedule 13G to report the acquisition that is the subject of this Schedule 13D, and is filing this schedule because of §§240.13d-1(e), 240.13d-1(f) or 240.13d-1(g), check the following box:

\* 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 disclosures provided in a prior cover page.

The information required on 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).

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1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	RiverVest Venture Fund III, L.P.	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS	
	WC	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)	
	<input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION	
	Delaware, USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER
		0
	8	SHARED VOTING POWER
		1,379,177
	9	SOLE DISPOSITIVE POWER
		0
	10	SHARED DISPOSITIVE POWER
		1,379,177
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON	
	1,379,177	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES	
	<input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)	
	6.0%(1)	
14	TYPE OF REPORTING PERSON	
	PN	

- (1) The percentage set forth in row (13) is based on the 23,163,593 outstanding shares of common stock, par value \$0.001 per share, of Spruce Biosciences, Inc., a Delaware corporation (the "Issuer"), reported by the Issuer to be outstanding immediately after the Issuer's initial public offering on the Issuer's prospectus filed under Rule 424(b)(4), filed with the Securities and Exchange Commission ("SEC") on October 10, 2020, after giving effect to the exercise in full of the underwriters' over-allotment option as reported by the Issuer on October 14, 2020.

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	RiverVest Venture Fund III (Ohio), L.P.	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS  WC	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)  <input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION  Delaware, USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER  0
	8	SHARED VOTING POWER  73,199
	9	SOLE DISPOSITIVE POWER  0
	10	SHARED DISPOSITIVE POWER  73,199
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON  73,199	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES  <input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)  0.3%(1)	
14	TYPE OF REPORTING PERSON  PN	

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	RiverVest Venture Partners III (Ohio), LLC	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS	
	AF	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)	
	<input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION	
	Delaware, USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER
		0
	8	SHARED VOTING POWER
		73,199(2)
	9	SOLE DISPOSITIVE POWER
		0
	10	SHARED DISPOSITIVE POWER
		73,199(2)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON	
	73,199(2)	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES	
	<input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)	
	0.3%(1)	
14	TYPE OF REPORTING PERSON	
	OO	

- (2) Represents 73,199 shares of Common Stock owned by RiverVest Venture Fund III (Ohio), L.P., a Delaware limited partnership ("RiverVest III (Ohio)"). RiverVest Venture Partners III (Ohio), LLC, a Delaware limited liability company ("RiverVest Partners III (Ohio)"), is the general partner of RiverVest III (Ohio).

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	RiverVest Venture Partners III, L.P.	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS	
	AF	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)	
	<input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION	
	Delaware, USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER
		0
	8	SHARED VOTING POWER
		1,452,376(3)
	9	SOLE DISPOSITIVE POWER
		0
	10	SHARED DISPOSITIVE POWER
		1,452,376(3)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON	
	1,452,376(3)	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES	
	<input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)	
	6.3%(1)	
14	TYPE OF REPORTING PERSON	
	PN	

- (3) Represents 1,379,177 shares of Common Stock owned by RiverVest Venture Fund III, L.P., a Delaware limited partnership ("RiverVest III"), and 73,199 shares of Common Stock owned by RiverVest III (Ohio). RiverVest Venture Partners III, L.P., a Delaware limited partnership ("RiverVest Partners III"), is the general partner of RiverVest III and the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio).

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	RiverVest Venture Partners III, LLC	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS	
	AF	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)	
	<input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION	
	Delaware, USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER
		0
	8	SHARED VOTING POWER
		1,452,376(4)
	9	SOLE DISPOSITIVE POWER
		0
	10	SHARED DISPOSITIVE POWER
		1,452,376(4)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON	
	1,452,376(4)	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES	
	<input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)	
	6.3%(1)	
14	TYPE OF REPORTING PERSON	
	OO	

- (4) Represents 1,379,177 shares of Common Stock owned by RiverVest Venture Fund III, L.P., a Delaware limited partnership ("RiverVest III"), and 73,199 shares of Common Stock owned by RiverVest III (Ohio). RiverVest Venture Partners III, L.P., a Delaware limited partnership ("RiverVest Partners III"), is the general partner of RiverVest III and the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio).

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	RiverVest Venture Fund IV, L.P.	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS  WC	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)  <input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION  Delaware, USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER  0
	8	SHARED VOTING POWER  695,905
	9	SOLE DISPOSITIVE POWER  0
	10	SHARED DISPOSITIVE POWER  695,905
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON  695,905	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES  <input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)  3.0%(1)	
14	TYPE OF REPORTING PERSON  PN	

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	RiverVest Venture Partners IV, L.P.	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS  AF	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)  <input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION  Delaware, USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER  0
	8	SHARED VOTING POWER  695,905 <sup>(5)</sup>
	9	SOLE DISPOSITIVE POWER  0
	10	SHARED DISPOSITIVE POWER  695,905 <sup>(5)</sup>
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON  695,905 <sup>(5)</sup>	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES  <input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)  3.0% <sup>(1)</sup>	
14	TYPE OF REPORTING PERSON  PN	

- (5) Represents 695,905 shares of Common Stock owned by RiverVest Venture Fund IV, L.P., a Delaware limited partnership ("RiverVest IV"). RiverVest Venture Partners IV, L.P., a Delaware limited partnership ("RiverVest Partners IV"), is the general partner of RiverVest IV.



1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	RiverVest Venture Partners IV, LLC	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS	
	AF	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)	
	<input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION	
	Delaware, USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER
		0
	8	SHARED VOTING POWER
		695,905(6)
	9	SOLE DISPOSITIVE POWER
		0
	10	SHARED DISPOSITIVE POWER
		695,905(6)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON	
	695,905(6)	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES	
	<input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)	
	3.0%(1)	
14	TYPE OF REPORTING PERSON	
	OO	

(6) Represents 695,905 shares of Common Stock owned by RiverVest IV. RiverVest Venture Partners IV, LLC, a Delaware limited liability company, is the general partner of RiverVest Partners IV, which is the general partner of RiverVest IV.

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	John P. McKearn, Ph.D.	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS  AF	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)  <input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION  USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER  0
	8	SHARED VOTING POWER  2,148,281(7)
	9	SOLE DISPOSITIVE POWER  0
	10	SHARED DISPOSITIVE POWER  2,148,281(7)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON  2,148,281(7)	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES  <input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)  9.3%(1)	
14	TYPE OF REPORTING PERSON  IN	

(7) Includes 1,379,177 shares of Common Stock owned by RiverVest III, 73,199 shares of Common Stock owned by RiverVest III (Ohio), and 695,905 shares of Common Stock owned by RiverVest IV.

Dr. McKearn is a member of RiverVest Venture Partners III, LLC, which is the general partner of RiverVest Partners III. RiverVest Partners III is (a) the general partner of RiverVest III and (b) the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio).

Dr. McKearn is a member of RiverVest Venture Partners IV, LLC, which is the general partner of RiverVest Partners IV. RiverVest Partners IV is the general partner of RiverVest IV.

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	Jay Schmelter	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS	
	AF	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)	
	<input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION	
	USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER
		0
	8	SHARED VOTING POWER
		2,148,281 <sup>(8)</sup>
	9	SOLE DISPOSITIVE POWER
		0
	10	SHARED DISPOSITIVE POWER
		2,148,281 <sup>(8)</sup>
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON	
	2,148,281 <sup>(8)</sup>	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES	
	<input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)	
	9.3% <sup>(1)</sup>	
14	TYPE OF REPORTING PERSON	
	IN	

(8) Includes 1,379,177 shares of Common Stock owned by RiverVest III, 73,199 shares of Common Stock owned by RiverVest III (Ohio), and 695,905 shares of Common Stock owned by RiverVest IV.

Mr. Schmelter is a member of RiverVest Venture Partners III, LLC, which is the general partner of RiverVest Partners III. RiverVest Partners III is (a) the general partner of RiverVest III and (b) the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio).

Mr. Schmelter is a member of RiverVest Venture Partners IV, LLC, which is the general partner of RiverVest Partners IV. RiverVest Partners IV is the general partner of RiverVest IV.

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	Thomas C. Melzer	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS  AF	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)  <input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION  USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER  0
	8	SHARED VOTING POWER  1,452,376(9)
	9	SOLE DISPOSITIVE POWER  0
	10	SHARED DISPOSITIVE POWER  1,452,376(9)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON  1,452,376(9)	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES  <input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)  6.3%(1)	
14	TYPE OF REPORTING PERSON  IN	

(9) Includes 1,379,177 shares of Common Stock owned by RiverVest III and 73,199 shares of Common Stock owned by RiverVest III (Ohio).

Mr. Melzer is a member of RiverVest Venture Partners III, LLC, which is the general partner of RiverVest Partners III. RiverVest Partners III is (a) the general partner of RiverVest III and (b) the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio).

1	NAME OF REPORTING PERSON I.R.S. IDENTIFICATION NO. (ENTITIES ONLY)	
	Niall O'Donnell, Ph.D.	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS	
	AF	
5	CHECK IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) OR 2(e)	
	<input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION	
	USA	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER
		0
	8	SHARED VOTING POWER
		695,905(10)
	9	SOLE DISPOSITIVE POWER
		0
	10	SHARED DISPOSITIVE POWER
		695,905(10)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON	
	695,905(10)	
12	CHECK IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES	
	<input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)	
	3.0%(1)	
14	TYPE OF REPORTING PERSON	
	IN	

(10) Represents 695,905 shares of Common Stock owned by RiverVest IV.

Mr. O'Donnell is a member of RiverVest Venture Partners IV, LLC, which is the general partner of RiverVest Partners IV. RiverVest Partners IV is the general partner of RiverVest IV.

**Item 1. Security and Issuer.**

The title and class of securities to which this Statement on Schedule 13D (this “Statement”) relates is the common stock, par value \$0.001 per share (the “Common Stock”), of Spruce Biosciences, Inc., a Delaware corporation (the “Issuer”). The address of the principal executive offices of the Issuer is 2001 Junipero Serra Boulevard, Suite 640, Daly City, California 94014. Information given in response to each item shall be deemed incorporated by reference in all other items as applicable.

**Item 2. Identity and Background.**

- (a) Name of Person Filing (each a “Reporting Person” and collectively, the “Reporting Person”)

RiverVest Venture Fund III, L.P., a Delaware limited partnership  
RiverVest Venture Fund III (Ohio), L.P., a Delaware limited partnership  
RiverVest Venture Partners III (Ohio), LLC, a Delaware limited liability company  
RiverVest Venture Partners III, L.P., a Delaware limited partnership  
RiverVest Venture Partners III, LLC, a Delaware limited liability company  
RiverVest Venture Fund IV, L.P., a Delaware limited partnership  
RiverVest Venture Partners IV, L.P., a Delaware limited partnership  
RiverVest Venture Partners IV, LLC, a Delaware limited liability company  
John P. McKearn, Ph.D.  
Jay Schmelter  
Thomas C. Melzer  
Niall O’Donnell, Ph.D.

Each of RiverVest III, RiverVest III (Ohio), and RiverVest IV are referred to herein as the “Control Entities.” Each of RiverVest Partners III (Ohio), RiverVest Partners III, RiverVest Venture Partners III, LLC, RiverVest Partners IV and RiverVest Venture Partners IV, LLC are referred to herein as the “Managing Entities.” Messers. McKearn, Schmelter, Melzer and O’Donnell are referred to herein as the “Managers.”

- (b) Residence or Business Address

101 S. Hanley Road, Suite 1850, St. Louis, MO 63105.

- (c) Present Principal Occupation or Employment

The principal business of each of the Control Entities is making venture capital investments. The principal business of each of the Managing Entities is acting as the general partner or member (directly or indirectly) of each of the Control Entities. The principal business of each of the Managers is managing one or more of the Managing Entities and a number of affiliated partnerships and other entities with similar businesses.

- (d) During the last five years, none of the Reporting Persons has been convicted in a criminal proceeding (excluding traffic violations or similar misdemeanors).

- (e) During the last five years, none of the Reporting Persons has been named as a party to a civil proceeding of a judicial or administrative body of competent jurisdiction and as a result of such proceeding was or is subject to a judgment, decree or final order enjoining future violations of, or prohibiting or mandating activities subject to, federal or state securities laws or finding any violation with respect to such laws.

- (f) Each of the Reporting Persons who is a natural person is a citizen of the United States of America.

**Item 3. Source and Amount of Funds or Other Consideration.**

Prior to the Issuer's initial public offering ("IPO"), the Control Entities acquired the following securities of the Issuer:

- In May 2016, (i) RiverVest III purchased 4,748,000 shares of Series A convertible preferred stock of the Issuer for \$1.00 per share and an aggregate purchase price of approximately \$4.7 million; and (ii) RiverVest III (Ohio) purchased 252,000 shares of Series A convertible preferred stock of the Issuer for \$1.00 per share and an aggregate purchase price of approximately \$0.3 million. The purchase price for these shares was paid by RiverVest III and RiverVest III (Ohio) from their working capital.
- In February 2019, (i) RiverVest III purchased 1,899,200 shares of Series A convertible preferred stock of the Issuer for \$1.00 per share and an aggregate purchase price of approximately \$1.9 million; and (ii) RiverVest III (Ohio) purchased 100,800 shares of Series A convertible preferred stock of the Issuer for \$1.00 per share and an aggregate purchase price of approximately \$0.1 million. The purchase price for these shares was paid by RiverVest III and RiverVest III (Ohio) from their working capital.
- In February 2020, (i) RiverVest III purchased 1,187,000 shares of Series B convertible preferred stock of the Issuer for \$1.20 per share and an aggregate purchase price of approximately \$1.4 million; (ii) RiverVest III (Ohio) purchased 63,000 shares of Series B convertible preferred stock of the Issuer for \$1.20 per share and an aggregate purchase price of approximately \$76,000; and (iii) RiverVest IV purchased 1,458,333 shares of Series B convertible preferred stock of the Issuer for \$1.20 per share and an aggregate purchase price of approximately \$1.7 million. The purchase price for these shares was paid by RiverVest III, RiverVest III (Ohio) and RiverVest IV from their working capital.
- In August 2020, (i) RiverVest III purchased 1,187,000 shares of Series B convertible preferred stock of the Issuer for \$1.20 per share and an aggregate purchase price of approximately \$1.4 million; (ii) RiverVest III (Ohio) purchased 63,000 shares of Series B convertible preferred stock of the Issuer for \$1.20 per share and an aggregate purchase price of approximately \$76,000; and (iii) RiverVest IV purchased 1,458,333 shares of Series B convertible preferred stock of the Issuer for \$1.20 per share and an aggregate purchase price of approximately \$1.7 million. The purchase price for these shares was paid by RiverVest III, RiverVest III (Ohio) and RiverVest IV from their working capital.
- On October 2, 2020, the Issuer effected a 1-for-6.541 reverse stock split of its Common Stock. Following this reverse stock split, the conversion price of RiverVest III, RiverVest III (Ohio) and RiverVest IV's shares of Series A convertible preferred stock and Series B convertible preferred stock was adjusted so that each share of convertible preferred stock was convertible into Common Stock on a 6.541-for-1 basis at any time at the shareholder's election and automatically upon the closing of the IPO.

On October 14, 2020, the closing date of the IPO:

- RiverVest III acquired an aggregate of 1,379,177 shares of Common Stock, RiverVest III (Ohio) acquired an aggregate of 73,199 shares of Common Stock, and RiverVest IV acquired an aggregate of 445,905 shares of Common Stock, in each case upon the automatic conversion of the convertible preferred stock that occurred upon the closing of the IPO; and

- RiverVest IV purchased 250,000 shares of Common Stock from the underwriters (the “IPO Shares”) at \$15.00 per share for an aggregate purchase price of \$3.75 million pursuant to the provisions of the Underwriting Agreement among the Issuer and the several underwriters for the IPO. The purchase price of the IPO Shares was paid by RiverVest IV from its working capital.
- Following these purchases in the IPO, RiverVest III held a total of 1,379,177 shares of Common Stock, (ii) RiverVest III (Ohio) held a total of 73,199 shares of Common Stock, and (iii) RiverVest IV held a total of 695,905 shares of Common Stock.

**Item 4. Purpose of the Transaction.**

The Reporting Persons purchased the shares of Series A convertible preferred stock, Series B convertible preferred stock and Common Stock described above for investment purposes. None of the Reporting Persons has any present plans which relate to or would result in:

- (a) The acquisition by any person of additional securities of the Issuer, or the disposition of securities of the Issuer;
- (b) An extraordinary corporate transaction, such as a merger, reorganization or liquidation, involving the Issuer or any of its subsidiaries;
- (c) A sale or transfer of a material amount of assets of the Issuer or any of its subsidiaries;
- (d) Any change in the present board of directors or management of the Issuer, including any plans or proposals to change the number or term of directors or to fill any existing vacancies on the board;
- (e) Any material change in the present capitalization or dividend policy of the Issuer;
- (f) Any other material change in the Issuer’s business or corporate structure;
- (g) Changes in the Issuer’s charter, bylaws or instruments corresponding thereto or other actions which may impede the acquisition of control of the Issuer by any person;
- (h) Causing a class of securities of the Issuer to be delisted from a national securities exchange or to cease to be authorized to be quoted in an inter-dealer quotation system of a registered national securities association;
- (i) A class of equity securities of the Issuer becoming eligible for termination of registration pursuant to Section 12(g)(4) of the Securities Exchange Act of 1934, as amended (the “Act”); or
- (j) Any action similar to any of those enumerated above.

However, each of the Reporting Persons reserves the right to propose or participate in future transactions which may result in one or more of such actions, including but not limited to, an extraordinary corporate transaction, such as a merger, reorganization or liquidation, sale of a material amount of assets of the Issuer or its subsidiaries, or other transactions which might have the effect of causing the Common Stock to become eligible for termination of registration under Section 12(g) of the Act. The Reporting Persons also retain the right to change their investment intent at any time, to acquire additional shares of Common Stock or other securities of the Issuer from time to time, or to sell or otherwise dispose of all or part of the Common Stock beneficially owned by them (or any shares of Common Stock into which such securities are converted) in any manner permitted by law. The Reporting Persons may engage from time to time in ordinary course transactions with financial institutions with respect to the securities described herein.



**Item 5. Interest in Securities of the Issuer.**

(a) and (b)

<b>Entity or Individual</b>	<b>Shares Held Directly</b>	<b>Sole Voting Power</b>	<b>Shared Voting Power</b>	<b>Sole Dispositive Power</b>	<b>Shared Dispositive Power</b>	<b>Beneficial Ownership</b>	<b>Percentage of Class(*)</b>
RiverVest Venture Fund III, L.P.	1,379,177	0	1,379,177	0	1,379,177	1,379,177	6.0%
RiverVest Venture Fund III (Ohio), L.P.	73,199	0	73,199	0	73,199	73,199	0.3%
RiverVest Venture Partners III (Ohio), LLC <sup>(1)</sup>	0	0	73,199	0	73,199	73,199	0.3%
RiverVest Venture Partners III, L.P. <sup>(2)</sup>	0	0	1,452,376	0	1,452,376	1,452,376	6.3%
RiverVest Venture Partners III, LLC <sup>(3)</sup>	0	0	1,452,376	0	1,452,376	1,452,376	6.3%
RiverVest Venture Fund IV, L.P.	695,905	0	695,905	0	695,905	695,905	3.0%
RiverVest Venture Partners IV, L.P. <sup>(4)</sup>	0	0	695,905	0	695,905	695,905	3.0%
RiverVest Venture Partners IV, LLC <sup>(5)</sup>	0	0	695,905	0	695,905	695,905	3.0%
John P. McKearn, Ph.D. <sup>(6)</sup>	0	0	2,148,281	0	2,148,281	2,148,281	9.3%
Jay Schmelter <sup>(7)</sup>	0	0	2,148,281	0	2,148,281	2,148,281	9.3%
Thomas C. Melzer <sup>(8)</sup>	0	0	1,452,376	0	1,452,376	1,452,376	6.3%
Niall O'Donnell <sup>(9)</sup>	0	0	695,905	0	695,905	695,905	3.0%

(\*) Based on the 23,163,593 outstanding shares of Common Stock reported by the Issuer to be outstanding immediately after the IPO on the Issuer's prospectus filed under Rule 424(b)(4), filed with the SEC on October 10, 2020, after giving effect to the exercise in full of the underwriters' over-allotment option as reported by the Issuer on October 14, 2020.

- (1) RiverVest Partners III (Ohio) is the general partner of RiverVest III (Ohio), and as a result, may be deemed to beneficially own the 73,199 shares of Common Stock owned by RiverVest III (Ohio).
- (2) RiverVest Partners III is the general partner of RiverVest III and the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio), and as a result, may be deemed to beneficially own the 1,379,177 shares of Common Stock owned by RiverVest III and the 73,199 shares of Common Stock owned by RiverVest III (Ohio).
- (3) RiverVest Venture Partners III, LLC is the general partner of RiverVest Partners III, which is (a) the general partner of RiverVest III and (b) the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio), and as a result, may be deemed to beneficially own the 1,379,177 shares of Common Stock owned by RiverVest III and the 73,199 shares of Common Stock owned by RiverVest III (Ohio).

- (4) RiverVest Partners IV is the general partner of RiverVest IV, and as a result, may be deemed to beneficially own the 695,905 shares of Common Stock owned by RiverVest IV.
- (5) RiverVest Venture Partners IV, LLC is the general partner of RiverVest Partners IV, which is the general partner of RiverVest IV, and as a result, may be deemed to beneficially own the 695,905 shares of Common Stock owned by RiverVest IV.
- (6) Dr. McKearn is a member of RiverVest Venture Partners III, LLC, which is the general partner of RiverVest Partners III. RiverVest Partners III is (a) the general partner of RiverVest III and (b) the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio). As a result, Dr. McKearn may be deemed to beneficially own the 1,379,177 shares of Common Stock owned by RiverVest III and the 73,199 shares of Common Stock owned by RiverVest III (Ohio).  
Dr. McKearn is a member of RiverVest Venture Partners IV, LLC, which is the general partner of RiverVest Partners IV. RiverVest Partners IV is the general partner of RiverVest IV. As a result, Dr. McKearn may be deemed to beneficially own the 695,905 shares of Common Stock owned by RiverVest IV.
- (7) Mr. Schmelter is a member of RiverVest Venture Partners III, LLC, which is the general partner of RiverVest Partners III. RiverVest Partners III is (a) the general partner of RiverVest III and (b) the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio). As a result, Mr. Schmelter may be deemed to beneficially own the 1,379,177 shares of Common Stock owned by RiverVest III and the 73,199 shares of Common Stock owned by RiverVest III (Ohio).  
Mr. Schmelter is a member of RiverVest Venture Partners IV, LLC, which is the general partner of RiverVest Partners IV. RiverVest Partners IV is the general partner of RiverVest IV. As a result, Dr. McKearn may be deemed to beneficially own the 695,905 shares of Common Stock owned by RiverVest IV.
- (8) Mr. Melzer is a member of RiverVest Venture Partners III, LLC, which is the general partner of RiverVest Partners III. RiverVest Partners III is (a) the general partner of RiverVest III and (b) the sole member of RiverVest Partners III (Ohio), which is the general partner of RiverVest III (Ohio). As a result, Mr. Melzer may be deemed to beneficially own the 1,379,177 shares of Common Stock owned by RiverVest III and the 73,199 shares of Common Stock owned by RiverVest III (Ohio).
- (9) Mr. O'Donnell is a member of RiverVest Venture Partners IV, LLC, which is the general partner of RiverVest Partners IV. RiverVest Partners IV is the general partner of RiverVest IV. As a result, Mr. O'Donnell may be deemed to beneficially own the 695,905 shares of Common Stock owned by RiverVest IV.

By virtue of the relationships described herein, the Reporting Persons may be deemed to constitute a "group" for purposes of Section 13(d)(3) of the Act. The filing of this Statement shall not be construed as an admission that the Reporting Persons are a group, or have agreed to act as a group. Each Reporting Person expressly disclaims beneficial ownership of the securities reported herein, except to the extent such Reporting Person actually exercises voting or dispositive power with respect to such securities.

(c) Except as set forth herein, none of the Reporting Persons has effected any transactions in shares of the Issuer's Common Stock during the last 60 days.

(d) No other person is known to have the right to receive or the power to direct the receipt of dividends from, or any proceeds from the sale of, the shares of Common Stock beneficially owned by any of the Reporting Persons.

(e) Not applicable.

**Item 6. Contracts, Arrangements, Understandings or Relationships With Respect to Securities of the Issuer.****Registration Rights**

Pursuant to the terms of an Amended and Restated Investors' Rights Agreement with the Issuer, dated February 19, 2020, certain holders of the Issuer's common stock, including RiverVest III, RiverVest III (Ohio) and RiverVest IV are entitled to rights with respect to the registration of their shares of Common Stock (the "registerable securities") under the Securities Act of 1933, as amended. Beginning 180 days after the effective date of the registration statement for the IPO, the holders of a majority of the then-outstanding registrable securities have demand rights to request the registration on Form S-1 of their registrable securities, provided the aggregate offering price is at least \$5 million. The stockholders may only require two registration statements on Form S-1. In addition, the holders of the then-outstanding registrable securities can request that the Issuer register all or part of their shares on Form S-3 if the Issuer is eligible to file a registration statement on Form S-3 and if the anticipated aggregate offering price, net of selling expenses, is at least \$1 million. The stockholders may only require two registration statements on Form S-3 in a 12-month period. If the Issuer registers any of its securities for public sale, holders of then-outstanding registrable securities or their permitted transferees will have the right to include their registrable securities in such registration statement, subject to certain exclusions. All of these registration rights will expire, with respect to any particular holder, on the earliest to occur of (a) five years following the completion of the Issuer's IPO, (b) at such time that all of the holder's registrable securities can be sold without limitation in any three-month period without registration in compliance with Rule 144 or a similar exemption or (c) the closing of a deemed liquidation event, as defined in the Issuer's certificate of incorporation.

The foregoing description of the Amended and Restated Investors' Rights Agreement is a summary only and is qualified in its entirety by the actual terms of the agreement, which is incorporated herein by reference. See Item 7 "Material to be Filed as Exhibits."

**Lock-up Agreement**

The Issuer, its directors and officers, and the holders of substantially all of its outstanding securities, including RiverVest III, RiverVest III (Ohio) and RiverVest IV, entered into lock-up agreements, pursuant to which they agreed with the underwriters that, for a period of 180 days following the date of the underwriting agreement in connection with the IPO, subject to certain exceptions, they will not, directly or indirectly, offer, sell, contract to sell, pledge, grant any option to purchase, make any short sale or otherwise dispose of or hedge any of the Issuer's shares of Common Stock, or any options or warrants to purchase any shares of its Common Stock, or any securities convertible into, or exchangeable for or that represent the right to receive shares of its Common Stock.

The foregoing description of the lockup agreements is a summary only and is qualified in its entirety by reference to the Form of Lock-up Agreement, which is incorporated herein by reference. See Item 7 "Material to be Filed as Exhibits."

**Item 7. Material to be Filed as Exhibits.**

Exhibit A: Joint Filing Agreement, dated October 23, 2020, by and among RiverVest Venture Fund III, L.P., RiverVest Venture Fund III (Ohio), L.P., RiverVest Venture Partners III (Ohio), LLC, RiverVest Venture Partners III, L.P., RiverVest Venture Partners III, LLC, RiverVest Venture Fund IV, L.P., RiverVest Venture Partners IV, L.P., RiverVest Venture Partners IV, LLC, John P. McKearn, Jay Schmelter, Thomas C. Melzer and Niall O'Donnell.

Exhibit B: Amended and Restated Investors' Rights Agreement, dated as of February 19, 2020 (incorporated by reference to Exhibit 4.2 to the Issuer's Registration Statement on Form S-1 filed with the SEC on September 18, 2020).

Exhibit C: Form of Lock-up Agreement (incorporated by reference to Exhibit I of Exhibit 1.1 to the Issuer's Amendment to Registration Statement on Form S-1/A (Registration No. 333-248924), filed with the SEC on October 5, 2020.

**SIGNATURES**

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

October 23, 2020

**RiverVest Venture Fund III, L.P.**

By: RiverVest Venture Partners III, L.P.,  
its general partner  
By: RiverVest Venture Partners III, LLC,  
its general partner

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

**RiverVest Venture Partners III (Ohio), LLC**

By: RiverVest Venture Partners III, L.P.,  
its sole member  
By: RiverVest Venture Partners III, LLC,  
its general partner

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

**RiverVest Venture Partners III, LLC**

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

**RiverVest Venture Partners IV, L.P.**

By: RiverVest Venture Partners IV, LLC,  
its general partner

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

/s/ John P. McKearn, Ph.D  
John P. McKearn, Ph.D.

**RiverVest Venture Fund III (Ohio), L.P.**

By: RiverVest Venture Partners III (Ohio), LLC,  
its general partner  
By: RiverVest Venture Partners III, L.P.,  
its sole member  
By: RiverVest Venture Partners III, LLC,  
its general partner

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

**RiverVest Venture Partners III, L.P.**

By: RiverVest Venture Partners III, LLC,  
its general partner

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

**RiverVest Venture Fund IV, L.P.**

By: RiverVest Venture Partners IV, L.P.,  
its general partner  
By: RiverVest Venture Partners IV, LLC,  
its general partner

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

**RiverVest Venture Partners IV, LLC**

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

/s/ Jay Schmelter  
Jay Schmelter

[Signature Page of Schedule 13D]

/s/ Thomas C. Melzer

/s/ Niall O'Donnell, Ph.D.

Thomas C. Melzer

Niall O'Donnell, Ph.D.

[Signature Page of Schedule 13D]

JOINT FILING AGREEMENT  
PURSUANT TO RULE 13d-1(k)

In accordance with Rule 13d-1(k) under the Securities Exchange Act of 1934, as amended, the undersigned persons agree and consent to the joint filing on their behalf of the Statement on Schedule 13D, including any amendments thereto, in connection with shares of common stock of Spruce Biosciences, Inc., and that this agreement shall be included as an Exhibit to Schedule 13D. Each of the undersigned agrees to be responsible for the timely filing of the Schedule 13D and any amendments thereto, and for the completeness and accuracy of the information concerning itself contained in the Schedule 13D and any amendments thereto.

IN WITNESS WHEREOF, the parties have executed this Joint Filing Agreement on October 23, 2020.

**RiverVest Venture Fund III, L.P.**

By: RiverVest Venture Partners III, L.P.,  
its general partner

By: RiverVest Venture Partners III, LLC,  
its general partner

By: /s/ Jay Schmelter

Name: Jay Schmelter

Title: Member

**RiverVest Venture Fund III (Ohio), L.P.**

By: RiverVest Venture Partners III (Ohio), LLC,  
its general partner

By: RiverVest Venture Partners III, L.P.,  
its sole member

By: RiverVest Venture Partners III, LLC,  
its general partner

By: /s/ Jay Schmelter

Name: Jay Schmelter

Title: Member

**RiverVest Venture Partners III (Ohio), LLC**

By: RiverVest Venture Partners III, L.P.,  
its sole member

By: RiverVest Venture Partners III, LLC,  
its general partner

By: /s/ Jay Schmelter

Name: Jay Schmelter

Title: Member

**RiverVest Venture Partners III, L.P.**

By: RiverVest Venture Partners III, LLC,  
its general partner

By: /s/ Jay Schmelter

Name: Jay Schmelter

Title: Member

**RiverVest Venture Partners III, LLC**

By: /s/ Jay Schmelter

Name: Jay Schmelter

Title: Member

**RiverVest Venture Fund IV, L.P.**

By: RiverVest Venture Partners IV, L.P.,  
its general partner

By: RiverVest Venture Partners IV, LLC,  
its general partner

By: /s/ Jay Schmelter

Name: Jay Schmelter

Title: Member

[Signature Page to Joint Filing Agreement]

**RiverVest Venture Partners IV, L.P.**

By: RiverVest Venture Partners IV, LLC,  
its general partner

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

/s/ John P. McKearn, Ph.D.  
John P. McKearn, Ph.D.

/s/ Thomas C. Melzer  
Thomas C. Melzer

**RiverVest Venture Partners IV, LLC**

By: /s/ Jay Schmelter  
Name: Jay Schmelter  
Title: Member

/s/ Jay Schmelter  
Jay Schmelter

/s/ Niall O'Donnell, Ph.D.  
Niall O'Donnell, Ph.D.

[Signature Page to Joint Filing Agreement]