

2905 U.S. PTO/SB/05 (12/97)

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UTILITY PATENT APPLICATION TRANSMITTAL <small>(Only) for new nonprovisional applications under 37 CFR 1.53(b)</small>	Attorney Docket No. X14173A
	First Named Inventor or Application Identifier
	NIYIKIZA Clet
Express Mail Label No. EL832896550 US	

Application Elements
See MPEP chapter 600 concerning utility patent application contents.

1. Fee Transmittal Form (Submit an original, and a duplicate for fee processing)

2. Specification [Total Pages **21**]
 (preferred arrangement set forth below)

- Descriptive title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claims
- Abstract of the Disclosure

3. Drawing(s) (35 USC 113) [Total Sheets]

4. Oath or Declaration [Total Pages **3**]

a. Newly executed (original or copy)

b. Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed) [Note Box 5 below]

i. DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).

5. Incorporation By Reference (useable if Box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

ADDRESS TO: Commissioner for Patents
 Mail Stop Patent Application
 P.O. Box 1450
 Alexandria, VA 22313-1450

6. Microfiche Computer Program (Appendix)

7. Nucleotide and/or Amino Acid Sequence Submission applicable, all necessary

a. Computer Readable Copy

b. Paper Copy (identical to computer copy)

c. Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. Assignment Papers (cover sheet & document(s))

9. 37 CFR 3.73(b) Statement (when there is an assignee) Power of Attorney

10. English Translation Document (if applicable)

11. Information Disclosure Statement (IDS)/PTO-1449 2 Copies of IDS Citations

12. Preliminary Amendment

13. Return Receipt Postcard (MPEP 503) (Should be specifically itemized)

14. Small Entity Statement filed in prior application, Status still proper and desired

15. Certified Copy of Priority Document(s) (if foreign priority is claimed)

16. Other:
Amendment and Petition to Correct Inventorship

17. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:
 Continuation Divisional Continuation-in-part (CIP) of prior application No. **10/ 297,821**

18. CORRESPONDENCE ADDRESS

Customer Number or Bar Code Label **25885** or Correspondence address below
 (Insert Customer No. Or Attach bar code label here)

Eli Lilly and Company

ADDRESS
 Patent Division
 P.O. Box 6288

25885
 PATENT TRADEMARK OFFICE

CITY	Indianapolis	STATE	Indiana	ZIP CODE	46206-6288
COUNTRY	U.S.A.	TELEPHONE	317-277-7443	FAX	317-276-3861

SUBMITTED BY

Typed or Printed Name	Elizabeth A. McGraw	Complete (if applicable)	
Signature	<i>Elizabeth A. McGraw</i>	Reg. Number	44,646
		Date	29 Nov 2005

"Express Mail" mailing label number **EL 832896550 US**
 Date of Deposit **29 Nov. 2005**

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QUEEN THOMAS Printed Name *Queen Thomas* Signature

112905
1128807
13261 U.S. PTO

112905

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FEE TRANSMITTAL

Effective December 8, 2004

638 U.S. PTO

Complete if Known	
Serial No.	
Application Date	
US Nat'l Entry Date (if applicable)	
First Named Inventor	NIYIKIZA Clet
Group Art Unit	
Examiner Name	
Conf. No.	
Attorney Docket Number	X14173A

TOTAL AMOUNT OF PAYMENT (\$) 1360.00

METHOD OF PAYMENT (check one)

FEE CALCULATION (continued)

1. The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number: 05-0840

Deposit Account Name: Eli Lilly and Company

Charge Any Additional Fee Required

Charge the Issue Fee Set in 37 CFR 1.18 at the time of allowance

Large Entity Fee Code	Large Entity Fee (\$)	Fee Description	Fee Paid
1051	130	Surcharge-late filing fee or oath	
1052	50	Surcharge-late provisional filing fee or cover sheet.	
1053	130	Non-English specification	
1251	120	Extension for reply within first month	
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Code	Description	Fee	Fee Paid
1011	Basic filing fee (Utility)	\$300.00	300.00
1111	Utility search fee	\$500.00	500.00
1311	Utility examination fee	\$200.00	200.00
SUBTOTAL (1)		(\$1,000)	

Code	Total claims	Extra	Fee Paid (\$)
1202	10 - 20 =	X 50 =	\$

Independent claims

1201 2 - 3 = X 200 = \$

Multiple Dependent Claim

1203 Yes or No 360 = \$360 (if yes)

Claims and Excess Length Fees

1081 Total length (spec + drawings) 21 - 100 = excess pages \$

No extra charge for first 100 pages. Must pay \$250 for each adtl 50 pages (or fraction thereof).

SUBTOTAL (2) (\$) 360.-

Other fee (specify)	Fee Paid
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Other fee (specify)	
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Other fee (specify)	
SUBTOTAL (3)	(\$)

SUBMITTED BY

Typed or Printed Name: Elizabeth A. McGraw

Signature: *E.A. McGraw*

Reg. Number: 44,646

Date: 29-Nov-2005

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Examiner Name
Conf. No.

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FEE CALCULATION (continued)

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Other fee (specify)

Other fee (specify)

Other fee (specify)

SUBTOTAL (3) (\$)

Complete (if applicable)

Reg. Number: 44,646
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NOVEL ANTIFOLATE COMBINATION THERAPIES

5 Potentially, life-threatening toxicity remains a major limitation to the optimal administration of antifolates. (see, generally, Antifolate Drugs in Cancer Therapy, edited by Jackman, Ann L., Humana Press, Totowa, NJ, 1999.) In some cases, a supportive intervention is routinely used to permit safe, maximal dosing. For example, steroids, such as dexamethone, can be used to prevent the formation of skin rashes caused by the
10 antifolate. (Antifolate, pg 197.)

Antifolates represent one of the most thoroughly studied classes of antineoplastic agents, with aminopterin initially demonstrating clinical activity approximately 50 years ago. Methotrexate was developed shortly thereafter, and today is a standard component of effective chemotherapeutic regimens for malignancies such as lymphoma, breast cancer,
15 and head and neck cancer. (Bonnadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes: Ten year results. *JAMA* 1995;273(7):542-547; Bonnadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. *N Engl J*
20 *Med* 1995;332(14):901-906; and Hong WK, Schaefer S, Issell B, et al. A prospective randomized trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. *Cancer* 1983;52:206-210.) Antifolates inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways, in particular, thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycylamide
25 ribonucleotide formyltransferase (GARFT), by competing with reduced folates for binding sites of these enzymes. (Shih C, Habeck LL, Mendelsohn LG, Chen VJ, Schultz RM. Multiple folate enzyme inhibition: Mechanism of a novel pyrrolopyrimidine-based antifolate LY231514 (MTA). *Advan Enzyme Regul*, 1998; 38:135-152 and Shih C, Chen VJ, Gossett LS, et al. LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits
30 multiple folate-requiring enzymes. *Cancer Res* 1997;57:1116-1123.) Several antifolate drugs are currently in development. Examples of antifolates that have thymidylate

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