**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

March 16, 2011

Ms. Miette H. Michie
Interim Executive Director and CEO
UVA Patent Foundation
University of Virginia
250 W. Main St
Suite 300
Charlottesville, VA 22902

Re: Request for Waiver of the Preference for United States Industry

EIR No.: 1526401-07-0005 (UNIVERSITY OF VIRGINIA)
U.S. Patent Application 12/527,255, filed 8/14/2009.
Patent Docket No.: PLATTS-ANAPH (01360-04)
NIH Funding Agreement: AI020565

EIR Title: IgE Antibodies to Chimeric of Humanized IgG Therapeutic Monoclonal Antibodies
Inventors' Names: Thomas Platts-Mills and Tina Hatley.

Dear Ms. Michie:

This letter is in response to the US Manufacturing Waiver Request submitted by the University of Virginia (UVA) on the above-referenced invention conceived or first actually reduced to practice through an NIH funding agreement.

Below is a summary of the scientific, commercialization and licensing reviews of the Subject Invention that is the subject of this Manufacturing Waiver; this Office concurs with those reviews and further agrees that it is in accord with the terms and conditions of the funding agreements under which it was made.

Commercialization Background and Analysis

This technology concerns a diagnostic test to measure the level of IgE antibody against the alphaGal sugar moiety present on the commercially available therapeutic antibody Cetuximab. While the reagent components will be manufactured in the U.S., no companies have facilities in the U.S. that can manufacture the test. UVA is requesting a waiver on behalf of their current licensee (b)(4), so that the test can be manufactured in their (b)(4) facilities.

UVA states that they have made reasonable efforts to market this technology, including to the owner (ImClone) and distributors (Bristol Myers Squibb for the U.S. and Merck BKaA worldwide) of Cetuximab, (b)(4) UVA additionally believes the test will not provide enough of a profit margin to warrant construction of a new facility in the U.S. Only (b)(4) has technology able to measure IgE accurately enough to make the test viable.

Since there are no U.S. companies that are able to make this test even though certain components will be made in the U.S., requiring substantial U.S. manufacturing at this time would only further delay the development of the test. However, a future sublicense to a U.S. company is still a possibility in the future.

Summary

Based on the information you have provided about the current circumstances for this technology, your request for a manufacturing waiver has been approved. By each 3rd year anniversary of the date of this letter, you will need to keep our office apprised of what good faith efforts were continuing to be made during that period to consider substantially manufacturing in the U.S. for this technology. If we do not receive this information for each period, then this approval may need to be revisited. As this invention was made under Funding Agreements that involve Consortium Activity with Wellington School of Medicine and Health Sciences at the University of Otago in New Zealand and the Karolinska Institutet in Sweden, any consortium issues should be considered in acting on this Waiver Approval. All other terms and conditions of the funding agreements, with the exception of the Preference for United States Industry as outlined in this letter, remain in effect.

Please feel free to contact us should you have any additional questions regarding this issue.

Sincerely,

John Salzman
Assistant Extramural Inventions Policy Officer
Division of Extramural Inventions and Technology Resources
Office of Policy for Extramural Research Administration, OER, OD

**Please direct all correspondence to:**
**6705 Rockledge Drive**
**Suite 310, MSC 7980**
**Bethesda, MD 20892-7980**

**Phone: (301) 435-1986**
**Fax: (301) 480-0272**
**e-mail: waiver@nih.gov**

Pages 3 through 5 redacted for the following reasons:
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NIH internal documents

## iEdison Notification of Manufacturing Waiver Request

**Request ID :** 2312

Status **: Open**
Priority **: Not Assigned**

Requested by **Edison (NIH/OD)** on Oct 15, 2010 12:11 PM **Due Date** : **N/A**

**Subject**

iEdison Notification of Manufacturing Waiver Request

**Description**

The following Manufacturing Waiver Request was submitted on 10/15/2010 11:50 am by Ms Miette H Michie , miette@uvapf.org.
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Invention Report Number: 1526401-07-0005
Grantee/Contract Organization: NIH
Grant/Contract Number: AI-20565
Invention Title: IgE Antibodies to Chimeric or Humanized IgG Therapeutic Monoclonal Antibodies as a Screening Test for Anaphylaxis
Invention Docket Number: US application 12/527,255
Patent Docket Number: 01360-04

Reasonable but Unsuccessful Efforts to License:

The significance of the technology, including the availability of alternative products, the size of intended patient populations, whether requiring U.S. manufacture will delay entry of the product into the U.S. or foreign markets, and the effect such delay may have on the U.S. and foreign public health, is as follows:

This technology describes a diagnostic test to measure the level of IgE antibody against the alphaGal sugar moiety present on the commercially available therapeutic antibody Cetuximab. Hypersensitivity towards Cetuxamab is mainly observed in the southeastern regions of the United States, where up to 20% of the population display an allergic reaction which may be fatal. Based on $1.5 billion in sales, and $30,000 per treatment, an estimated 50,000 patients are treated annually with Cetuximab.

The past marketing strategy and efforts for the technology, including the number of companies contacted, the methods used for marketing and contacting companies, the types of licenses and terms offered to potential licensees, comparison of terms offered to potential foreign licensee and those offered to U.S. companies, and the responses of companies to marketing efforts is as follows:

The technology was marketed to the owner (ImClone) and distributors (Bristol Myers Squibb for the U.S. and Merck BKaA worldwide) of Cetuximab.

(b)(4)

Not Commercially Feasible

The factors that make domestic manufacture not commercially feasible, including the relative costs of U.S. and foreign manufacturing, the licensee's manufacturing capabilities within the U.S. and the efforts made by to locate, develop, or contract for such manufacturing capabilities, and any other circumstances that make foreign manufacture necessary are as follows:

There are to Foundation¢□□s knowledge no US companies with the ability to manufacture the test.

The part or percentage of products arising from the invention that would be manufactured outside the U.S. is:

According to (b)(4) the test system will be produced outside the US, whereas the reagent components may be produced within the US.

The value or benefit to the United States of licensing the technology even if it will not be manufactured in the United States, including I) the direct or indirect investment in U.S. plants or equipment, such as for marketing or packaging; ii) the creation of new or higher quality U.S.-based jobs, iii) the enhancement of the domestic skills base, iv) the further domestic development of the technology, v) a positive impact on the U.S. trade balance considering product and service exports as well as foreign licensing royalties and receipts, or vi) cross-licensing, sublicensing, and reassignment provisions in the license which seek to maximize benefits to the U.S is:

(b)(4) epresents to Foundation that the impact of the test may lead to more individuals employed to market the test by (b)(4), and continued research support and collaboration between US universities and (b)(4)

PLATTS-MILLS ANAPHYLAXIS

PATENT FOUNDATION
UNIVERSITY OF VIRGINIA

# Invention Disclosure Form

## Part 1. Written Description - Invention Information

A. TITLE OF INVENTION

IgE Antibodies to Chimeric or Humanized IgG Therapeutic Monoclonal Antibodies as a Screening Test for Anaphylaxis

B. BACKGROUND OF THE INVENTION

ERBITUX™ (Cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody manufactured by ImClone Systems Incorporated and distributed and marketed by Bristol-Myers Squibb Company 3% of patients receiving ERBITUX™ (Cetuximab) have an adverse reaction to the drug. 90% of the severe reactions are associated with initial drug infusion. Adverse reactions include rapid onset of airway obstruction (including anaphylaxis ) This rapid reaction is characteristic of an IgE mediated response To test this theory, 44 serum samples, from independent centers, have been collected from patients who have or have not had an anaphylactic response to the infusion of ERBITUX™ (Cetuximab).

Pages 7 through 20 redacted for the following reasons:
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Removed by Agreement (9/7/2012)

# Assignment of Invention

WHEREAS, we (I),

*Inventor names*

Thomas A.E. Platts-Mills
Tina Hatley

(the "Assignors"), have made an invention entitled

*Title*

IgE Antibodies to Chimeric or Humanized IgG Therapeutic Monoclonal Antibodies as a Screening Test for Anaphylaxis

and

WHEREAS, The University of Virginia, 314 Madison Hall, P.O. Box 400301, Charlottesville, Virginia 22904-4301 (the "Assignee"), is desirous of acquiring the entire right, title and interest in and to the aforesaid invention, including any tangible materials embodied in or encompassed by the invention and any trade secrets pertaining to the invention, and any improvements thereon, (the "Invention") and in and to said applications for Letters Patent thereon in the United States, its territories and possessions ("United States") and all foreign countries, including rights to claim priority, to any provisional applications, and in and to any Letters Patent of the United States or any foreign country which may be granted therefor, including any and all reissues, divisions, continuations, continuations-in-part, renewals, substitutes or extensions thereof (the "Rights");

NOW, THEREFORE, for and in consideration of the sum of One Dollar ($1.00) and other good and valuable consideration, the receipt of which is hereby acknowledged, Assignors have sold, assigned, transferred and conveyed, and does hereby sell, assign, transfer and convey to Assignee, its successors and assigns, the entire right, title and interest in and to the aforesaid Invention and Rights, except that Assignee hereby grants back to the Assignors a royalty free non-transferable license to make and use the Invention under the Rights for educational and research purposes, only. The aforesaid assignment includes the right in and to all income, royalties, damages and payments now or hereafter due or payable with respect to any Letters Patent which may be granted, and in and to all causes of action (either in law or in equity), and the right to sue, counterclaim, and recover for past, present and future infringement of the rights assigned or to be assigned under this Assignment, as fully and entirely as the same would have been held and enjoyed by Assignors if this sale and assignment had not been made;

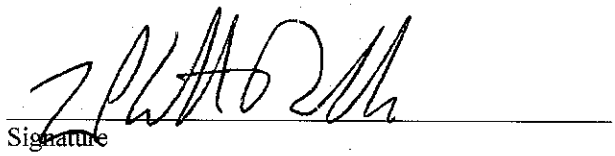
AND Assignors hereby authorize and request the appropriate governmental officials to issue any and all such United States or foreign Letters Patent under said invention, or resulting from any of said applications thereof, to the Assignee, as the assignee of the entire right, title and interest in and to the same;

AND Assignors hereby represent, warrant and covenant that it has the full right to convey the entire interest herein assigned, that its has not executed and will not execute any instrument or assignment in conflict herewith, and that the rights assigned herein are not otherwise encumbered by any grant, license or right;

AND Assignors further covenant and agree that Assignors will at any time upon request make, execute and deliver without further compensation, any and all other instruments in writing, including further applications, papers, affidavits, power of attorney, assignments, and other documents, and do all lawful acts and things, which, in the opinion of counsel for said Assignee, its successors and assigns, may in any country be required or necessary more effectively to secure to and vest in said Assignee, its successors and assigns the entire right, title and interest in and to said Invention and Rights hereby sold, assigned, transferred and conveyed, and that Assignors will sign any applications for reissue, division, continuation, continuation-in-part, renewal, substitute or extension of said application for Letters Patent or any resulting Letters Patent;

AND Assignors further covenant and agree that Assignors will at any time upon request communicate to the Assignee, its successors, assigns or other legal representatives any facts relating to the aforesaid invention known to it, and will testify as to the same in any interference, litigation, mediation, arbitration or other proceeding when requested to do so.

IN WITNESS WHEREOF, Assignors have hereunto set their hands and seals

Signature of Inventor: 
Signature

Inventor's Name: Thomas A.E. Platts-Mills
Printed Name

Inventor's Address of Residence: Personal Info

Date of Execution: 12/12/06

PATENT FOUNDATION
UNIVERSITY OF VIRGINIA

Signature of Inventor: _____
Signature

Inventor's Name: Tina Hatley See attached assignment
Printed Name

Inventor's Address of Residence: Personal Info

Date of Execution: 12/10/06

Signature of Inventor: _____
Signature

Inventor's Name: _____
Printed Name

Inventor's Address of Residence: _____

_____

Date of Execution: _____

Signature of Inventor: _____
Signature

Inventor's Name: _____
Printed Name

Inventor's Address of Residence: _____

_____

Date of Execution: _____

**Note: Please copy this page for additional inventors.**

**ASSIGNMENT**

WHEREAS, IINA HAILEY, M D , a citizen of the United States, residing at Personal Info Personal Info (the "ASSIGNOR"), has invented certain new and useful improvements in DEVELOPMENT OF ASSAYS FOR IgE Ab TO A CHIMERIC MONOCLONAL ANTIBODY;

WHEREAS, The University of Virginia, 314 Madison Hall, P O Box 400301, Charlottesville, Virginia 22904-4301 (the "ASSIGNEE"), is desirous of acquiring the entire right, title and interest in and to the aforesaid invention, including any tangible materials embodied in or encompassed by the invention and any trade secrets pertaining to the invention, and any improvements thereon, (the "Invention") and in and to said applications for Letters Patent thereon in the United States, its territories and possessions ("United States") and all foreign countries, including rights to claim priority, to any provisional applications, and in and to any Letters Patent of the United States or any foreign country which may be granted therefore, including any and all reissues, divisions, continuations, continuations-in-part, renewals, substitutes or extensions thereof (the "Rights");

NOW, THEREFORE, for and in consideration of the royalty share of (b)(4) for all licensing income and other good and valuable consideration, the receipt of which is hereby acknowledged, ASSIGNOR has sold, assigned, transferred and conveyed, and does hereby sell, assign, transfer and convey to ASSIGNEE, its successors and assigns, the entire right, title and interest in and to the aforesaid Invention and Rights, except that ASSIGNEE hereby grants back to the ASSIGNOR a royalty fee non-transferable license to make and use the Invention under the Rights for educational and research purposes, only The aforesaid assignment includes the right in and to all income, royalties, damages and payments now or hereafter due or payable with

respect to any Letters Patent which may be granted, and in and to all causes of action (either in law or in equity), and the right to sue, counterclaim and recover for past, present and future infringement of the rights assigned or to be assigned under this Assignment, as fully and entirely as the same would have been held and enjoyed by ASSIGNOR if this sale and assignment had not been made;

AND ASSIGNOR hereby authorizes and requests the appropriate governmental officials to issue any and all such United States or foreign Letters Patent under said invention, or resulting from any of said applications thereof, to the ASSIGNEE, as the assignee of the entire right, title and interest in and to the same;

AND ASSIGNOR hereby represents, warrants and covenants that she has the full right to convey the entire interest herein assigned, that she has not executed and will not execute any instrument or assignment in conflict herewith, and that the rights assigned herein are not otherwise encumbered by any grant, license or right;

AND ASSIGNOR further covenants and agrees that ASSIGNOR will at any time upon request make, execute and deliver without further compensation, any and all other instruments in writing, including further applications, papers, affidavits, power of attorney, assignments, and other documents, and do all lawful acts and things, which, in the opinion of counsel for said ASSIGNEE, its successors and assigns, may in any country be required or necessary more effectively to secure to and vest in said ASSIGNEE, its successors and assigns the entire right, title and interest in and to said Invention and Rights hereby sold, assigned, transferred and conveyed, and that ASSIGNOR will sign any applications for reissue, division, continuation, continuation-in-part, renewal, substitute or extension of said application for Letters Patent or any resulting Letters Patent;

AND ASSIGNOR further covenants and agrees that ASSIGNOR will at any time upon request communicate to the ASSIGNEE, its successors, assigns or other legal representatives any facts relating to the aforesaid invention known to it, and will testify as to the same in any interference, litigation, mediation, arbitration or other proceeding when requested to do so

IN WITNESS WHEREOF, ASSIGNOR has hereunto set her hand and seal

3/27/06
Date

Tina Hatley MD
Tina Hatley, M D., ASSIGNOR

STATE OF ARKANSAS )
) ss
COUNTY OF WASHINGTON )

On this 27th day of March, 2006, before me personally appeared Tina Hatley, M D , to me known to be the person described hereinabove who executed the foregoing Assignment, and who acknowledged to me that she executed the same for the reasons and purpose therein set forth

My Commission Expires:

1-31-2014

Charles A Carey
Notary Public

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UNIVERSITY OF VIRGINIA

CERTIFICATION
By signing below, each inventor certifies the following to be true:

1 I am an inventor of the present invention (see the Appendix C for guidelines in determining inventorship);

2 to the best of my knowledge, the other named inventors are properly included as inventors;

3 to the best of my knowledge, there are no other inventors that should be included as inventors;

4 I agree to the stated royalty shares for each inventor, and that such apportionment of royalties is made among the inventors by mutual agreement, of our own free will, and without coercion of any kind

Any income received as a result of licensing will be distributed according to the UVA policy and then will be divided among the inventors in the percentages indicated below If the royalty distribution is NOT completed, the UVA patent policy dictates that royalties be shared equally among inventors

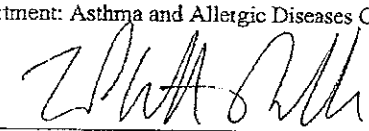
You must notify UVAPF of any change of address If you cannot be contacted, any patent applications may be abandoned and you will not receive any royalties

**Please indicate with an asterisk the inventor who will serve as the principal contact with the Patent Foundation** All correspondence with, and questions for, the inventors will be addressed to the principal contact

| | | | |
|---|---|---|---|
| Name: | Thomas A E Platts-Mills | Royalty share in %: | (b)(4) |
| SS#: | Personal Info | Citizenship: | Personal Info |
| Hm Address: | Personal Info | Office Address: | Box 801355<br>Bld MR4 Rm 5086<br>Charlottesville VA 22908 |
| Hm Phone: | Personal Info | Office Phone: | 434-924-5917 |
| | | Email: | Tap2z@virginia edu |

Please check one:
_#__ I am a UVA inventor
___ I am not a UVA inventor
___ I invented this technology while at UVA but I am no longer at UVA

Department: Asthma and Allergic Diseases Center



*Inventor Signature*

3/31/06

*Date*

Platts-Mills-162

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| | | | |
|---|---|---|---|
| Name: | Tina Whytsell Hatley MD<br>White Cell Research and Development, LLC | Royalty share in %: | (b)(4) |
| SS#: | Personal Info | Citizenship: | Personal Info |
| Hm Address: | Personal Info | Office Address: | 2703 SE G St Ste 7<br>Bentonville AR 72712 |
| Hm Phone: | Personal Info | Office Phone: | 479-254-9777 |
| | | Email: | Allergy_office@yahoo com |

Please check one:
___ I am a UVA inventor
_x_ I am not a UVA inventor
___ I invented this technology while at UVA but I am no longer at UVA

Department (if different than that of first inventor): ___NA_____

Tina Hatley MD
*Inventor Signature*

3/27/06
*Date*

| | | | |
|---|---|---|---|
| Name: | | Royalty share in %: | |
| SS#: | | Citizenship: | |
| Hm Address: | | Office Address: | |
| Hm Phone: | | Office Phone: | |
| | | Email: | |

Please check one:
___ I am a UVA inventor
___ I am not a UVA inventor
___ I invented this technology while at UVA but I am no longer at UVA

Department (if different than that of first inventor): _____

*Inventor Signature*

*Date*

Pages 29 through 174 redacted for the following reasons:
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Removed by Agreement (9/7/2012)

Pages 196 through 204 redacted for the following reasons:
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NIH internal documents

Removed by agreement (9/7/2012)