

Award Number: W81XWH-10-2-0196

TITLE: CHEMOTHERAPY OF CUTANEOUS LEISHMANIASIS

PRINCIPAL INVESTIGATOR: DR. ARBA AGER

CONTRACTING ORGANIZATION: UNIVERSITY OF MIAMI  
MIAMI, FL 33177

REPORT DATE: October 2012

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Material Command  
Fort Detrick, Maryland 21702-5012

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# REPORT DOCUMENTATION PAGE

*Form Approved*  
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|   |                         |                                |                                   |  |  |
|---|-------------------------|--------------------------------|-----------------------------------|--|--|
| <b>1. REPORT DATE</b><br>October 2012   |                         | <b>2. REPORT TYPE</b><br>Final |                                   | <b>3. DATES COVERED</b><br>01Sep2010–31 Dec 2012 |  |
| <b>4. TITLE AND SUBTITLE</b><br>CHEMOTHERAPY OF CUTANEOUS LEISHMANIASIS   |                         |                                |                                   | <b>5a. CONTRACT NUMBER</b>                       |  |
|   |                         |                                |                                   | <b>5b. GRANT NUMBER</b><br>W81XWH-10-2-0196      |  |
|   |                         |                                |                                   | <b>5c. PROGRAM ELEMENT NUMBER</b>                |  |
| <b>6. AUTHOR(S)</b><br>Arba Ager, Ph.D.<br><br><b>E-Mail:</b> aager@med.miami.edu   |                         |                                |                                   | <b>5d. PROJECT NUMBER</b>                        |  |
|   |                         |                                |                                   | <b>5e. TASK NUMBER</b>                           |  |
|   |                         |                                |                                   | <b>5f. WORK UNIT NUMBER</b>                      |  |
| <b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b><br>University of Miami<br>Miami, FL 33177   |                         |                                |                                   | <b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>  |  |
| <b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b><br>U.S. Army Medical Research and Materiel Command<br>Fort Detrick, Maryland 21702-5012  |                         |                                |                                   | <b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>          |  |
|   |                         |                                |                                   | <b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>    |  |
| <b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b><br>Approved for Public Release; Distribution Unlimited   |                         |                                |                                   |  |  |
| <b>13. SUPPLEMENTARY NOTES</b>  |                         |                                |                                   |  |  |
| <b>14. ABSTRACT</b><br>Two antileishmanial test systems (MLS and MLL) were used to evaluate compounds at one or more levels. These test systems used female BALB/c mice infected with Leishmania major. There were 11 MLS tests done and 242 compounds used. The following 19 compounds were active; BU55197, BU5504, BP20206, BQ90098, BQ90552, BS81946, BS83191, BS86085, BU30118, BQ90981, BQ92145, AQ52825, BS04930, BS80690, BS93553, BU26730, BU59640, BS84858 and BU68416. In the MLS test parasites were injected intradermally (ID) at the base of the tail. Drug treatment was started on day 3 post infection IP for 10 days. In addition, 13 MLL tests were done and 113 compounds used. Results indicated 4 actives: BG32694, BU59640, BU59640 and BU68452. In the MLL test, mice were infected ID at the base of the tail and treatment was started IP for 10 days when the lesions reached between 20-70 mm <sup>2</sup> . AmBiosome was used as the positive control for all test systems. The Oracle database was used for tabulation of data and statistically analyzing the results. |                         |                                |                                   |  |  |
| <b>15. SUBJECT TERMS-</b> Leishmania major, Cutaneous Leishmaniasis, antileishmanial drugs  |                         |                                |                                   |  |  |
| <b>16. SECURITY CLASSIFICATION OF:</b>  |                         |                                | <b>17. LIMITATION OF ABSTRACT</b> | <b>18. NUMBER OF PAGES</b>                       | <b>19a. NAME OF RESPONSIBLE PERSON</b>           |
| <b>a. REPORT</b><br>U   | <b>b. ABSTRACT</b><br>U | <b>c. THIS PAGE</b><br>U       |                                   |  | USAMRMC  |
|   |                         |                                | UU                                | 38   | <b>19b. TELEPHONE NUMBER</b> (include area code) |

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## INTRODUCTION

Leishmaniasis is a disease that has several different types of clinical pathology ranging from visceral pathology to simple cutaneous lesions. Cutaneous Leishmaniasis It has been around for centuries and remains a serious problem in areas such as Iraq, Afghanistan, Iran, Saudi Arabia, Yemen, Peru and Brazil. The US Army has had over 3,500 troops infected with this protozoan parasite. Kabul is believed to have the greatest number of cutaneous leishmania cases in the world with an incidence of over 67,000 cases per year. It is also found in more than 70 countries in the world. In the South American country of Colombia a large numbers of cutaneous leishmania cases (over 40,000) were reported between 2005 and 2009. It was caused by *Leishmania braziliensis* and many dogs serve as reservoir hosts that the vector (a sand fly) bites and gets infected then bites a human and transmit the disease. There is no vaccine for this parasite in humans so treatment relies on chemotherapy. The treatment for this disease is complicated because of several reasons; long treatment schedules, toxic drugs with many serious side effects, they are becoming less effective and many are expensive. Pentavalent antimonials are one of the major drugs used today but toxicity is a problem, resistance has developed and it must be administered by trained medical personnel for a prolonged time period. Miltifosine (an Alkyl-lysopholipid) is an oral preparation that has low efficacy and resistance has developed to it. Amphotericin B intravenous formulations are used in many areas of the world but they are very expensive and there are many side effects. Several other parental drugs such as pentamidine and oral triazoles like fluconazole and itraconazole have been used but their efficacy is still not very good. Paromomycin has been shown to be effective in some cases when administered topically in combination with Gentamicin. The majority of cases of cutaneous leishmaniasis from the Middle East are cause by *Leishmania major* and new therapies are desperately needed. We are using this parasite in a rodent model to find new effective chemotherapeutic agents.

## BODY

There were 2 mouse models of cutaneous antileishmanial used in female BALB/c mice infected with *Leishmania major*. The first test is the Mouse Leishmania Suppressive (MLS) test system. The second test system tested compounds found active in the MLS test is called the Miami Leishmania Lesion (MLL) test system. Metacyclic parasites ( $1 \times 10^6$ ) obtained from cultures of donor mice infected footpads were used as an inoculum for each test. In the MLS test model and the MLL model the mice were injected with the parasites intradermally (ID) in the shaved area of the back about 1 inch forward from the tail. Test compounds were administered intraperitoneally (IP) once a day for 10 days starting 3 days post infection for the MLS tests and once a day for 10 days IP to mice in the MLL test once the developing lesion sizes were between 20-70 mm<sup>2</sup>. The lesions were measured on days 14, 21 and 28 days after infection for the MLS test. For the MLL test the lesions were measures at the start of treatment then on days 7, 14, 21 and 28. The female BALB/c mice were weighed on the day of infection and daily during treatment then once a week for the duration of the MLS test. For the MLL test the mice were weighed on the day of infection then weekly until administration of test compounds. They were then weighed daily during treatment and then weekly until the end of the test. All of the data was entered into an Oracle database and at the conclusion of each test and an analysis of the data was made and a % suppression of the lesion sizes in both the MLS and MLL tests. In both the MLS and MLL tests the data obtained from the treated mice where compared with the infected non-treated control mice. The positive control was AmBisome at 12.5 mg/kg/day for 10 days in the MLS test and 37.5 mg/kg/day for 10 days in the MLL test. In the MLS and MLL tests compounds were considered active if the lesion size was suppressed by at least 50%.

For the MLS 242 compounds were tested and 19 were found to be active. There were 133 compounds tested in the MLL test system with only 13 exhibiting activity.

## KEY RESEARCH ACCOMPLISHMENT

- Performed 11 MLS tests evaluating 242 compounds and found 19 actives.
- Performed 13 MLL tests evaluating 133 compounds and found 4 active.
- The new Oracle data base developed by WRAIR for data obtained in the Leishmanial MLS and MLL Test Systems was modified to enable changes in the protocol to be incorporated and it worked well for the following activities measured; mortality, mouse body weights, survival times, clinical pathology, toxicity, statistics including the % suppression of lesion size which was used to determine if a compound was active (need at least a 50% suppressive figure to be considered an active compound).

## REPORTABLE OUTCOMES

The Oracle database developed by WRAIR for entering and analyzing data obtained from the Antileishmanial MLS and MLL Test Systems and was further validated. This database allows one to enter data for the MLS and MLL test systems as it is obtained directly into the database and analyzes it. Such data includes mouse body weights, drugs and their dosages, clinical observations of the mice, % suppression of lesion size, toxicity and mortality values. A similar database is being developed for the data obtained from the drug combination tests in the MLS and MLL Test Systems and the Miami Leishmania Hamster test system using *L. panamensis*.

There were 11 MLS tests where 242 compounds were tested with 19 active. In the MLL test system there were 13 tests with 133 compounds and found 4 active.

## CONCLUSIONS

Two antileishmanial drug test systems (MLS and MLL) were validated in mice infected with *Leishmania major*.

Nineteen active compounds were found out of 242 in the MLS system. In the MLL system there were 4 active out of 133 compounds.

The Oracle Data Base System has been updated and validated to enter and analyze data for the MLS and MLL Test Systems. This data base allows all of the data in this system to be computerized and made available to Army researchers at Walter Reed on a regular basis.

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## APPENDICES

### CURRICULUM VITAE

1. Date: DECEMBER, 2012

### PERSONAL

2. Name: Arba L. Ager, Jr.
3. Home Phone:
4. Office Phone:
5. Home Address:
6. Current Academic Rank: Research Associate Professor
7. Primary Department: Microbiology and Immunology
8. Secondary or Joint Appointments:
9. Citizenship: USA
10. Visa Type (if non-citizen): None

### HIGHER EDUCATION

11. Institutional (institution; degree; date conferred):
- |                           |              |        |      |
|---------------------------|--------------|--------|------|
| University of Oregon      | Biology      | B.S.   | 1964 |
| Portland State University | Zoology      | M.S.T. | 1966 |
| University of Georgia     | Parasitology | Ph.D.  | 1972 |
12. Non-Institutional (description; dates): None
13. Certification, licensure (description; board or agency; dates): None

### EXPERIENCE

14. Academic (institutions; rank/status; dates):
- |   |                      |           |
|---|----------------------|-----------|
| Michigan State University<br>Department of Microbiology | Assistant Instructor | 1966-1969 |
|---|----------------------|-----------|



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**20. Other works accepted for publication:**

None

**PROFESSIONAL**

**21. Editorial Responsibilities:** *Acta Tropica*

**22. Professional and Honorary Organizations** (member; officer; date):

American Society of Microbiology  
 American Society of Parasitology  
 American Society of Tropical Medicine and Hygiene

**23. Honors and Awards:**

World Health Organizations Special Training Fellowship, April, 1978. University of Liverpool, England, Department of Tropical Medicine and Parasitology.

National Institute of Health Malariology Traineeship Fellow, University of Georgia, 1969-1972

Sociedad Ecuatoriana de Medicina Tropical y Parasitologia. (Honorary Member). 1988.

- 24. Other Professional activities** (e.g., papers presented; performances; conference proceedings; seminar or conference panel member; catalogue work; etc.):

### **Conferences**

First Rodent Malaria Genomics Meeting, Atlanta, Ga. Presented a paper entitled: The role of rodent malaria in antimalarial drug screening. 2001.

First American and Caribbean Workshop on Emerging and Re-emerging Diseases. Tegucigalpa, Honduras. Presented a paper entitled: Malaria: Drug resistance and control in Central America. 1997.

### **Invited outside lectureships**

Lectureships in Medical Parasitology, University of the West Indies, School of Medicine, Kingston, Jamaica, 1978, 1979, 1980, 1981.

Lectureship in Medical Parasitology, American University of the Caribbean, School of Medicine, Montserrat, 1982.

### **Consultantships**

Consultant in Medical Parasitology to Universidad Cayetano Heredia, Lima, Peru.

## **25. TEACHING**

Teach Medical Parasitology to MD students as part of MIC 501.

Teach Medical Parasitology to MD/MPH students

Teach Medical Parasitology MIC 322.

Teach Special Project Parasitology MIC 452 (Laboratory Course).

Teach Medical Parasitology part of MIC 301.

- 26. Thesis and Dissertation Advising/Post-doctoral student supervision** (chairman or committee member; topic; student name; date):

David Lowery, Ph.D. June 1985.

Mary Kalscheuer, M.S. Biology Department, 1986.

Jorge Bonilla, Ph.D. Dept of Pathobiology, University of Florida 2004.

Tereza Magalhaes, Ph.D. Dept of Epidemiology 2005.

Appendix *Leishmania***TABLE 1 MLS RESULTS**

| TEST | GROUP | COMPOUND | MKD  | %<br>SUPPRESSION |
|------|-------|----------|------|------------------|
| 960  | 1     | BQ97891  | 10   | -52              |
|      | 2     | BS80118  | 160  | -77              |
|      | 3     | BS82658  | 80   | -151             |
|      | 4     | BS83397  | 20   | -61              |
|      | 5     | BS83637  | 80   | -85              |
|      | 6     | BS83646  | 80   | -20              |
|      | 7     | BS84027  | 10   | -151             |
|      | 8     | BS85293  | 40   | -3               |
|      | 9     | BS85355  | 40   | -192             |
|      | 10    | BU24067  | 20   | -13              |
|      | 11    | BU30654  | 160  | -18              |
|      | 12    | BU55197  | 160  | 56               |
|      | 13    | BU55204  | 160  | 100              |
|      | 14    | BS82354  | 80   | -76              |
|      | 15    | BS79660  | 15   | -8               |
|      | 16    | AF84868  | 80   | -6               |
|      | 17    | BD36704  | 160  | -88              |
|      | 18    | BM18573  | 160  | -2               |
|      | 19    | BN34143  | 40   | 1                |
|      | 20    | BN43106  | 20   | -87              |
|      | 21    | BN62067  | 160  | 38               |
|      | 22    | BN68532  | 5    | -21              |
|      | 23    | BS94407  | 12.5 | 100              |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 961  | 1     | BN79704  | 20   | Toxic         |
|      | 2     | BP16828  | 160  | 26            |
|      | 3     | BP20206  | 80   | 59            |
|      | 4     | BP21187  | 160  | -29           |
|      | 5     | BQ35168  | 20   | -48           |
|      | 6     | BQ35346  | 160  | 36            |
|      | 7     | BQ35382  | 160  | 33            |
|      | 8     | BQ35435  | 160  | -29           |
|      | 9     | BQ90098  | 40   | 67            |
|      | 10    | BQ90552  | 10   | 51            |
|      | 11    | BQ90605  | 80   | 22            |
|      | 12    | BQ91942  | 80   | -13           |
|      | 13    | BQ93197  | 40   | -14           |
|      | 14    | BQ94836  | 10   | -44           |
|      | 15    | BQ95235  | 40   | 14            |
|      | 16    | BQ95397  | 5    | -17           |
|      | 17    | BQ95548  | 160  | -54           |
|      | 18    | BQ95860  | 20   | -66           |
|      | 19    | BQ96303  | 40   | -59           |
|      | 20    | BR36919  | 80   | -2            |
|      | 21    | BS81946  | 160  | 100           |
|      | 22    | BS82265  | 160  | -14           |
|      | 23    | BS94407  | 12.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 969  | 1     | BS83191  | 160  | 51            |
|      | 2     | BS83413  | 160  | 37            |
|      | 3     | BS84296  | 5    | 25            |
|      | 4     | BS84732  | 10   | -2            |
|      | 5     | BS85051  | 10   | 20            |
|      | 6     | BS85999  | 80   | 25            |
|      | 7     | BS86085  | 80   | 73            |
|      | 8     | BS86245  | 40   | -4            |
|      | 9     | BS89442  | 80   | -6            |
|      | 10    | BS89951  | 10   | 20            |
|      | 11    | BS93384  | 40   | 12            |
|      | 12    | BS93768  | 160  | -65           |
|      | 13    | BS96474  | 160  | -37           |
|      | 14    | BU25304  | 10   | -11           |
|      | 15    | BU25939  | 10   | -30           |
|      | 16    | BU30118  | 40   | 53            |
|      | 17    | BQ90767  | 80   | 34            |
|      | 18    | BQ90794  | 5    | -34           |
|      | 19    | BQ90810  | 20   | 9             |
|      | 20    | BQ90838  | 20   | 18            |
|      | 21    | BQ90981  | 160  | 52            |
|      | 22    | BQ91086  | 10   | -27           |
|      | 23    | BS94407  | 12.5 | 97            |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 970  | 1     | BQ91540  | 160  | 6             |
|      | 2     | BQ91602  | 80   | 23            |
|      | 3     | BQ92029  | 160  | -63           |
|      | 4     | BQ92083  | 160  | -13           |
|      | 5     | BQ92145  | 160  | 54            |
|      | 6     | BQ92494  | 160  | 7             |
|      | 7     | BQ92761  | 10   | 14            |
|      | 8     | BQ93142  | 20   | -20           |
|      | 9     | BQ93160  | 80   | -47           |
|      | 10    | BQ93188  | 160  | -23           |
|      | 11    | BQ93375  | 160  | 25            |
|      | 12    | BQ93400  | 160  | -20           |
|      | 13    | BQ93446  | 10   | 7             |
|      | 14    | BQ93482  | 80   | -36           |
|      | 15    | BQ93642  | 160  | -30           |
|      | 16    | BQ93688  | 40   | -45           |
|      | 17    | BQ93768  | 40   | -30           |
|      | 18    | BQ94345  | 5    | 23            |
|      | 19    | BQ94381  | 40   | -99           |
|      | 20    | BQ94416  | 40   | -58           |
|      | 21    | BQ94443  | 20   | -27           |
|      | 22    | BQ94452  | 20   | 12            |
|      | 23    | BS94407  | 12.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 971  | 1     | BQ94461  | 80   | -86           |
|      | 2     | BQ94470  | 10   | -31           |
|      | 3     | BQ94505  | 80   | -12           |
|      | 4     | BS83495  | 80   | -92           |
|      | 5     | BS83575  | 10   | -73           |
|      | 6     | BU25957  | 20   | 40            |
|      | 7     | BU30047  | 20   | -51           |
|      | 8     | BQ91219  | 40   | -29           |
|      | 9     | BQ91264  | 20   | -5            |
|      | 10    | BQ91291  | 40   | -66           |
|      | 11    | BQ91308  | 160  | -65           |
|      | 12    | BQ91317  | 160  | 43            |
|      | 13    | BQ91399  | 80   | -65           |
|      | 14    | BQ91433  | 20   | -101          |
|      | 15    | BQ91451  | 80   | -19           |
|      | 16    | BQ91479  | 4    | -134          |
|      | 17    | BQ92798  | 20   | Toxic         |
|      | 18    | BQ93035  | 20   | -30           |
|      | 19    | BQ93295  | 10   | 21            |
|      | 20    | BQ93339  | 40   | -33           |
|      | 21    | BQ93491  | 160  | -103          |
|      | 22    | AG03635  | 10   | -36           |
|      | 23    | BS94407  | 12.5 | 99            |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 972  | 1     | AJ64549  | 40   | -39           |
|      | 2     | AR12559  | 80   | 4             |
|      | 3     | AW46149  | 10   | -1            |
|      | 4     | BJ01377  | 16   | 1             |
|      | 5     | BM39769  | 20   | -66           |
|      | 6     | BQ94498  | 40   | 33            |
|      | 7     | BQ94514  | 16   | 31            |
|      | 8     | BQ94569  | 20   | -9            |
|      | 9     | BQ94578  | 10   | 11            |
|      | 10    | BQ94587  | 20   | -67           |
|      | 11    | BQ94783  | 10   | -71           |
|      | 12    | BQ94809  | 10   | 12            |
|      | 13    | BQ94818  | 20   | -15           |
|      | 14    | BQ94854  | 2.5  | -50           |
|      | 15    | BQ94872  | 20   | -117          |
|      | 16    | BQ94916  | 5    | -44           |
|      | 17    | BQ94934  | 160  | -91           |
|      | 18    | BQ95137  | 10   | -110          |
|      | 19    | BQ95164  | 10   | -67           |
|      | 20    | BQ95379  | 10   | -66           |
|      | 21    | BQ95404  | 20   | -15           |
|      | 22    | BQ95511  | 40   | -76           |
|      | 23    | BS94407  | 12.5 | 100           |



| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 973  | 1     | BQ95628  | 40   | -17           |
|      | 2     | BQ95691  | 160  | 8             |
|      | 3     | BQ95717  | 20   | -20           |
|      | 4     | BQ95799  | 10   | 15            |
|      | 5     | BQ96107  | 40   | -1            |
|      | 6     | BQ96125  | 160  | -3            |
|      | 7     | BQ96223  | 160  | -14           |
|      | 8     | BQ96232  | 40   | -5            |
|      | 9     | BS05259  | 10   | -8            |
|      | 10    | BS80529  | 160  | -14           |
|      | 11    | BS80583  | 40   | Toxic         |
|      | 12    | BS80592  | 5    | -11           |
|      | 13    | BS83360  | 160  | 11            |
|      | 14    | BS83904  | 80   | -51           |
|      | 15    | BS83959  | 40   | -52           |
|      | 16    | BS85257  | 10   | -10           |
|      | 17    | BU24594  | 160  | 0             |
|      | 18    | BU29357  | 5    | -88           |
|      | 19    | BU30109  | 80   | -17           |
|      | 20    | BU30243  | 40   | -65           |
|      | 21    | BQ92547  | 2.5  | -4            |
|      | 22    | BQ94701  | 80   | 27            |
|      | 23    | BS94407  | 12.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 985  | 1     | BU24281  | 40   | 18            |
|      | 2     | BS93740  | 160  | 29            |
|      | 3     | BS94069  | 40   | 17            |
|      | 4     | BS96670  | 160  | -5            |
|      | 5     | AR49261  | 40   | 43            |
|      | 6     | AK55401  | 5    | 28            |
|      | 7     | AK78459  | 40   | Toxic         |
|      | 8     | AQ52825  | 20   | 88            |
|      | 9     | BQ91424  | 20   | 27            |
|      | 10    | BQ97220  | 20   | 23            |
|      | 11    | BQ99215  | 2.5  | 23            |
|      | 12    | BS04930  | 20   | 50            |
|      | 13    | BS05268  | 5    | 16            |
|      | 14    | BS57459  | 160  | 47            |
|      | 15    | BS79464  | 160  | 20            |
|      | 16    | BS79624  | 80   | -51           |
|      | 17    | BS80690  | 80   | 51            |
|      | 18    | BS82470  | 80   | 18            |
|      | 19    | BS83299  | 5    | Toxic         |
|      | 20    | BS85284  | 160  | -43           |
|      | 21    | BS88132  | 2.5  | -57           |
|      | 22    | BS92449  | 20   | -13           |
|      | 23    | BS94407  | 12.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 989  | 1     | BS93553  | 5    | 100           |
|      | 2     | BS94265  | 40   | 41            |
|      | 3     | BS96189  | 20   | -10           |
|      | 4     | BU24790  | 10   | 5             |
|      | 5     | BU26730  | 160  | 78            |
|      | 6     | BU59640  | 40   | 100           |
|      | 7     | BU60063  | 20   | -75           |
|      | 8     | BH13827  | 20   | 47            |
|      | 9     | BM36240  | 80   | -4            |
|      | 10    | BQ96296  | 160  | -2            |
|      | 11    | BQ96483  | 160  | -11           |
|      | 12    | BS82005  | 80   | -23           |
|      | 13    | BS82032  | 160  | 38            |
|      | 14    | BS82210  | 80   | 7             |
|      | 15    | BS83440  | 80   | -16           |
|      | 16    | BS83548  | 160  | -8            |
|      | 17    | BS84652  | 80   | -6            |
|      | 18    | BS85131  | 160  | -18           |
|      | 19    | BS85168  | 20   | 32            |
|      | 20    | BU22223  | 40   | 27            |
|      | 21    | BU23177  | 160  | -25           |
|      | 22    | BU23239  | 20   | -46           |
|      | 23    | BS94407  | 12.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 990  | 1     | BU24325  | 80   | 15            |
|      | 2     | BQ97248  | 80   | -81           |
|      | 3     | BS82489  | 80   | -7            |
|      | 4     | BS82505  | 40   | 6             |
|      | 5     | BS84858  | 60   | 54            |
|      | 6     | BS85408  | 40   | -1            |
|      | 7     | BS85757  | 160  | -21           |
|      | 8     | BU28421  | 20   | 9             |
|      | 9     | BS82336  | 80   | 3             |
|      | 10    | BS84849  | 20   | -74           |
|      | 11    | BS86192  | 40   | 0             |
|      | 12    | BS88016  | 10   | -70           |
|      | 13    | BU23720  | 40   | 37            |
|      | 14    | BQ97613  | 40   | 2             |
|      | 15    | BQ97640  | 20   | -45           |
|      | 16    | BQ97659  | 40   | -35           |
|      | 17    | BS82550  | 40   | Toxic         |
|      | 18    | BS82612  | 40   | 38            |
|      | 19    | BS83271  | 80   | -34           |
|      | 20    | BS83342  | 40   | -51           |
|      | 21    | BS83708  | 80   | -18           |
|      | 22    | BS83806  | 80   | -32           |
|      | 23    | BS94407  | 12.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 991  | 1     | BS83959  | 20   | -9            |
|      | 2     | BS84741  | 160  | 28            |
|      | 3     | BS85202  | 160  | -2            |
|      | 4     | BS86254  | 20   | 9             |
|      | 5     | BS92501  | 60   | Toxic         |
|      | 6     | BS96483  | 80   | -270          |
|      | 7     | BU22876  | 20   | 15            |
|      | 8     | BU24085  | 20   | -55           |
|      | 9     | BU24101  | 20   | -21           |
|      | 10    | BU26114  | 40   | -32           |
|      | 11    | BQ99242  | 2.5  | -42           |
|      | 12    | BQ99279  | 20   | 11            |
|      | 13    | BR29496  | 10   | -29           |
|      | 14    | BR29521  | 10   | -27           |
|      | 15    | BR29567  | 10   | 25            |
|      | 16    | BS82621  | 80   | -84           |
|      | 17    | BU68407  | 40   | -7            |
|      | 18    | BU68416  | 20   | 99            |
|      | 19    | BU68425  | 160  | 6             |
|      | 20    | BU68434  | 160  | 8             |
|      | 21    | BU68443  | 5    | -64           |
|      | 22    | BU68452  | 80   | 3             |
|      | 23    | BS94407  | 12.5 | 100           |

**TABLE 2 MLS ACTIVES**

| <b><u>TEST</u></b> | <b><u>COMPOUND</u></b> | <b><u>MG/KG/DAY</u></b> | <b><u>%<br/>SUPPRESSION</u></b> |
|--------------------|------------------------|-------------------------|---------------------------------|
| 960                | BU 55197               | 160                     | 56                              |
|                    | BU 55204               | 160                     | 100                             |
| 960                | BP 20206               | 80                      | 59                              |
|                    | BQ 90098               | 40                      | 67                              |
|                    | BQ 90552               | 10                      | 51                              |
|                    | BS 81946               | 160                     | 100                             |
| 969                | BS 83191               | 160                     | 51                              |
|                    | BS 86085               | 80                      | 73                              |
|                    | BU 30118               | 40                      | 53                              |
|                    | BQ 90981               | 160                     | 52                              |
| 970                | BQ 92145               | 160                     | 54                              |
| 985                | AQ 52825               | 20                      | 88                              |
|                    | BS 04930               | 20                      | 50                              |
|                    | BS 80690               | 80                      | 51                              |
| 989                | BS 93553               | 5                       | 100                             |
|                    | BU 26730               | 160                     | 78                              |
|                    | BU 59640               | 40                      | 100                             |
| 990                | BS 84858               | 60                      | 54                              |
|                    | BU 68416               | 20                      | 99                              |

TABLE 3 MLL TESTS

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 965  | 1     | AB11829  | 160  | -19           |
|      | 2     | AB65390  | 160  | -5            |
|      | 3     | AR18631  | 40   | 3             |
|      | 4     | AR18631  | 20   | 3             |
|      | 5     | AR18631  | 10   | 3             |
|      | 6     | BQ91102  | 20   | 4             |
|      | 7     | BQ92001  | 40   | -2            |
|      | 8     | BQ92001  | 20   | -2            |
|      | 9     | BQ92001  | 10   | -2            |
|      | 10    | BQ92314  | 40   | -7            |
|      | 11    | BQ95833  | 40   | 19            |
|      | 12    | BQ95833  | 20   | 19            |
|      | 13    | BQ95833  | 10   | 19            |
|      | 14    | BS84983  | 160  | -9            |
|      | 15    | BS94407  | 37.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 966  | 1     | BS84821  | 40   | 16            |
|      | 2     | BS84821  | 20   | 16            |
|      | 3     | BS84821  | 10   | 16            |
|      | 4     | BS82247  | 80   | 1             |
|      | 5     | AC97879  | 80   | 6             |
|      | 6     | AT29027  | 80   | 7             |
|      | 7     | BG21744  | 20   | -17           |
|      | 8     | BG21744  | 40   | 2             |
|      | 9     | BQ93179  | 40   | -3            |
|      | 10    | BQ93795  | 40   | -9            |
|      | 11    | BQ93795  | 40   | -9            |
|      | 12    | BQ94532  | 80   | -3            |
|      | 13    | BQ97506  | 160  | Toxic         |
|      | 14    | BS79786  | 40   | -21           |
|      | 15    | BS80029  | 20   | 15            |
|      | 16    | BU25331  | 40   | 17            |
|      | 17    | BS94407  | 37.5 | 100           |



| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 967  | 1     | BG32694  | 80   | 1             |
|      | 2     | BH30346  | 10   | 6             |
|      | 3     | BL23622  | 160  | 10            |
|      | 4     | BM13827  | 80   | -2            |
|      | 5     | BN08009  | 80   | 7             |
|      | 6     | BQ35177  | 10   | 20            |
|      | 7     | BQ93624  | 80   | -12           |
|      | 8     | BQ95762  | 40   | -1            |
|      | 9     | BQ97186  | 10   | 4             |
|      | 10    | BS83244  | 10   | -13           |
|      | 11    | BS85444  | 10   | 34            |
|      | 12    | BS88025  | 80   | 5             |
|      | 13    | BU25180  | 40   | 26            |
|      | 14    | BU27997  | 40   | Toxic         |
|      | 15    | BS94407  | 37.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 976  | 1     | BU30574  | 40   | -8            |
|      | 2     | BG32694  | 80   | -27           |
|      | 3     | BL23622  | 160  | -3            |
|      | 4     | BM13827  | 80   | 20            |
|      | 5     | BN08009  | 80   | 10            |
|      | 6     | BQ93624  | 80   | -17           |
|      | 7     | BQ95762  | 40   | -11           |
|      | 8     | BS88025  | 80   | -16           |
|      | 9     | BU25180  | 40   | 15            |
|      | 10    | BU27997  | 40   | 4             |
|      | 11    | BU30574  | 40   | -8            |
|      | 12    | BS94407  | 37.5 | 99            |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 978  | 1     | BQ35177  | 5    | -2            |
|      | 2     | BS85444  | 5    | Toxic         |
|      | 3     | BU27997  | 20   | -5            |
|      | 4     | BS82247  | 40   | -34           |
|      | 5     | AC97879  | 40   | -33           |
|      | 6     | BQ97506  | 80   | Toxic         |
|      | 7     | BQ97506  | 40   | Toxic         |
|      | 8     | BS79786  | 20   | -28           |
|      | 9     | BL23622  | 80   | 5             |
|      | 10    | BL23622  | 40   | 5             |
|      | 11    | BS88025  | 40   | -26           |
|      | 13    | BS88025  | 20   | -9            |
|      | 14    | BN08009  | 40   | 5             |
|      | 15    | BN08009  | 20   | 5             |
|      | 16    | BS94407  | 37.5 | 96            |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 981  | 1     | BG32694  | 40   | 50            |
|      | 2     | BG32694  | 25   | 50            |
|      | 3     | BG32694  | 15   | 50            |
|      | 4     | BM13827  | 40   | 37            |
|      | 5     | BM13827  | 20   | 37            |
|      | 6     | BM13827  | 10   | 37            |
|      | 7     | BM13827  | 5    | 37            |
|      | 8     | BU25180  | 20   | 33            |
|      | 9     | BU25180  | 10   | 33            |
|      | 10    | BU25180  | 5    | 33            |
|      | 11    | BS94407  | 37.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 983  | 1     | BU59640  | 10   | 27            |
|      | 2     | BU59640  | 10   | 64            |
|      | 3     | BU59640  | 20   | 27            |
|      | 4     | BU59640  | 20   | 64            |
|      | 5     | BU59640  | 40   | 27            |
|      | 6     | BU59640  | 40   | 64            |
|      | 7     | BS94407  | 37.5 | 76            |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 984  | 1     | BU60072  | 20   | 0             |
|      | 2     | BU60072  | 40   | 11            |
|      | 3     | BU60081  | 0    | 2             |
|      | 4     | BU60081  | 0    | -20           |
|      | 5     | BS94407  | 37.5 | 96            |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 986  | 1     | BG32694  | 40   | 22            |
|      | 2     | BG32694  | 25   | 22            |
|      | 3     | BG32694  | 15   | 22            |
|      | 4     | BM13827  | 40   | 22            |
|      | 5     | BM13827  | 20   | 22            |
|      | 6     | BM13827  | 10   | 22            |
|      | 7     | BM13827  | 5    | 22            |
|      | 8     | BU25180  | 20   | 28            |
|      | 9     | BU25180  | 10   | 28            |
|      | 10    | BU25180  | 5    | 28            |
|      | 11    | BS94407  | 37.5 | 99            |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 987  | 1     | BS83191  | 160  | -30           |
|      | 2     | BS83413  | 160  | -58           |
|      | 3     | BS84296  | 5    | -50           |
|      | 4     | BS86085  | 40   | -35           |
|      | 5     | BS85999  | 80   | -28           |
|      | 6     | BS89951  | 10   | -59           |
|      | 7     | BU30118  | 40   | -63           |
|      | 8     | BQ90981  | 160  | -32           |
|      | 9     | BS94407  | 37.5 | 85            |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 988  | 1     | BS94407  | 37.5 | 82            |
|      | 2     | BU59640  | 40   | 67            |
|      | 3     | NONE     | 0    |               |
|      | 4     | BQ95762  | 20   | 16            |
|      | 5     | BQ95762  | 10   | 16            |
|      | 6     | BQ95762  | 5    | 16            |
|      | 7     | BQ93624  | 40   | 23            |
|      | 8     | BQ93624  | 20   | 23            |
|      | 9     | BQ93624  | 10   | 23            |
|      | 10    | BN62067  | 80   | 8             |
|      | 11    | BU55197  | 80   | 7             |
|      | 12    | BU55204  | 80   | 6             |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 993  | 1     | BU68407  | 40   | -31           |
|      | 2     | BU68416  | 20   | 14            |
|      | 3     | BU68425  | 160  | -10           |
|      | 4     | BU68434  | 160  | -14           |
|      | 5     | BU68443  | 5    | 22            |
|      | 6     | BS94407  | 37.5 | 100           |

| TEST | GROUP | COMPOUND | MKD  | % SUPPRESSION |
|------|-------|----------|------|---------------|
| 996  | 1     | BU68452  | 80   | 64            |
|      | 2     | BU59640  | 40   | -1            |
|      | 3     | BS93553  | 5    | -4            |
|      | 4     | BS81508  | 160  | -4            |
|      | 5     | BQ93786  | 40   | -22           |
|      | 6     | BU26730  | 80   | -28           |
|      | 7     | BQ93759  | 80   | -29           |
|      | 8     | ZP74275  | 10   | -17           |
|      | 9     | BU30190  | 160  | -17           |
|      | 10    | ZW61835  | 160  | -22           |
|      | 11    | BS94407  | 37.5 | 100           |

**TABLE 4 MLL ACTIVES**

| <b>TEST</b> |  | <b>COMPOUND</b> | <b>MKD</b> | <b>%<br/>SUPPRESSION</b> |
|-------------|--|-----------------|------------|--------------------------|
| 981         |  | BG 32694        | 40         | 50                       |
| 983         |  | BU 59640        | 40         | 64                       |
| 988         |  | BU 59640        | 40         | 67                       |
| 996         |  | BU 68452        | 80         | 80                       |