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

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**FORM S-8**  
**REGISTRATION STATEMENT**  
*UNDER*  
**THE SECURITIES ACT OF 1933**

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**Upstream Bio, Inc.**  
(Exact name of registrant as specified in its charter)

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**Delaware**  
(State or other jurisdiction of  
incorporation or organization)

**38-4187694**  
(I.R.S. Employer  
Identification No.)

**Upstream Bio, Inc.**  
**890 Winter Street, Suite 200**  
**Waltham, MA 02451**  
**(781) 208-2466**  
(Address, including zip code and telephone number, including area code, of registrant's principal executive offices)

**Upstream Bio, Inc. 2021 Stock Option and Grant Plan**  
**Upstream Bio, Inc. 2024 Stock Option and Incentive Plan**  
**Upstream Bio, Inc. 2024 Employee Stock Purchase Plan**  
(Full title of the plans)

**E. Rand Sutherland, M.D., M.P.H.**  
**Chief Executive Officer**  
**890 Winter Street, Suite 200**  
**Waltham, MA 02451**  
**(781) 208-2466**  
(Name, address, including zip code, and telephone number, including area code, of agent for service)

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*Copies to:*

**Gabriela Morales-Rivera**  
**William D. Collins**  
**Kathryn W. Clerici**  
**Goodwin Procter LLP**  
**100 Northern Avenue**  
**Boston, Massachusetts 02210**  
**(617) 570-1000**

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Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	<input type="checkbox"/>	Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input checked="" type="checkbox"/>	Smaller reporting company	<input checked="" type="checkbox"/>
		Emerging growth company	<input checked="" type="checkbox"/>

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act.

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**Part I**  
**INFORMATION REQUIRED IN THE SECTION 10(a) PROSPECTUS**

**Item 1. Plan Information.**

The documents containing the information specified in this Item 1 will be sent or given to participants as specified by Rule 428(b)(1) under the Securities Act of 1933, as amended (the “Securities Act”). In accordance with the rules and regulations of the U.S. Securities and Exchange Commission (the “Commission”) and the instructions to Form S-8, such documents are not being filed with the Commission either as part of this Registration Statement on Form S-8 (this “Registration Statement”) or as prospectuses or prospectus supplements pursuant to Rule 424 under the Securities Act.

**Item 2. Registrant Information and Employee Plan Annual Information.**

The documents containing the information specified in this Item 2 will be sent or given to participants as specified by Rule 428(b)(1) under the Securities Act. In accordance with the rules and regulations of the Commission and the instructions to Form S-8, such documents are not being filed with the Commission either as part of this Registration Statement or as prospectuses or prospectus supplements pursuant to Rule 424 under the Securities Act.

**Part II**  
**INFORMATION REQUIRED IN THE REGISTRATION STATEMENT**

**Item 3. Incorporation of Documents by Reference.**

The registrant hereby incorporates by reference into this Registration Statement the following documents filed with the SEC:

- (a) Amendment No. 1 to the registrant’s Registration Statement on [Form S-1](#) filed with the SEC on October 7, 2024 (File No. 333-282197), which contains the registrant’s audited financial statements for the latest fiscal year for which such statements have been filed;
- (b) The prospectus filed by the registrant with the SEC pursuant to [Rule 424\(b\)](#) under the Securities Act, on October 11, 2024, relating to the Registration Statement on Form S-1, as amended (File No. 333-282197); and
- (b) The description of the registrant’s common stock contained in the registrant’s Registration Statement on [Form 8-A](#) (File No. 001-42366), filed by the registrant with the SEC under Section 12(b) of the Securities Exchange Act of 1934, as amended (the “Exchange Act”), on October 8, 2024, including any amendments or reports filed for the purpose of updating such description.

All documents that the registrant subsequently files pursuant to Sections 13(a), 13(c), 14 and 15(d) of the Exchange Act prior to the filing of a post-effective amendment to this registration statement which indicates that all of the shares of common stock offered have been sold or which deregisters all of such shares then remaining unsold, shall be deemed to be incorporated by reference in this registration statement and to be a part hereof from the date of the filing of such documents.

Any statement contained in a document incorporated or deemed to be incorporated by reference herein shall be deemed to be modified or superseded to the extent that a statement contained herein or in any other subsequently filed document which also is or is deemed to be incorporated by reference herein modifies or supersedes such statement. Any such statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this registration statement.

Under no circumstances will any information filed under current items 2.02 or 7.01 of Form 8-K be deemed incorporated herein by reference unless such Form 8-K expressly provides to the contrary.

**Item 4. Description of Securities.**

Not applicable.

## **Item 5. Interests of Named Experts and Counsel.**

Not applicable.

## **Item 6. Indemnification of Directors and Officers.**

Section 145 of the Delaware General Corporation Law (“DGCL”) authorizes a corporation to indemnify its directors and officers against liabilities arising out of actions, suits and proceedings to which they are made or threatened to be made a party by reason of the fact that they have served or are currently serving as a director or officer to a corporation. The indemnity may cover expenses (including attorneys’ fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by the director or officer in connection with any such action, suit or proceeding. Section 145 permits corporations to pay expenses (including attorneys’ fees) incurred by directors and officers in advance of the final disposition of such action, suit or proceeding. In addition, Section 145 provides that a corporation has the power to purchase and maintain insurance on behalf of its directors and officers against any liability asserted against them and incurred by them in their capacity as a director or officer, or arising out of their status as such, whether or not the corporation would have the power to indemnify the director or officer against such liability under Section 145.

The registrant has adopted provisions in its third amended and restated certificate of incorporation, which will become effective immediately prior to the completion of its initial public offering, and the amended and restated bylaws, which became effective upon the effectiveness of the Registration Statement on Form S-1 for its initial public offering, that limit or eliminate the personal liability of the registrant’s directors and officers to the fullest extent permitted by the DGCL, as it now exists or may in the future be amended. Consequently, the registrant’s directors and officers will not be personally liable to it or its stockholders for monetary damages or breach of fiduciary duty as directors or officers, except for liability for:

- any breach of their duty of loyalty to the registrant or its stockholders;
- any act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- for the registrant’s directors, any unlawful payments related to dividends or unlawful stock purchases, redemptions or other distributions;
- any transaction from which they derived an improper personal benefit; or
- for the registrant’s officers, any derivative action by or in the right of the corporation.

These limitations of liability do not alter director and officer liability under the federal securities laws and do not affect the availability of equitable remedies such as an injunction or rescission.

In addition, the registrant’s amended and restated bylaws provide that:

- it will indemnify our directors, officers and, in the discretion of its board of directors, certain employees to the fullest extent permitted by the DGCL, as it now exists or may in the future be amended; and
- it will advance reasonable expenses, including attorneys’ fees, to its directors and, in the discretion of our board of directors, to its officers and certain employees, in connection with legal proceedings relating to their service for or on behalf of the registrant, subject to limited exceptions.

The registrant has entered into indemnification agreements with each of its directors and executive officers. These agreements provide that the registrant will indemnify each of its directors, its executive officers and, at times, their affiliates to the fullest extent permitted by Delaware law. The registrant will advance expenses, including attorneys’ fees (but excluding judgments, fines and settlement amounts), to each indemnified director, executive officer or affiliate in connection with any proceeding in which indemnification is available and the registrant will indemnify its directors and officers for any action or proceeding arising out of that person’s services as a director or officer brought on behalf of the registrant or in furtherance of its rights. Additionally, certain of the registrant’s directors or officers may have certain rights to indemnification, advancement of expenses or insurance provided by their affiliates or other third parties, which indemnification relates to and might apply to the same proceedings arising out of such director’s or officer’s services as a director referenced herein. Nonetheless, the registrant has agreed in the indemnification agreements that its obligations to those same directors or officers are primary and any obligation of such affiliates or other third parties to advance expenses or to provide indemnification for the expenses or liabilities incurred by those directors are secondary.

The registrant also maintains general liability insurance which covers certain liabilities of its directors and officers arising out of claims based on acts or omissions in their capacities as directors or officers, including liabilities under the Securities Act.

#### Item 7. Exemption from Registration Claimed.

Not applicable.

#### Item 8. Exhibits.

##### EXHIBIT INDEX

Exhibit No.	Description
4.1	<a href="#">Form of Third Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.2 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-282197)).</a>
4.2	<a href="#">Form of Second Amended and Restated Bylaws (incorporated by reference to Exhibit 3.4 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-282197)).</a>
4.3	<a href="#">Amended and Restated Investors' Rights Agreement, among the Registrant and certain of its stockholders, dated June 6, 2023 (incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-282197)).</a>
5.1*	<a href="#">Opinion of Goodwin Procter LLP.</a>
23.1*	<a href="#">Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm.</a>
23.2*	<a href="#">Consent of Goodwin Procter LLP (included in Exhibit 5.1).</a>
24.1*	<a href="#">Power of Attorney (included on signature page).</a>
99.1	<a href="#">2021 Stock Option and Grant Plan, as amended, and form of award agreements thereunder (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-282197)).</a>
99.2	<a href="#">Upstream Bio, Inc. 2024 Stock Option and Incentive Plan and form of award agreements thereunder (incorporated by reference to Exhibit 10.2 to the registrant's Registration Statement on Form S-1, as amended (File No. 333-282197)).</a>
99.3	<a href="#">Upstream Bio, Inc. 2024 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-282197)).</a>
107*	<a href="#">Filing Fee Table.</a>

\* Filed herewith.

#### Item 9. Undertakings.

(a) The registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this Registration Statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the Registration Statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the Registration Statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective Registration Statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the Registration Statement or any material change to such information in the Registration Statement;

*provided, however*, that paragraphs (a)(1)(i) and (a)(1)(ii) herein do not apply if the Registration Statement is on Form S-8, and the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to Section 13 or Section 15(d) of the Exchange Act that are incorporated by reference in the Registration Statement;

(2) That, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof; and

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in the Registration Statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(h) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

## SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-8 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Waltham, Massachusetts, on this 11<sup>th</sup> day of October, 2024.

### UPSTREAM BIO, INC.

By: /s/ E. Rand Sutherland

Name: E. Rand Sutherland, M.D., M.P.H.

Title: Chief Executive Officer

## POWER OF ATTORNEY AND SIGNATURES

Each individual whose signature appears below hereby constitutes and appoints each of E. Rand Sutherland, M.D., M.P.H. and Michael Paul Gray, M.B.A. as such person's true and lawful attorney-in-fact and agent with full power of substitution and resubstitution, for such person in such person's name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this Registration Statement on Form S-8, and to file the same, with all exhibits thereto, and all documents in connection therewith, with the Securities and Exchange Commission granting unto each said attorney-in-fact and agent full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as such person might or could do in person, hereby ratifying and confirming all that any said attorney-in-fact and agent, or any substitute or substitutes of any of them, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities and on the date indicated.

Name	Title	Date
<u>/s/ E. Rand Sutherland</u> E. Rand Sutherland, M.D., M.P.H.	Chief Executive Officer and Director <i>(Principal Executive Officer)</i>	October 11, 2024
<u>/s/ Michael Paul Gray</u> Michael Paul Gray, M.B.A.	Chief Financial Officer <i>(Principal Financial Officer and Principal Accounting Officer)</i>	October 11, 2024
<u>/s/ Ronald C. Renaud, Jr.</u> Ronald C. Renaud, Jr., M.B.A.	Director and Chairman	October 11, 2024
<u>/s/ Daniella Beckman</u> Daniella Beckman	Director	October 11, 2024
<u>/s/ Erez Chimovits</u> Erez Chimovits, M.B.A., M.Sc.	Director	October 11, 2024
<u>/s/ H. Edward Fleming, Jr.</u> H. Edward Fleming, Jr., M.D.	Director	October 11, 2024
<u>/s/ Liam Ratcliffe</u> Liam Ratcliffe, M.B.Ch.B., Ph.D., M.B.A.	Director	October 11, 2024
<u>/s/ Marcella Kuhlman Ruddy</u> Marcella Kuhlman Ruddy, M.D., M.S.	Director	October 11, 2024

October 11, 2024

Upstream Bio, Inc.  
890 Winter Street, Suite 200  
Waltham, Massachusetts 02451

Re: Securities Being Registered under Registration Statement on Form S-8

We have acted as counsel to you in connection with your filing of a Registration Statement on Form S-8 (the "Registration Statement") pursuant to the Securities Act of 1933, as amended (the "Securities Act"), on or about the date hereof relating to an aggregate of 9,906,440 shares (the "Shares") of Common Stock, par value \$0.001 per share ("Common Stock"), of Upstream Bio, Inc., a Delaware corporation (the "Company"), that may be issued pursuant to the Company's 2021 Stock Option and Grant Plan, 2024 Stock Option and Incentive Plan and 2024 Employee Stock Purchase Plan (collectively, the "Plans").

We have reviewed such documents and made such examination of law as we have deemed appropriate to give the opinions set forth below. We have relied, without independent verification, on certificates of public officials and, as to matters of fact material to the opinion set forth below, on certificates of officers of the Company.

The opinion set forth below is limited to the Delaware General Corporation Law.

For purposes of the opinion set forth below, we have assumed that no event occurs that causes the number of authorized shares of Common Stock available for issuance by the Company to be less than the number of then unissued Shares.

Based on the foregoing, we are of the opinion that the Shares have been duly authorized and, upon issuance and delivery against payment therefor in accordance with the terms of the Plans, will be validly issued, fully paid and nonassessable.

This opinion letter and the opinion it contains shall be interpreted in accordance with the Core Opinion Principles as published in *74 Business Lawyer* 815 (Summer 2019).

We hereby consent to the inclusion of this opinion as Exhibit 5.1 to the Registration Statement. In giving our consent, we do not admit that we are in the category of persons whose consent is required under Section 7 of the Securities Act or the rules and regulations thereunder.

Very truly yours,

/s/ GOODWIN PROCTER LLP  
GOODWIN PROCTER LLP

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in this Registration Statement on Form S-8 of Upstream Bio, Inc. of our report dated June 12, 2024, except for the effects of the stock split discussed in Note 18 to the consolidated financial statements, as to which the date is October 7, 2024, relating to the financial statements, which appears in Upstream Bio, Inc.'s Amendment No. 1 to the Registration Statement on Form S-1 (No. 333-282197).

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts  
October 11, 2024



**Calculation of Filing Fee Table**

**Form S-8**  
(Form Type)

**Upstream Bio, Inc.**  
(Exact Name of Registrant as Specified in its Charter)

Table 1: Newly Registered Securities

Security Type	Security Class Title	Fee Calculation Rule	Amount to be Registered <sup>(1)</sup>	Proposed Maximum Offering Price Per Share	Maximum Aggregate Offering Price	Fee Rate	Amount of Registration Fee
Equity	Common Stock, \$0.001 par value per share	457(h)	6,237,973 shares <sup>(2)</sup>	\$4.99 <sup>(3)</sup>	\$31,127,485.27	0.00015310	\$4,765.62
Equity	Common Stock, \$0.001 par value per share	457(h) and 457(c)	3,180,000 shares <sup>(4)</sup>	\$17.00 <sup>(5)</sup>	\$54,060,000.00	0.00015310	\$8,276.59
Equity	Common Stock, \$0.001 par value per share	457(h) and 457(c)	488,467 shares <sup>(6)</sup>	\$14.45 <sup>(7)</sup>	\$7,058,348.15	0.00015310	\$1,080.64
<b>Total Offering Amounts</b>					\$92,245,833.42		\$14,122.85
<b>Total Fee Offsets</b>							—
<b>Net Fee Due</b>							\$14,122.85

- (1) Pursuant to Rule 416 under the Securities Act of 1933, as amended (the “Securities Act”), this Registration Statement shall also cover any additional shares of the Registrant’s common stock that become issuable under the Registrant’s 2024 Stock Option and Incentive Plan (the “2024 Plan”), the Registrant’s 2024 Employee Stock Purchase Plan (the “2024 ESPP”) and/or the Registrant’s 2021 Stock Option and Grant Plan (the “2021 Plan”) by reason of any stock dividend, stock split, recapitalization or any other similar transaction effected without the receipt of consideration which results in an increase in the number of our outstanding shares of common stock. Pursuant to Rule 416(c) under the Securities Act, this Registration Statement shall also cover an indeterminate amount of interests to be offered or sold pursuant to the employee benefit plans described herein.
- (2) Represents shares of common stock issuable upon the exercise of outstanding equity awards under the 2021 Plan as of the date of this Registration Statement. No further grants will be made under the 2021 Plan. To the extent outstanding options granted under the 2021 Plan are cancelled, forfeited or otherwise terminated without being exercised and would otherwise have been returned to the share reserve under the 2021 Plan, the number of shares underlying such awards will be available for future grant under the 2024 Plan.

- (3) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(h) of the Securities Act, and based on \$4.99, the weighted average exercise price (rounded to the nearest cent) of the outstanding option awards under the 2021 Plan as of the date of this Registration Statement.
- (4) Represents 124,161 shares of common stock issuable upon the exercise of outstanding stock options under the 2024 Plan, and 3,055,839 shares of common stock reserved for issuance under the 2024 Plan. In addition to the shares registered under the 2024 Plan, to the extent that awards outstanding under the 2021 Plan as of the date of this Registration Statement are cancelled, forfeited, are held back upon exercise or settlement of an award to cover any exercise price, as applicable, or tax withholding, are reacquired by the Registrant prior to vesting, are satisfied without the issuance of stock or are otherwise terminated (other than by exercise) subsequent to the date of this Registration Statement, the shares reserved for issuance pursuant to such awards will become available for issuance under the 2024 Plan. The 2024 Plan provides that an additional number of shares will automatically be added to the shares authorized for issuance under the 2024 Plan on January 1, 2025 and each January 1 thereafter. The number of shares added each year will be equal to the lesser of: (i) five percent (5%) of the number of shares of common stock issued and outstanding on the immediately preceding December 31, or (ii) such lesser number of shares as determined by the Administrator (as such term is defined in the in the 2024 Plan).
- (5) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(h) and 457(c) of the Securities Act, and based on \$17.00, the initial public offering price of the registrant's common stock set forth in the registrant's final prospectus, dated October 10, 2024 relating to its initial public offering. Pursuant to the 2024 Plan, the purchase price of the shares of common stock reserved for issuance thereunder will be the fair market value of a share of common stock as set forth on the cover page for the final prospectus relating to the Registrant's initial public offering.
- (6) Represents shares of common stock reserved for future issuance under the 2024 ESPP. The number of shares of common stock reserved for future issuance under the 2024 ESPP will automatically increase on January 1, 2025 and each January 1 thereafter through January 1, 2034, in an amount equal to the least of: (i) 1,023,984 shares of common stock, (ii) one percent (1%) of the outstanding shares of common stock issued and outstanding on the immediately preceding December 31, or (iii) such number of shares as determined by the Administrator (as such term is defined in the 2024 ESPP).
- (7) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(h) and 457(c) of the Securities Act, and based on 85% of \$17.00, the initial public offering price of the registrant's common stock set forth in the registrant's final prospectus, dated October 10, 2024 relating to its initial public offering. Pursuant to the 2024 ESPP, the purchase price of the shares of common stock reserved for issuance thereunder will be 85% of the fair market value of a share of common stock on the first trading day of the offering period or on the exercise date, whichever is less.