

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-K/A
ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE
SECURITIES EXCHANGE ACT OF 1934
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2000
COMMISSION FILE NUMBER 0-19125

ISIS PHARMACEUTICALS, INC.
(Exact name of Registrant as specified in its charter)

DELAWARE
(State or other jurisdiction of
incorporation or organization)

33-0336973
(IRS Employer Identification No.)

2292 FARADAY AVE., CARLSBAD, CA 92008
(Address of principal executive offices, including zip code)

760-931-9200
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the
Act: None Securities registered pursuant to Section
12(g) of the Act:
COMMON STOCK, \$.001 PAR VALUE

Indicate by check mark whether the Registrant (1) has filed all reports
required to be filed by Section 13 or 15(d) of the Securities and Exchange Act
of 1934 during the preceding 12 months (or for such shorter period that the
Registrant was required to file such reports), and (2) has been subject to such
filing requirements for the past 90 days. Yes X No .

Indicate by check mark if disclosure of delinquent filers pursuant to
Item 405 of Regulation S-K is not contained herein, and will not be contained to
the best of Registrant's knowledge, in definitive proxy or information
statements incorporated by reference in Part III of this Form 10-K or any
amendment to this Form 10-K. Yes X No .

The approximate aggregate market value of the voting common stock held
by non-affiliates of the Registrant, based upon the last sale price of the
common stock reported on the National Association of Securities Dealers
Automated Quotation National Market System was \$299,046,755 as of January 12,
2001. *

The number of shares of voting common stock outstanding as of
January 12, 2001 was 40,119,564.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Registrant's definitive Proxy Statement filed on or about February 28,
2001 with the Securities and Exchange Commission in connection with Registrant's
annual meeting of stockholders to be held on April 6, 2001 is incorporated by
reference into Part III of this Report.

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*Excludes 10,584,082 shares of common stock held by directors and
officers and by stockholders whose beneficial ownership is known by the
registrant to exceed 10% of the common stock outstanding at January 12, 2001.
Exclusion of shares held by any person should not be construed to indicate that
such person possesses the power, direct or indirect, to direct or cause the
direction of the management or policies of the Registrant, or that such person
is controlled by or under common control with the Registrant.

EXPLANATORY NOTE

This Amendment to the Annual Report on Form 10-K for Isis Pharmaceuticals, Inc. is being filed solely to amend Item 14(a)(3) and Item 14(c) by adding Exhibit 10.25.

PART IV

ITEM 14. EXHIBITS, FINANCIAL STATEMENT SCHEDULES, AND REPORTS ON FORM 8-K

(a)(1) INDEX TO FINANCIAL STATEMENTS

The financial statements required by this item are submitted in a separate section beginning on page F-1 of this Report.

(a)(2) INDEX TO FINANCIAL STATEMENT SCHEDULES

These schedules are omitted because they are not required, or are not applicable, or the required information is shown in the financial statements or notes thereto.

(a)(3) INDEX TO EXHIBITS

See Index to Exhibits on pages 32 through 33.

(b) REPORTS ON FORM 8-K

On December 12, 2000, the registrant filed a report on Form 8-K relating to the adoption of a stockholder rights plan.

(c) EXHIBITS

The exhibits required by this Item are listed under Item 14(a)(3).

(d) FINANCIAL STATEMENT SCHEDULES

The financial statement schedules required by this Item are listed under Item 14(a)(2).

SIGNATURES

Pursuant to the requirements of Section 14 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K/A to be signed on its behalf by the undersigned, thereunto duly authorized on the 2nd day of April, 2001.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. LYNNE PARSHALL

 B. Lynne Parshall
 Executive Vice President,
 Chief Financial Officer and Director

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

SIGNATURES -----	TITLE -----	DATE ----
STANLEY T. CROOKE, M.D., PH.D.* ----- Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, Chief Executive Officer and Director (Principal executive officer)	April 2, 2001
/s/ B. LYNNE PARSHALL ----- B. Lynne Parshall	Executive Vice President, Chief Financial Officer and Director (Principal financial and accounting officer)	April 2, 2001
CHRISTOPHER F. O. GABRIELI* ----- Christopher F. O. Gabrieli	Director	April 2, 2001
WILLIAM R. MILLER* ----- William R. Miller	Director	April 2, 2001
/s/ FRED T. MUTO ----- Fred T. Muto	Director	April 2, 2001
MARK B. SKALETSKY* ----- Mark B. Skaletsky	Director	April 2, 2001
JOSEPH H. WENDER* ----- Joseph H. Wender	Director	April 2, 2001

*By: /s/ B. LYNNE PARSHALL

 B. Lynne Parshall
 Attorney-in-Fact

INDEX TO EXHIBITS

Exhibit NUMBER -----	DESCRIPTION OF DOCUMENT -----
1.1	- Form of Common Stock Purchase Agreement between the Registrant and Ridgeway Investment Limited. (16)
3.1	- Amended and Restated Certificate of Incorporation filed June 19, 1991. (1)
3.2	- Bylaws. (1)
3.3	- Certificate of Designation of the Series A Convertible Preferred Stock. (11)
3.4	- Certificate of Designation of the Series B Convertible Preferred Stock. (14)
3.5	- Certificate of Designation of the Series C Junior Participating Preferred Stock. (17)
4.1	- Reference is made to Exhibits 3.1 through 3.5.
4.2	- Specimen Stock Certificate. (1)
4.3	- Specimen Series A Preferred Stock Certificate. (18)
4.4	- Specimen Series B Preferred Stock Certificate. (18)
4.5	- Form of Right Certificate. (17)
10.1	- Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule. (1)
10.2	* - Registrant's 1989 Stock Option Plan, as amended. (6)
10.3	* - Registrant's 1992 Non-Employee Directors Stock Option Plan, as amended. (4)
10.4	* - Form of Performance-Based Supplemental Stock Option Agreement dated January 6, 2000 under the 1989 Stock Option Plan entered into between the Registrant and certain of its officers together with related schedule. (19)
10.5	* - Registrant's Employee Stock Purchase Plan. (10)
10.6	* - Form of Employee Assignment of Patent Rights. (1)
10.7	* - Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan. (10)
10.8	* - Severance Agreement dated January 11, 2000 entered into between the Registrant and its executive officers, together with related schedule. (10)
10.9	- Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted). (2)
10.10	- Collaborative Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted). (3)
10.11	- Agreement between the Registrant and CIBA Vision Corporation (now Novartis Ophthalmics) dated July 10, 1997 (with certain confidential information deleted). (5)
10.12	- Amendment No. 2 to the Agreement between the Registrant and CIBA Vision Corporation, dated September 14, 1998 (with certain confidential information deleted). (8)
10.13	- Imperial Bank Note Secured by Deed of Trust dated March 24, 1997 in the amount of \$6,000,000, together with the related Deed of Trust and Assignment of Rents dated March 24, 1997. (5)

- 10.14 - Imperial Bank Note Secured by Deed of Trust dated March 24, 1997 in the amount of \$3,706,620, together with the related Deed of Trust and Assignment of Rents dated March 24, 1997. (5)
- 10.15 - Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated October 24, 1997 (with certain confidential information deleted). (6)
- 10.16 - First Supplement to Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated May 1, 1998 (with certain confidential information deleted). (7)
- 10.17 - Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted). (6)
- 10.18 - Research Collaboration and License Agreement between Merck & Co., Inc. and the Registrant dated June 1, 1998 (with certain confidential information deleted). (7)
- 10.19 - Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted). (9)
- 10.20 - Subscription, Joint Development and Operating Agreement, dated April 20, 1999 by and among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. And Orasense, Ltd. (with certain

confidential information deleted); together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreements and License Agreements. (12)

- 10.21 - Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and the Registrant; together with related Amendment to the Stock Purchase Agreement. (13)
- 10.22 - Subscription, Joint Development and Operating Agreement, dated January 14, 2000 by and among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and HepaSense, Ltd. (with certain confidential information deleted); together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreements and License Agreements. (14)
- 10.23 - Agreement between the Registrant and Agouron Pharmaceuticals, dated June 9, 2000 (with certain confidential information deleted). (15)
- 10.24 - Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company. (17)
- 10.25 - Agreement between the Registrant and Coley Pharmaceutical Group, Inc., f/k/a CpG ImmunoPharmaceuticals, Inc., dated September 27, 2000.
- 23.1 - Consent of Ernst & Young LLP, Independent Auditors. (19)
- 24.1 - Power of Attorney. (19)
- 99.1 - Form of Confidentiality Agreement. (11)

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- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
- (2) Filed as an exhibit to the Registrant's Report on Form 8-K dated July 18, 1995 and incorporated herein by reference.
- (3) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1995 and incorporated herein by reference.
- (4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1996 and incorporated herein by reference.
- (5) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1997 and incorporated herein by reference.
- (6) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997 and incorporated herein by reference.
- (7) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1998 and incorporated herein by reference.
- (8) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1998 and incorporated herein by reference.
- (9) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1998 and incorporated herein by reference.
- (10) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1999 and incorporated herein by reference.
- (11) Filed as an exhibit to the Registrant's Registration Statement

on Form S-3 (No. 333-71911) or amendments thereto and incorporated herein by reference.

- (12) Filed as an exhibit to the Registrant's Report on Form 8-K dated April 20, 1999 and incorporated herein by reference.
- (13) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 31, 1999 and incorporated herein by reference.
- (14) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000 and incorporated herein by reference.
- (15) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2000 and incorporated herein by reference.
- (16) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-90811) or amendment thereto and incorporated by reference.
- (17) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.

- (18) Filed as an exhibit to the Registrant's Report on Form 10-Q/A for the quarter ended June 30, 2000 and incorporated herein by reference.
- (19) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the year ended December 31, 2000 and incorporated herein by reference.

* Indicates management compensatory plans and arrangements as required to be filed as exhibits to this Report pursuant to Item 14(c).

AGREEMENT

This Agreement (this "AGREEMENT") is entered into this 27th day of September, 2000 (the "EFFECTIVE DATE") by and between Coley Pharmaceutical Group, Inc., f/k/a CpG ImmunoPharmaceuticals, Inc. ("COLEY"), a Delaware corporation with its principal offices at 20 William Street, Suite 115, Wellesley, MA 02481, and Isis Pharmaceuticals, Inc. ("ISIS"), a Delaware corporation with its principal offices at 2292 Faraday Avenue, Carlsbad, CA 92009.

A. WHEREAS, Coley and Isis have entered into a License Agreement dated as of August 6, 1998 (the "LICENSE AGREEMENT");

B. WHEREAS, certain disagreements have arisen with respect to the License Agreement which are currently the subject of pending arbitration between Coley and Isis; and

C. WHEREAS, Coley and Isis mutually desire to clarify that the intent of Isis is to design and develop antisense oligonucleotides and the intent of Coley is to design and develop immunomodulatory oligonucleotides;

D. WHEREAS, Coley desires to acquire certain patent rights from Isis, and redeem Isis' equity interest in Coley, and Isis is willing to assign such patent rights and sell such equity interest to Coley in exchange for an exclusive license under such patent rights to design and develop antisense oligonucleotides and other consideration set forth herein; and

E. WHEREAS Coley and Isis mutually desire to resolve such aforementioned disagreements in accordance with the terms and conditions of this Agreement.

NOW THEREFORE, in consideration of the mutual covenants and conditions contained in this Agreement, and other good and valuable consideration, the receipt and sufficiency of which are hereby mutually acknowledged, Coley and Isis agree as follows:

1. UP-FRONT PAYMENT. Upon execution of this Agreement, Coley agrees to pay Isis seven million dollars (\$7,000,000).

2. REDEMPTION OF SERIES C PREFERRED STOCK. Upon execution of this Agreement, Isis shall sell, transfer and deliver to Coley, and Coley shall purchase, acquire and accept from Isis, for a purchase price of three million seven hundred forty-eight thousand seven hundred eleven dollars (\$3,748,711), all three hundred fifty-two thousand five hundred (352,500) shares of the Series C Convertible Preferred Stock, par value \$.01 per share, of Coley (the "SERIES C SHARES") held by Isis, free and clear of any lien, claim or other encumbrance and of any restriction or limitation of any nature whatsoever (collectively, "LIENS"). Each certificate representing the Series C Shares shall be duly endorsed by Isis in blank for transfer or accompanied by a stock power duly executed by Isis assigning the Series C Shares in blank.

3. ASSIGNMENT OF PATENT RIGHTS; DELIVERY OF RECORDS; COOPERATION. Upon execution of this Agreement, Isis shall irrevocably sell, convey, assign, transfer and deliver to Coley, and Coley shall purchase, acquire and accept from Isis, for no additional cash consideration, all rights, title and interest of Isis in, to and under (i) US Patent 5,663,153, (ii) US

Patent 5,723,335, (iii) pending US Application 09/009,634, (iv) all patents and applications claiming priority to U.S. Application 08/217,988 filed on March 25, 1994, and (v) all continuations, continuations-in-part and divisionals of the foregoing and patents issuing thereon or reissues thereof, and any and all foreign patents and patent applications corresponding thereto (collectively, the "PATENT RIGHTS"), free and clear of all Liens. Upon execution of this Agreement, Isis will provide Coley with the full file wrapper and prosecution history of the issued and pending patents included in the Patent Rights (including without limitation all drawings or figures and official correspondence with patent offices). To the extent reasonably necessary to prosecute, maintain, enforce or defend the Patent Rights, Isis will make available to Coley at the offices of Isis (or to Coley's authorized attorneys, agents or representatives), at no charge to Coley, laboratory notebooks and/or other records embodying the data contained in the patents and patent applications which comprise the Patent Rights. Isis will also similarly make available to Coley, at no charge to Coley, its employees for such purposes for reasonable periods of time at Isis facilities. Attached hereto as EXHIBIT A-1 and EXHIBIT A-2 are copies of the Proprietary Information and Inventions Agreements for each inventor under the Patent Rights. Each inventor under the Patent Rights has assigned his or her rights to Isis pursuant to such agreements. Isis will, at Coley's reasonable request, and at no charge to Coley, enforce the Proprietary Information and Inventions Agreements against the inventors to the extent reasonably required to prosecute, maintain, enforce or defend the Patent Rights.

4. LICENSE TO ISIS UNDER PATENT RIGHTS IN ISIS FIELD.

Effective upon the execution of this Agreement, and subject to the terms and conditions of this Agreement, Coley hereby grants to Isis an exclusive, perpetual, fully-paid, worldwide license, with the right to sublicense, under the Patent Rights to make, have made, use, sell and import products designed to work via the antisense mechanism (the "ISIS FIELD"). As used in this Agreement, the term "ANTISENSE" shall mean a polynucleotide, oligonucleotide or oligonucleotide analog which hybridizes in a sequence specific manner under physiological conditions to RNA or DNA. An oligonucleotide analog may include naturally occurring or non-natural heterocycles, sugar and/or backbone linkages, and may be molecules in which the sugar may be absent, in which the backbone linkages may be phosphate based, amide based, or based on other chemistries and which may or may not include stem loop or structural units. For purposes of clarification, "antisense" does not include polynucleotides, oligonucleotides and oligonucleotide analogs that are designed to have enhanced content of CpG or other immunomodulatory sequences such as in the stem loop or structural units, for increasing immunomodulatory effects. The parties acknowledge that drugs that are designed to work through an antisense mechanism may happen to contain CpG and/or other immunomodulatory sequences and may, as a secondary mechanism of action, happen to cause immune stimulation. Such drugs will be deemed to be antisense hereunder, as long as such drugs were not enhanced to have such immunomodulatory properties during the design process.

For purposes of clarification, the Isis Field shall not include, among other things, the design, development, manufacture, use, sale or importation of phosphorothioate oligonucleotides (i) as human or veterinary adjuvants or potentiators used as part of a Vaccine or in conjunction with an antibody or (ii) as a stand-alone, active ingredient administered for prophylactic purposes. For purposes of the foregoing sentence, "VACCINE" shall mean an immunogen administered for therapeutic or prophylactic purposes alone or in a program of administration in combination with adjuvant that elicits a specific long-lasting immune response to that

immunogen following no more than 15 administrations in a 1-year period (immunogens may consist of one or more of the following: polysaccharides, polysaccharide conjugates, live attenuated pathogens, whole killed pathogens, naturally occurring proteins, recombinant proteins or peptides).

For purposes of further clarification, the Isis Field shall include antisense applications where the phosphorothioate oligonucleotide is used alone or as a portion of a drug as a therapeutically active ingredient. For the purposes of the foregoing sentence, therapeutic activity shall not include the use of antisense to a nucleic acid in an individual whose condition would be unaffected by regulation of the nucleic acid and shall also not include potentiation or enhancement of a specific immune response to a specific antigen or induction of an antibody - dependent cellular cytotoxicity (ADCC) response to be targeted by a specific antibody.

5. PATENT RIGHTS.

(a) FILING, PROSECUTION AND MAINTENANCE OF PATENT RIGHTS.

Coley shall be responsible and have sole discretion for the filing, prosecution and maintenance of all patent applications and patents comprising the Patent Rights at its own expense. Subject to paragraph (b) of this Section 5, Coley shall use commercially reasonable efforts to file and prosecute patent applications and maintain the patents comprising the Patent Rights in such countries as Coley chooses in its sole discretion. Coley shall have the right to take any action that it determines, in its reasonable judgment, is necessary or appropriate in connection with the activities under this Section 5(a).

(b) DISCONTINUATION OF PATENT MAINTENANCE.

With respect to any patent application or patent included as part of the Patent Rights, notwithstanding anything to the contrary contained in this Agreement, Coley may, at its sole discretion, determine at any time to discontinue prosecution, maintenance and financial support of such application or patent, PROVIDED that if such patent application or patent relates to the Isis Field, then prior to making such election, Coley shall notify Isis of its intention not less than sixty (60) days prior to the first date following such determination that any payment is due or action is required with respect to the discontinued application or patent. If Isis thereafter desires to file, maintain or prosecute such a patent or application in the Isis Field, it may do so in Coley's name on behalf of Coley at Isis' sole discretion and expense.

6. ENFORCEMENT OF PATENT RIGHTS; DEFENSE OF CLAIMS. Each of the parties hereto shall promptly notify the others in writing (i) of any alleged or threatened infringement by a third party of any of the Patent Rights, (ii) of any notice from a third party of any alleged infringement of a patent or other intellectual property right held by such third party because of the practice of Patent Rights by a party, (iii) of attempts by third parties to invalidate the Patent Rights, or (iv) if any of the parties, or to their knowledge any of their respective Affiliates, shall be individually named as a defendant in a legal proceeding by a third party in connection with any of the foregoing. As used in this Agreement, the term "AFFILIATE" means any entity that directly or indirectly owns, is owned by, or is under common ownership with a party to this Agreement, where "OWNS" or "OWNERSHIP" means direct or indirect ownership with the right to vote at least fifty percent (50%) of the outstanding voting securities of a corporation, or a

comparable equity interest in any other type of entity, or such other relationship as, in fact, constitutes actual control.

(a) FIRST RIGHT TO RESPOND. Coley shall have, at its sole cost, the first right to (i) assert any claim of alleged infringement by a third party of the Patent Rights or (ii) respond to or defend against any challenge to the Patent Rights. In the event Coley elects to so assert, respond or defend, then Isis will cooperate with Coley's legal counsel, join in any suits as may be brought by Coley or as may be brought against Coley, and be available at Coley's reasonable request to be an expert witness or otherwise to assist in such proceedings. All reasonable out-of-pocket expenses incurred by Isis in furnishing such cooperation shall be paid or reimbursed by Coley. Coley shall have no right to settle any claim that would materially diminish or materially adversely affect the scope, exclusivity or duration of the Patent Rights in the Isis Field, or would conflict with this Agreement, without the prior written consent of Isis.

(b) SECOND RIGHT TO RESPOND. If Coley does not exercise its right to assert a claim or to respond to or defend against the charges or challenges set forth above in Section 5(a) in the Isis Field within one hundred eight (180) days after becoming aware of or being notified of such infringement, charges or challenges, then Isis, upon ten (10) days prior written notice to Coley, shall have the option to do so in Coley's name and at Isis' sole cost. In the event Isis elects to so assert, respond or defend, then Coley will cooperate with Isis' legal counsel, join in any suits as may be brought against Isis and be available at its reasonable request to be an expert witness or otherwise to assist in such proceedings. All reasonable out-of-pocket expenses incurred by Coley in furnishing such cooperation shall be paid or reimbursed by Isis. Isis shall have no right to settle any claim that would materially diminish or materially adversely affect the scope, exclusivity or duration of the Patent Rights, or would conflict with this Agreement, without the prior written consent of Coley.

(c) DIVISION OF AWARD OR SETTLEMENT. All amounts recovered from any third party in connection with such dispute or the settlement thereof shall first be used to pay the legal costs and expenses of the party bringing or defending a claim, and then the reasonable unreimbursed legal costs and expenses of the other party, and any remaining amount will be divided between the parties in proportion to each party's respective expenses in connection with such dispute and the settlement thereof.

7. LICENSE TO COLEY UNDER BLOCKING TECHNOLOGIES.

(a) Without in any way limiting the representation and warranty of Isis set forth in Section 14(g) hereof, effective upon execution of this Agreement, Isis hereby grants to Coley a perpetual, fully-paid, royalty-free, transferable and sub-licensable, worldwide license under any Blocking Technologies (as such term is defined in Section 14(g) hereof), whether now owned or controlled or, subject to paragraph (b) of this Section 7, hereafter owned or controlled by Isis or its Affiliates (to the extent Isis is not prevented from doing so under the terms of an arms-length written agreement with such Affiliate), to the extent required for Coley to practice the Patent Rights. For purposes of this Section 7 and Section 14(g), if viable alternative ways are available to Coley to practice the Patent Rights, then no particular method will be deemed required to practice the Patent Rights.

(b) In connection with any Blocking Technology that Isis or an Affiliate may own or control after the Effective Date by acquisition or license ("ACQUIRED BLOCKING TECHNOLOGY"), Isis or such Affiliate will only be required to license or sublicense such Acquired Blocking Technology to Coley hereunder to the extent Isis or such Affiliate is permitted to do so by the terms of such acquisition or license, provided that Isis covenants that it shall use commercially reasonable efforts in connection with any such acquisition or license to ensure that it obtains, or causes such Affiliate to obtain the right to license or sublicense any such Acquired Blocking Technology to Coley hereunder. If Isis does not have actual control over an Affiliate that owns or controls Acquired Blocking Technology, then Isis shall use commercially reasonable efforts to assure that the Affiliate complies with the provisions of this Section 7(b). If the licensing or sublicensing of any Acquired Blocking Technology by Isis or an Affiliate imposes financial obligations on Isis or such Affiliate (e.g., license fees, royalties, milestone payments, etc.) or requires specific commitments from a licensee or sublicensee in connection with the license or sublicense thereunder (e.g., confidentiality agreements, agreements to be audited, due diligence commitments, etc.), then the license or sublicense under such Additional Blocking Technology to Coley will be effective under paragraph (a) of this Section 7 only if Coley agrees in writing, in a manner reasonably satisfactory to Isis or such Affiliate, to be directly responsible for such obligations, or a fair portion of such obligations, and to make such commitments; provided, however, that in the event that Coley does not so agree in a manner reasonably acceptable to Isis or such Affiliate, Isis nevertheless agrees that neither it nor its Affiliates shall sue Coley or its Affiliates, or their respective licensees and sublicensees, for infringement of any such Acquired Blocking Technologies (unless Isis is obligated under the terms of an arms-length license or acquisition agreement to enforce such Acquired Blocking Technologies against any third party or, by failing to do so, would lose substantial rights under such an agreement or would suffer a financial loss pursuant to the terms of such agreement).

8. DELIVERIES AT CLOSING. Upon execution of this Agreement, Coley and Isis shall execute and deliver to each other such other documents of assignment and other instruments, with any required documentary stamps affixed, as, in the reasonable judgment of the respective parties, are necessary to consummate the transactions, including without limitation assignments of the Patent Rights in the forms attached hereto as EXHIBIT B. Additionally, Coley shall deliver payment to Isis, by check or wire transfer, of the amounts provided for in Sections 1 and 2, and Isis (and, as appropriate, the Inventors) shall deliver to Coley the stock certificate(s) representing the Series C Shares.

9. INTERDEPENDENCE. The transfers, assignments, licenses and deliveries described in Sections 1 through 8 hereof are mutually interdependent and regarded as occurring simultaneously, and unless waived by each of the parties hereto, none of the transactions described in Sections 1 through 8 hereof shall become effective unless and until all other transfers, assignments, licenses and deliveries provided for in such sections have also been consummated.

10. EXCLUSIVE RIGHT OF FIRST NEGOTIATION FOR EXCLUSIVE RIGHTS TO FUTURE TECHNOLOGIES FOR USE IN COLEY FIELD.

(a) CONSULTATION AND COORDINATION. Effective upon execution of this Agreement and until the tenth anniversary of the Effective Date (the "NEGOTIATION TERM"), Isis

shall keep Coley informed as to the status of any Future Technologies (as defined below) that it, or its Affiliates (to the extent Isis is not prevented from doing so under the terms of an arms-length written agreement with such Affiliate), may own or control after the Effective Date, whether through research and development, licensing, sublicensing, acquisition or otherwise, and that relate to the Coley Field (as defined below); provided however, that Isis will not be required to inform Coley about any Future Technology that is not sublicensable or that Isis is precluded from disclosing under confidentiality restrictions with a third party for so long as such sublicensing or confidentiality restrictions continue to apply. Isis shall notify Coley of the existence of any such Future Technologies immediately upon the earlier of (i) the filing of any patent application covering, claiming or disclosing such Future Technologies, (ii) the execution of license, sublicense or similar rights to such Future Technologies, or (iii) the consummation of the acquisition of such Future Technologies by Isis, or its Affiliates (to the extent Isis is not prevented from doing so under the terms of an arms-length written agreement with such Affiliate), and shall thereafter regularly inform Coley as to the status of such Future Technologies. Without limiting the generality of the foregoing, Isis shall provide Coley with a reasonable opportunity, on a regular basis, to visit with Isis' senior scientists to discuss Isis' activities and Future Technologies that may be of potential interest to Coley in the Coley Field. For purposes of this Section 10, the term "FUTURE TECHNOLOGIES" shall mean any and all patents, patent applications, conceptions, ideas, innovations, discoveries, inventions, processes, compositions of matter, improvements, enhancements, modifications, technological developments, know-how, methods, techniques, systems, designs, specifications, data, information and products, whether patentable, copyrightable, or susceptible to any other form of legal protection, that are hereafter owned or controlled by Isis or its Affiliates that relate to the Coley Field. Also for purposes of this Section 10, the term "COLEY FIELD" shall mean the field of immunomodulation based on molecules that function other than through an antisense mechanism. As used in this Agreement, the term "IMMUNOMODULATION" shall mean downregulation, upregulation, alteration, or any biological influence or modulation of the immune system.

(b) RIGHT OF FIRST NEGOTIATION. During the Negotiation Term, and according to the procedures set forth in paragraph (c) of this Section 10, Isis hereby grants Coley an exclusive right of first negotiation to negotiate with Isis for exclusive rights (e.g. by license or acquisition), to the extent Isis or an Affiliate of Isis has exclusive rights, in, to and under any and all Future Technologies that relate to the Coley Field which Isis (or an Affiliate of Isis, to the extent Isis is not prevented from doing so under the terms of an arms-length written agreement with such Affiliate) has decided, in its sole discretion, to license, sublicense or assign for use in the Coley Field.

(c) METHOD OF EXERCISE. If at any time Isis, or an Affiliate (to the extent Isis is not prevented from doing so under the terms of an arms-length written agreement with such Affiliate), intends to license, sublicense, or assign Future Technologies for use in the Coley Field, it shall provide Coley with written notice of such intention (the "ISIS NOTICE") together with information as to the current status of such Future Technology, and Coley shall respond in writing within thirty (30) days after receipt of the Isis Notice as to whether or not it exercises its Right of First Negotiation. If Coley elects to exercise its Right of First Negotiation as to a particular Future Technology as provided in the foregoing sentence, then the parties shall promptly thereafter negotiate in good faith a definitive agreement for an acquisition, exclusive

license, exclusive sublicense, or similar exclusive arrangement (a "DEFINITIVE AGREEMENT"), in, to and under such Future Technology for any and all uses and application(s) thereof within the Coley Field. In the event that the parties do not execute a Definitive Agreement within one hundred twenty (120) days after receipt of an Isis Notice by Coley, then Isis shall be free to pursue the said subject matter or enter into an agreement with any third party if Isis believes, based on good faith reasonable business judgment, that the Coley licensing proposal is not at least as favorable on the whole as an alternative proposal.

11. NON-COMPETITION. For a period of seven (7) years after the Effective Date, both parties agree as follows: Isis will not, either directly or through a collaborative relationship, design or develop oligonucleotides to be immunomodulatory via non-antisense mechanisms; further, Isis will not, either directly or through a collaborative relationship, design or develop small molecules to bind to proteins to cause immunomodulation; and further, Isis will not establish any Affiliates for the purpose of doing the foregoing and will ensure that any Affiliates over which it has actual control do not do any of the foregoing. All Affiliates of Isis will not, either directly or through a collaborative relationship, design oligonucleotides to be immunomodulatory via non-antisense mechanisms; further, all Affiliates of Isis will not, either directly or through a collaborative relationship, design small molecules to bind to proteins to cause immunomodulation. Coley and its Affiliates will not, either directly or through a collaborative relationship, design or develop oligonucleotides to work via an antisense mechanism. Additionally, during such seven year period, neither party, nor any of their respective Affiliates, shall grant any license, sublicense or similar rights to any third party that would allow or purport to allow such third party to engage in any of the aforementioned prohibited activities.

12. EFFECT OF ACQUISITION. Sections 10 and 11 shall be binding on all successors and assigns of either party; provided, however, that in the event of a bona fide acquisition of a party by any person (an "ACQUIRER") that is not an Affiliate of such party prior to the acquisition, whether through a merger or consolidation of such party into or with an Acquirer, or a binding share exchange, in either case as a result of which in excess of 50% of the voting power of such party is transferred to an Acquirer, or the sale of all or substantially all the assets of such party to an Acquirer (an "ACQUISITION"), then the provisions of Sections 10 and 11 shall thereafter be limited to oligonucleotides, and not to any other chemical moiety; and provided further that the parties expressly agree and acknowledge that the aforementioned restrictions on competition shall not prohibit an Acquirer from conducting or continuing to conduct any research, development, commercialization or other bona fide business activities in a field in which it was actively engaged prior to the consummation of such Acquisition, provided that such activities (i) were not being conducted pursuant to a license, sublicense or similar arrangement prohibited by Section 10 or 11 and (ii) do not constitute an infringement or misappropriation of any of the intellectual property rights of the other party. Each party further expressly agrees and acknowledges that nothing in the foregoing sentence shall be deemed to constitute an implied license, sublicense, or similar right to any Acquirer under any of the intellectual property rights of the other party.

13. REPRESENTATIONS AND WARRANTIES OF COLEY. Coley hereby represents and warrants to Isis as follows:

(a) ORGANIZATION, STANDING AND AUTHORITY OF COLEY. Coley is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware, with full corporate power and authority to carry on its business as now conducted. Coley has all requisite corporate power and authority to enter into and perform all of its obligations under this Agreement. The execution and delivery of this Agreement and the consummation of the transactions contemplated hereby have been duly and validly authorized by all necessary corporate action in respect thereof on the part of Coley. This Agreement constitutes the legal, valid and binding obligation of Coley, enforceable against it in accordance with its terms, subject, as to enforceability, to bankruptcy, insolvency and other laws of general applicability relating to or affecting creditors' rights and to general equity principles.

(b) GOVERNMENT APPROVAL. No authorization or consent, and no registration or filing with any governmental or regulatory official, body or authority is required in connection with the execution, delivery and performance of this Agreement by Coley or the consummation of the transactions contemplated hereby.

(c) CONSENTS; NO BREACH. The execution, delivery and performance of this Agreement by Coley does not (i) conflict with or result in a breach of any provision of the certificate of incorporation or by-laws of Coley, (ii) require any consent by any person under, constitute or result in a breach of any term, condition or provision of, or constitute a default or give rise to any right of termination or acceleration under any note, bond, mortgage, indenture, license, agreement or other instrument or obligation to which Coley is a party or by which it is bound, other than such consents as have been obtained by Coley, (iii) violate any law, order, writ, judgment, injunction, decree, statute, rule or regulation applicable to Coley or (iv) result in the creation or imposition of any Lien on any assets of Coley.

(d) ACTIONS AND PROCEEDINGS. There are no outstanding orders, judgments, injunctions, awards or decrees of any court, governmental or regulatory body or arbitration tribunal against or involving Coley which are reasonably likely to affect or relate to the transactions contemplated hereunder. There are no actions, suits or claims or legal, administrative (other than patent office proceedings not involving third parties) or arbitral proceedings or, to the best knowledge of Coley, governmental investigations (whether or not the defense thereof or liabilities in respect thereof are covered by insurance) pending or, to the best knowledge of Coley, threatened against or involving Coley which are reasonably likely to affect or relate to the Patent Rights or the transactions contemplated hereunder.

14. REPRESENTATIONS AND WARRANTIES OF ISIS. Isis hereby represents and warrants to Coley as follows:

(a) ORGANIZATION, STANDING AND AUTHORITY OF ISIS. Isis is a corporation duly organized, validly existing and in good standing under the laws of Delaware, with full corporate power and authority to carry on its business as now conducted. Isis has all requisite corporate power and authority to enter into and perform all of its obligations under this

Agreement. The execution and delivery of this Agreement and the consummation of the transactions contemplated hereby have been duly and validly authorized by all necessary corporate action in respect thereof on the part of Isis. This Agreement constitutes the legal, valid and binding obligation of Isis, enforceable against it in accordance with its terms, subject, as to enforceability, to bankruptcy, insolvency and other laws of general applicability relating to or affecting creditors' rights and to general equity principles.

(b) GOVERNMENT APPROVAL. No authorization or consent, and no registration or filing with any governmental or regulatory official, body or authority is required in connection with the execution, delivery and performance of this Agreement by Isis or the consummation of the transactions contemplated hereby.

(c) CONSENTS; NO BREACH. The execution, delivery and performance of this Agreement by Isis does not (i) conflict with or result in a breach of any provision of the certificate of incorporation or by-laws of Isis, (ii) require any consent by any person under, constitute or result in a breach of any term, condition or provision of, or constitute a default or give rise to any right of termination or acceleration under any note, bond, mortgage, indenture, license, agreement or other instrument or obligation to which Isis is a party or by which it is bound, other than such consents as have been obtained by Isis, (iii) violate any law, order, writ, judgment, injunction, decree, statute, rule or regulation applicable to Isis or (iv) result in the creation or imposition of any Lien on any assets of Isis.

(d) ACTIONS AND PROCEEDINGS. There are no outstanding orders, judgments, injunctions, awards or decrees of any court, governmental or regulatory body or arbitration tribunal against or involving Isis which are reasonably likely to affect or relate to the Patent Rights or the transactions contemplated hereunder. There are no actions, suits or claims or legal, administrative (other than patent office proceedings not involving third parties) or arbitral proceedings or, to the best knowledge of Isis, governmental investigations (whether or not the defense thereof or liabilities in respect thereof are covered by insurance) pending or, to the best knowledge of Isis, threatened against or involving Isis which are reasonably likely to affect or relate to the Patent Rights or the transactions contemplated hereunder.

(e) PATENT RIGHTS. All of the Patent Rights have been duly registered in, filed in or issued by the United States Patent and Trademark Office, and have been properly maintained and renewed in accordance with all applicable provisions of law and administrative regulations in the United States, and Isis has fully met its disclosure requirements to the United States Patent and Trademark Office in connection with the Patent Rights.

(f) TITLE TO PATENT RIGHTS; LIENS. Isis owns outright and has good title to all the Patent Rights, free and clear of any Liens, and upon delivery of the Patent Assignments as herein provided, Coley will acquire all right, title and interest thereto, free and clear of any Liens. Isis has not granted any license rights or similar rights under the Patent Rights to any third party, has not granted any third party the right to receive royalties or similar compensation in connection with the Patent Rights, and has not entered into any arrangement, written or oral, that would obligate it to grant any of the aforementioned rights or any similar rights to any third party.

(g) BLOCKING TECHNOLOGIES. As of the date of this Agreement, Isis does not own or control whatsoever any patents, patent applications, inventions, discoveries, improvements, developments, technologies, options, licenses or other intellectual property rights (collectively, "BLOCKING TECHNOLOGIES") that are required to practice the Patent Rights.

(h) OWNERSHIP OF THE SERIES C SHARES. Isis is the owner, beneficially and of record, of Series C Shares, and the Series C Shares are owned free and clear of any Liens. By delivery of the Series C Shares, in exchange for the consideration provided in Section 2, Isis will convey to Coley good and marketable title to the Series C Shares, free and clear of any Lien. Isis has not granted any warrants, options or other rights, or entered into any agreement or other commitment, which obligate Isis to sell, transfer or otherwise dispose of any of the Series C Shares to anyone other than Coley or which affect the right of Isis as holder of the Series C Shares to vote or to dispose of the Series C Shares.

(i) NO OTHER TECHNOLOGY. As of the Effective Date, Isis does not own or control any patents that claim CpG-based immunomodulation or phosphorothioate-based immunomodulation other than through an antisense mechanism, has filed no patent applications relating thereto, and is not currently preparing the filing of any such applications, and has not received a record of inventions ("ROI") from an employee that is likely to result in the filing of any such applications, except an ROI relating to the use of 2,2-diaminopurine and/or inosine residues to modulate immunostimulatory effects of oligonucleotides, on which Isis is not currently planning to file a patent application, but may choose to do so in the future if and when it further investigates the utility. Isis agrees that the disclosure set forth in such ROI would be deemed a Future Technology subject to the provisions of Section 10.

15. CONFIDENTIALITY.

(a) CONFIDENTIALITY. For a period of five years after any disclosure, the receiving party will maintain in confidence all Confidential Information (as defined below) disclosed by the disclosing party, using measures at least equivalent to those used by the receiving party to protect its own Confidential Information. The receiving party will not use, disclose, transfer or grant use of such Confidential Information so disclosed by the disclosing party except as expressly authorized by this Agreement. The receiving party may disclose, subject to the confidentiality restrictions contained herein, such Confidential Information of the disclosing party to licensees and sublicensees, provided such licensees and sublicensees execute confidentiality agreements containing terms no less strict than those contained herein. The receiving party will promptly notify the disclosing party upon discovery of any unauthorized use or disclosure of the disclosing party's Confidential Information.

(b) AUTHORIZED DISCLOSURE. The receiving party may disclose the Confidential Information only to the extent such disclosure is reasonably necessary in prosecuting or defending litigation or complying with applicable foreign or domestic governmental regulations (including, without limitation, securities laws), provided that if the receiving party is required to make any such disclosure of the Confidential Information it will to the extent practicable give reasonable advance notice to the disclosing party of such disclosure requirement and will use its best efforts to secure confidential treatment of any such Confidential Information to be disclosed.

(c) "CONFIDENTIAL INFORMATION" will include but not be limited to, business information (including the fact and content of any discussion between the parties), trade secrets, records, data, formulae, processes, developments, designs, inventions, models, techniques, improvements, or discoveries disclosed in confidence by either party to the other and clearly marked or identified as confidential at the time of disclosure, or so identified in writing by the disclosing party written thirty (30) days after disclosure. Confidential Information will not include information which:

(i) is known by the receiving party at the time of its receipt, and not through a prior disclosure by the disclosing party or a third party that is under an obligation of confidentiality to the disclosing party, as documented by business records;

(ii) is properly in the public domain;

(iii) is subsequently disclosed to a receiving party by a third party who may lawfully do so and is not under an obligation of confidentiality to the disclosing party; or

(iv) is developed by the receiving party independently of Confidential Information received from the other party, as documented by written records.

16. DISCLAIMER; LIMITATION OF LIABILITY.

(a) DISCLAIMER OF WARRANTIES. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH HEREIN, EACH OF THE PARTIES HEREBY EXPRESSLY DISCLAIMS ANY AND ALL WARRANTIES OF ANY KIND OR NATURE, WHETHER EXPRESS OR IMPLIED, INCLUDING ANY EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OF THE PATENT RIGHTS, OR OF THE VALIDITY OR ENFORCEABILITY OF ANY PATENT RIGHTS, OR THAT THE PRACTICE OF THE PATENT RIGHTS, OR THE USE OF THE KNOW-HOW, OR THE MANUFACTURE, USE OR SALE, OF ANY PRODUCT COVERED BY ANY PATENT RIGHT, WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK OR OTHER RIGHTS OF THIRD PARTIES.

(b) LIMITATION OF LIABILITY. IN NO EVENT WILL EITHER PARTY, ITS DIRECTORS, OFFICERS, EMPLOYEES, AGENTS OR AFFILIATES BE LIABLE TO THE OTHER PARTY FOR ANY INDIRECT, INCIDENTAL, SPECIAL, EXEMPLARY OR CONSEQUENTIAL DAMAGES, WHETHER BASED UPON A CLAIM OR ACTION OF CONTRACT, WARRANTY, NEGLIGENCE, STRICT LIABILITY OR OTHER TORT, OR OTHERWISE, ARISING OUT OF THIS AGREEMENT.

17. INDEMNIFICATION.

(a) COLEY INDEMNITY. Coley agrees to indemnify, hold harmless and defend Isis, its officers, directors, employees and agents, from and against any and all claims, suits, losses, damages, costs, fees and expenses (collectively, "CLAIMS") resulting from or arising out of (a) the development, manufacture, storage, sale or other distribution or any other use of products covered by a Patent Right by Coley and its Affiliates, sublicensees, distributors, agents

and representatives ("COLEY PRODUCTS") or use by end users and other third parties of Coley Products including, without limitation, any Claim that the use of a Coley Product infringes any third party patent rights; and (b) the exercise by Coley and its Affiliates, sublicensees, distributors, agents and representatives of any rights granted hereunder.

(b) ISIS INDEMNITY. Isis agrees to indemnify, hold harmless and defend Coley, its officers, directors, employees and agents, from and against any and all Claims resulting from or arising out of (a) the development, manufacture, storage, sale or other distribution or any other use of products covered by a Patent Right by Isis and its Affiliates, sublicensees, distributors, agents and representatives ("ISIS PRODUCTS") or use by end users and other third parties of Isis Products including, without limitation, any Claim that the use of an Isis Product infringes any third party patent rights; and (b) the exercise by Isis and its Affiliates, sublicensees, distributors, agents and representatives of any rights granted hereunder.

(c) NOTICE AND PROCEDURES. In all cases where one party (the "INDEMNITEE") seeks indemnification by the other party (the "INDEMNITOR") under this Article 15, the Indemnitor shall promptly notify the Indemnitor of receipt of any claim or lawsuit covered by such indemnification obligation and shall cooperate fully with the Indemnitor in connection with the investigation and defense of such claim or lawsuit. The Indemnitor shall have the right to control the defense, with counsel of its choice, provided that the Indemnitee shall have the right to be represented by advisory counsel at its own expense. The Indemnitor shall not settle or dispose of the matter in any manner which could negatively and materially affect the rights or liability of the Indemnitee without the Indemnitee's prior written consent, which shall not be unreasonably withheld.

18. ISIS RELEASE. Isis hereby releases and forever discharges Coley, each parent, subsidiary and affiliate of Coley, and their respective representatives, agents, shareholders, officers, directors, employees, successors, and assigns from any and all claims, demands, actions causes of action, debts, dues, liabilities, and controversies of every kind and nature (collectively, "CLAIMS"), whether presently known or unknown, vested or contingent, arising or accruing at any time on or before the Effective Date, which relate to or arise out of the License Agreement or the subject matter thereof.

19. COLEY RELEASE. Coley hereby releases and forever discharges Isis, each parent, subsidiary, and affiliate of Isis, and their respective representatives, agents, shareholders, officers, directors, employees, successors, and assigns from any and all Claims, whether presently known or unknown, vested or contingent, arising or accruing at any time on or before the Effective Date, which relate to or arise out of the License Agreement or the subject matter thereof.

20. WARRANTY AND INDEMNIFICATION REGARDING RELEASED CLAIMS. Isis and Coley each represents and warrants that it has not heretofore assigned or transferred or purported to assign or transfer to any person, firm or corporation whatsoever any claims, demands, causes of action, debts, dues, liabilities or controversies herein released. Isis and Coley shall indemnify and hold harmless each other against all damages, judgments, debts, dues, liabilities and expenses, including costs and attorney's fees, arising out of, resulting from or incurred in

connection with any assignment or transfer inconsistent with the foregoing representation and warranty.

21. TERMINATION OF AGREEMENTS. Subject to the terms, conditions, agreements and acknowledgements set forth herein, Coley and Isis each hereby agree that as of the Effective Date (i) the License Agreement and the Stock Subscription Agreement dated as of September 16, 1998 are hereby terminated and (ii) that Isis shall cease to be a party to, and shall cease to have any rights or obligations under, the Amended and Restated Registration Rights Agreement, Amended and Restated Stock Restriction Agreement and the Amended and Restated Investor Rights Agreement, each dated as of September 18, 2000. Notwithstanding anything to the contrary in Section 11.5 (SURVIVAL) of the License Agreement, Coley and Isis hereby agree that none of the provisions of the License Agreement shall survive and continue in effect after the Effective Date.

22. NO ADMISSION OF LIABILITY. This Agreement has been entered solely to avoid the expense and inconvenience of arbitration and litigation and shall not constitute an admission of liability by either party as to any claim, defense or allegation of the other party.

23. PUBLIC DISCLOSURE. Each party hereby acknowledges and agrees that it will not disclose the terms of this Agreement or any other information relating to the subject matter to any third party without the express written consent of the other party, except that (i) either party may use the text of a written statement approved in advance by both parties without further approval, (ii) either party may disclose the terms of this Agreement to a third party if required to do so under the terms of a contract with the third party that is authorized or contemplated by this Agreement, and (iii) either party shall have the right to identify the other party and to disclose the terms of this Agreement as required by applicable securities laws or other applicable laws or regulations. The parties shall mutually agree upon any press release or similar public disclosure concerning this Agreement, and have agreed upon the Press Release attached hereto as EXHIBIT C.

24. FURTHER ASSURANCES. Each party hereto, at any time after the Effective Date, shall execute, acknowledge and deliver any further assignments, conveyances and other assurances, documents and instruments of transfer reasonably requested by the other party and will take any other action consistent with the terms of this Agreement that may be reasonably requested by the other party for the purpose of concluding the transactions contemplated by this Agreement.

25. NOTICES. All notices and other communications hereunder will be in writing in English and will be deemed given if delivered personally or by facsimile transmission (receipt verified), e-mailed, or sent by express courier service, to the parties as the following addressed (or at such other address for a party as will be specified by like notice; provided that notices of a change of address will be effective only upon receipt thereof):

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92009
Attn: Chief Executive Officer
cc: General Counsel
Tel: (760) 931-9200
Fax: (760) 931-9636

Coley Pharmaceutical Group, Inc.
20 William Street, Ste 115
Wellesley, MA 02481
Attn: Chief Executive Officer
Tel: (781) 431-6400
Fax: (781) 431-6403

26. ENTIRE AGREEMENT. Except for the License Agreement and this Agreement and the attachments hereto and thereto constitute the entire agreement and understanding between Isis and Coley relating to the subject hereof. No verbal agreement, conversation or representation between any officers, agents, or employees of the parties hereto either before or after the execution of this Agreement shall affect or modify any of the terms or obligations herein contained.

27. MODIFICATION. No change, modification extension, termination or waiver of this Agreement, or any of the provisions herein contained, shall be valid unless made in writing and signed by a duly authorized representative of each party hereunder.

28. GOVERNING LAW. This Agreement shall be governed by and construed in accordance with the laws of the State of Delaware.

29. DISPUTE RESOLUTION. Any controversy, claim or dispute arising out of or relating to this Agreement shall be resolved as follows: (i) for a period of 30 days after a dispute arises, such 30 days beginning on the date of receipt of written notice by the notified party, the Chief Executive Officer of Isis and the Chief Executive Officer of Coley, or their fully authorized representatives, shall negotiate in good faith in an effort to resolve the dispute and (ii) if the dispute has not been resolved at the close of such 30-day period, the matter will be finally settled by binding arbitration under the Rules of Arbitration of the American Arbitration Association, by their arbitrators appointed in accordance with said rules; provided that if the parties cannot agree on who is to serve as the arbitrator, each party shall appoint one nominee and those nominees shall in turn jointly appoint a third arbitrator. Arbitration will take place in Dallas, Texas. The costs of the arbitration, including administrative and arbitrators' fees, shall be shared equally by the parties; provided that each party shall bear the costs of its own attorneys' fee and expert witness fees. Judgment on an award rendered by an arbitrator or arbitrators may be entered in any court having jurisdiction thereof. Notwithstanding the foregoing, the parties may apply to any court of competent jurisdiction for preliminary or interim equitable relief without breach of this arbitration provision.

30. EXPENSES. All costs and expenses incurred in connection with (i) the pending arbitration relating to the License Agreement and (ii) the negotiation, execution and delivery of this Agreement, and the transactions contemplated hereby, shall be paid by the party incurring such cost or expense, PROVIDED that Isis shall be responsible for any and all filing fees, attorney's fees, and similar costs relating to the Patent Rights that have accrued or may be due on or before the Effective Date.

31. BINDING EFFECT. This Agreement shall be binding upon and shall inure to the benefit of, the parties hereto, their Affiliates, and their respective successors and permitted assigns.

[The remainder of this page is intentionally left blank]

IN WITNESS WHEREOF, the parties hereto have executed this Agreement as of the date first above written.

ISIS PHARMACEUTICALS, INC.

COLEY PHARMACEUTICAL GROUP, INC.

B. Lynne Parshall

Robert Forrester

Name (typed or printed)

Name (typed or printed)

/s/ B. Lynne Parshall

/s/ Robert Forrester

Signature

Signature

Executive Vice President, CFO

SVP Finance & Development

Title

Title

EXHIBITS A-1 AND A-2
AGREEMENTS WITH INVENTORS

EXHIBIT B
FORMS OF PATENT ASSIGNMENTS

EXHIBIT C
PRESS RELEASE