EXPLORATORY/DEVELOPMENT GRANT **Issue Date:** 08/27/2014

Department of Health and Human Services
National Institutes of Health
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Grant Number: 1R21AI109896-01
FAIN: R21AI109896

Principal Investigator(s):
MINGDI YAN, PHD

Project Title: Maltoheptaose based nanotherapeutics for multidrug resistant bacterial infection

Concino, Linda
Dir, Grants and Contract Admin
Office of Research Administration
600 Suffolk Street, 2nd Floor South
Lowell, MA 018543648

Award e-mailed to: Linda_Concino@uml.edu

Budget Period: 09/01/2014 – 08/31/2015
Project Period: 09/01/2014 – 08/31/2016

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $204,975 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF MASSACHUSETTS LOWELL in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health under Award Number R21AI109896. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Chernay L. Mason
Grants Management Officer
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Additional information follows

SECTION I – AWARD DATA – 1R21AI109896-01

Award Calculation (U.S. Dollars)

Federal Direct Costs	$141,875
Federal F&A Costs	$63,100
Approved Budget	$204,975
Federal Share	$204,975
TOTAL FEDERAL AWARD AMOUNT	$204,975
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$204,975

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$204,975	$204,975
2	$239,175	$239,175

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Number:	93.855
EIN:	1043167352E5
Document Number:	RAI109896A

PMS Account Type:	P (Subaccount)
Fiscal Year:	2014

IC	CAN	2014	2015
AI	8472364		$239,175
AI	8480846	$204,975	

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: M30C BR / **OC**: 414A / **Released**: PII 08/21/2014
Award Processed: 05/08/2014 01:52:21 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R21AI109896-01

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1R21AI109896-01

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 74 or 45 CFR Part 92 as applicable.
d. The NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase V Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the Central Contractor Registration. Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R21AI109896. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

Treatment of Program Income:
Additional Costs

SECTION IV – AI Special Terms and Conditions – 1R21AI109896-01

This is a Modular Award without direct cost categorical breakdowns in accordance with the guidelines published in the NIH Grants Policy Statement, October 2013, see http://grants.nih.gov/grants/policy/nihgps_2013/nihgps_ch13.htm#_Toc271265237. Recipients are required to allocate and account for costs related to this award by category within their institutional accounting system in accordance with applicable cost principles.
*****
This award includes funds awarded for consortium activity with the University of Massachusetts Medical School. Consortiums are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH Grants Policy Statement is available at http://grants.nih.gov/grants/policy/nihgps_2013/nihgps_ch15.htm#_Toc271265264.
*****
Select Agents:

Awardee of a project that at any time involves a restricted experiment with a select agent, is responsible for notifying and receiving prior approval from the NIAID. Please be advised that changes in the use of a Select Agent will be considered a change in scope and require NIH awarding office prior approval. The approval is necessary for new select agent experiments as well as changes in on-going experiments that would require change in the biosafety plan and/or biosafety containment level. An approval to conduct a restricted experiment granted to an individual cannot be assumed an approval to other individuals who conduct the same restricted experiment as defined in the Select Agents Regulation 42 CFR Part 73, Section 13.b (http://www.selectagents.gov/Regulations.html).

Highly Pathogenic Agent:

NIAID defines a Highly Pathogenic Agent as an infectious Agent or Toxin that may warrant a biocontainment safety level of BSL3 or higher according to the current edition of the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories (BMBL) (http://www.cdc.gov/OD/ohs/biosfty/bmbl5/bmbl5toc.htm). Research funded under this grant must adhere to the BMBL, including using the BMBL-recommended biocontainment level at a minimum. If your Institutional Biosafety Committee (or equivalent body) or designated institutional biosafety official recommend a higher biocontainment level, the highest recommended containment level must be used.

When submitting future Progress Reports indicate at the beginning of the report:

If no research with a Highly Pathogenic Agent or Select Agent has been performed or is planned to be performed under this grant.

If your IBC or equivalent body or official has determined, for example, by conducting a risk assessment, that the work being planned or performed under this grant may be conducted at a biocontainment safety level that is lower than BSL3.

If the work involves Select Agents and/or Highly Pathogenic Agents, also address the following points:

Any changes in the use of the Agent(s) or Toxin(s) including its restricted experiments that have resulted in a change in the required biocontainment level, and any resultant change in location, if applicable, as determined by your IBC or equivalent body or official.

If work with a new or additional Agent(s)/Toxin(s) is proposed in the upcoming project period, provide:

o A list of the new and/or additional Agent(s) that will be studied;

o A description of the work that will be done with the Agent(s), and whether or not the work is a restricted experiment;

The title and location for each biocontainment resource/facility, including the name of the organization that operates the facility, and the biocontainment level at which the work will be conducted, with documentation of approval by your IBC or equivalent body or official. It is important to note if the work is being done in a new location.

*****

NIAID Grants staff will be moving to a new building effective October 1, 2014. As a result of the move the telephone numbers listed on this NoA for your grants management specialist and program officers may no longer be active. Please check the website below to find their new telephone numbers
https://ned.nih.gov/search/

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Roberta D. Wolcott
Email: wolcottr@niaid.nih.gov **Phone**: 301-451-2685 **Fax**: 301-493-0597

Program Official: Zuoyu Xu
Email: xuzuoyu@mail.nih.gov **Phone**: 240-627-3394

SPREADSHEET SUMMARY
GRANT NUMBER: 1R21AI109896-01

INSTITUTION: UNIVERSITY OF MASSACHUSETTS LOWELL

Budget	Year 1	Year 2
TOTAL FEDERAL DC	$141,875	$207,375
TOTAL FEDERAL F&A	$63,100	$31,800
TOTAL COST	$204,975	$239,175

Facilities and Administrative Costs	Year 1	Year 2
F&A Cost Rate 1	52.5%	53%
F&A Cost Base 1	$100,000	$60,000
F&A Costs 1	$52,500	$31,800
F&A Cost Rate 2	53%	
F&A Cost Base 2	$20,000	
F&A Costs 2	$10,600	

PI: **YAN, MINGDI**	Title: Maltoheptaose based nanotherapeutics for multidrug resistant bacterial infection	
Received: 04/05/2013	FOA: PA11-261	Council: 10/2013
Competition ID: ADOBE-FORMS-B2	FOA Title: NIH EXPLORATORY/DEVELOPMENTAL RESEARCH GRANT PROGRAM (PARENT R21)	
1 R21 AI109896-01	Dual:	Accession Number: 3581914
IPF: 850905	Organization: UNIVERSITY OF MASSACHUSETTS LOWELL	
Former Number:	Department: Chemistry	
IRG/SRG: ZRG1 BST-U (02)M	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 125,000 Year 2: 150,000	Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Mingdi Yan	University of Massachusetts Lowell	PD/PI
Robert Finberg	University of Massachusetts Medical School	Co-Investigator

OMB Number: 4040-0001
Expiration Date: 06/30/2011

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. * TYPE OF SUBMISSION

☐ Pre-application ☒ Application ☐ Changed/Corrected Application

2. DATE SUBMITTED: 04/05/2013

Applicant Identifier:

4. a. Federal Identifier:

b. Agency Routing Identifier:

5. APPLICANT INFORMATION

*** Organizational DUNS:** 956072490

* Legal Name: University of Massachusetts Lowell

Department: | Division:

* Street1: Office of Research Administration

Street2: 600 Suffolk Street, 2nd Floor South

* City: Lowell | County / Parish: Middlesex

* State: MA: Massachusetts | Province:

* Country: USA: UNITED STATES | * ZIP / Postal Code: 01854-3648

Person to be contacted on matters involving this application

Prefix: | * First Name: Linda | Middle Name:

* Last Name: Concino | Suffix:

* Phone Number: 978-934-4723 | Fax Number: 978-934-2027

Email: Linda_Concino@uml.edu

6. * EMPLOYER IDENTIFICATION *(EIN) or (TIN)*: 04-3167352-E5

7. * TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education

Other (Specify):

Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:

☒ New ☐ Resubmission

☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).

☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration

☐ E. Other (specify):

* Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. * NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

Maltoheptaose based nanotherapeutics for multidrug resistant bacterial infection

12. PROPOSED PROJECT:

* Start Date: 12/01/2013 | * Ending Date: 11/30/2015

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT**: MA-003

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: | * First Name: Mingdi | Middle Name:

* Last Name: Yan | Suffix:

Position/Title:

* Organization Name: University of Massachusetts Lowell

Department: Chemistry | Division:

* Street1: One University Avenue

Street2:

* City: Lowell | County / Parish: Middlesex

* State: MA: Massachusetts | Province:

* Country: USA: UNITED STATES | * ZIP / Postal Code: 01854-3648

* Phone Number: 978 934-3467 | Fax Number: 978 934-3013

* Email: Mingdi_Yan@uml.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	446,004.00
b. Total Non-Federal Funds	0.00
c. Total Federal & Non-Federal Funds	446,004.00
d. Estimated Program Income	0.00

16. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR

☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

☒ * I agree

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or other Explanatory Documentation

Add Attachment | Delete Attachment | View Attachment

19. Authorized Representative

Prefix: * First Name: Linda Middle Name:

* Last Name: Concino Suffix:

* Position/Title: Dir, Grants and Contract Admin

* Organization: University of Massachusetts Lowell

Department: Research Administration Division:

* Street1: 600 Suffolk Street

Street2: Second Floor, South

* City: Lowell County / Parish: Middlesex

* State: MA: Massachusetts Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 01854-3648

* Phone Number: 978-934-4723 Fax Number: 978-934-2027

* Email: Linda_Concino@uml.edu

*** Signature of Authorized Representative**

Linda Concino

*** Date Signed**

04/05/2013

20. Pre-application

Add Attachment | Delete Attachment | View Attachment

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 08/31/2011

Project/Performance Site Location(s)

Project/Performance Site Primary Location ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Massachusetts Lowell

DUNS Number: 9560724900000

* Street1: One University Avenue

Street2:

* City: Lowell County: Middlesex

* State: MA: Massachusetts

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: 01854-3648 * Project/ Performance Site Congressional District: MA-003

Project/Performance Site Location 1 ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Massachusetts

DUNS Number: 6038473930000

* Street1: 55 Lake Avenue, North

Street2:

* City: Worcester County: Worcester

* State: MA: Massachusetts

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: 01655-0002 * Project/ Performance Site Congressional District: MA-002

Additional Location(s) Add Attachment Delete Attachment View Attachment

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ☐ Yes ☒ No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☐ No

If yes, check appropriate exemption number. ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

If no, is the IRB review Pending? ☐ Yes ☐ No

IRB Approval Date:

Human Subject Assurance Number:

2. * Are Vertebrate Animals Used? ☒ Yes ☐ No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ☒ Yes ☐ No

IACUC Approval Date:

Animal Welfare Assurance Number A3867-01

3. * Is proprietary/privileged information included in the application? ☒ Yes ☐ No

4.a. * Does this project have an actual or potential impact on the environment? ☐ Yes ☒ No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ☐ Yes ☐ No

4.d. If yes, please explain:

5. * Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No

5.a. If yes, please explain:

6. * Does this project involve activities outside of the United States or partnerships with international collaborators? ☒ Yes ☐ No

6.a. If yes, identify countries: Sweden

6.b. Optional Explanation: Professor Olof Ramstrom of KTH Sweden will serve as con

7. * Project Summary/Abstract 001_Project_Summary1004426479.pdf | Add Attachment | Delete Attachment | View Attachment

8. * Project Narrative 002_Project_Narrative1004426480.pdf | Add Attachment | Delete Attachment | View Attachment

9. Bibliography & References Cited 003_References1004426496.pdf | Add Attachment | Delete Attachment | View Attachment

10. Facilities & Other Resources 004_Facilities1004426492.pdf | Add Attachment | Delete Attachment | View Attachment

11. Equipment 005_Equipment1004426493.pdf | Add Attachment | Delete Attachment | View Attachment

12. Other Attachments Add Attachments | Delete Attachments | View Attachments ☐

PROJECT SUMMARY

Antimicrobial resistance has become a major public health risk where drugs are no longer effective against microorganisms. Once powerful antimicrobial agents have now become virtually useless, and the situation is spreading rapidly over the globe. The objective of this proposal is to develop a new strategy for targeting multidrug-resistant bacteria, composed of therapeutics-encapsulated nanoparticles with maltoheptaose (G7) as the targeting agent. The key hypothesis is that G7 will greatly facilitate the uptake of nanoparticles by bacterial cells whereas the multivalent nanoparticles will deliver high local doses of therapeutics into bacterial cells to achieve significantly enhanced antibiotic potency. G7, a maltodextrin that is the largest carbon source for metabolic activity, will be used as the targeting agent as we have shown that it drastically increased the uptake of nanoparticles by bacterial cells whereas it had minimal impact on mammalian cells. In addition, we hypothesize that G7-tagged nanoparticles will improve considerably the efficacy of antibiotics in treating multidrug-resistant bacterial infection. During the two-year project period, we will synthesize and study the antimicrobial activities of antibiotics-encapsulated G7-liposomes and G7-micelles against multidrug-resistant *Pseudomonas aeruginosa in vitro*. We will also evaluate the *in vivo* efficacy of the new nanotherapeutics using a mice model. The completion of these studies will demonstrate that G7-based nanotherapeutics will improve appreciably the therapeutic efficacy of antibiotics and revert the antimicrobial resistance of *P. aeruginosa*. The proposal is innovative because it represents the first study to use a nutrient as the targeting strategy for drug delivery. The project is significant because results from these studies can be readily applied to other systems, thus a universal platform can be envisioned for enhancing the delivery of a diverse class of therapeutic agents to treat multidrug-resistant bacterial infections.

PROJECT NARRATIVE

Drug-resistance has become a major public health risk causing drastic increases in healthcare cost as well as mortality and morbidity. This proposal focuses on developing a new platform for treating drug-resistant infections. The strategy uses a bacterial nutrient, maltoheptaose, as the "bait" to facilitate the entry of antibiotic-encapsulated nanoparticles into bacterial cells. This "sweet Trojan horse" will greatly enhance the therapeutic efficacy of antibiotics, making them effective in treating drug-resistant bacterial infections.

Facilities and Resources

Yan Research Lab Resources

The Yan lab has three laboratory suites, 1,730, 570 and 680 ft^2, respectively. The wet chemical lab (1730 ft^2) is furnished with six 8-foot and one 6-foot fume hoods, a laminar flow hood, bench spaces, and sinks. Fume hoods are equipped with water, aspirators, gas, compressed air lines, N_2 and Ar tanks, and vacuum lines. An additional equipment room, 250 ft^2, houses some of the instruments listed below. The cell culture room (570 ft^2) is a suite consisting of 3 separate small rooms, one of which has been certified to conduct biosafety level 2 work. Two biosafety hoods, freezers, and all the cell culture equipment are housed in the culture room. The complete list of instruments can be found in the "Instrument" section.

The students/postdocs occupy the offices that are part of the laboratory suites. The offices are furnished, and are equipped with Mac and PC computers, printers, bookshelves, filing cabinets, telephones, and high-speed internet connection. In addition, the PI and her group members have access to chemistry graduate student resource room which is furnished with tables, microwave ovens, shelves. We also have access to the shared facilities in the Chemistry department and on UML campus.

UML Chemistry Department Resources

The department has an NMR laboratory which houses 4 Bruker NMR spectrometers (200 MHz, 250 MHz, and 500 MHz multinuclear spectrometers, and 1 solid state NMR spectrometer). Other instruments include Waters GPC systems equipped with autosamplers, Knauer Vapor Pressure Osmometer, TA Instrument TGA and DSC. A glass blowing laboratory is equipped with all the necessary apparatus and facility for glass work.

UML Center for Materials Characterization Laboratory (CMCL)

CMCL is one of the signature research facilities on UML campus, supporting research and education in materials characterization for faculty and students. UML faculty and students have self-use/operator access to all instruments after completing a comprehensive training program. CMCL staff is also available for technical support in conducting advanced characterization. Major research instrumentations at CMCL include *Sample Characterization Equipment* and *Sample Preparation Equipment.* The complete list of Sample Characterization Equipment and Sample Preparation Equipment is included in the "Instrument" section.

UML Emerging Technologies & Innovation Center (ETIC)

The ETIC building is the newest addition to the UML campus in Oct. 2012. It houses research laboratories and facilities in nanomanufacturing, nanomedicine, sensors, and flexible electronics. One floor is dedicated to drug discovery, drug delivery, therapeutics, cancer mechanism studies. It has a 4200 ft^2 Class 1000/100 Clean Room with Bio-Bay, which houses instruments for the fabrication of templates for life sciences applications, micro- and nanodevices, sensors, lab-on-a-chip devices. It has two acid etch wet stations, one base wet station, and one solvent wet station. The instruments have already been installed and in operation are listed in the "Instrument" section. Additional instruments are in the process of being acquired and purchased.

Finberg Research Lab Resources

Finberg will carry out the proposed work in 2,600 sq. ft. of laboratory space on the 2nd floor of the University of Massachusetts Medical School (UMMS) Lazare Medical Research Building which is equipped with chemical fume hoods, laminar flow hoods, CO_2 incubators, binocular and inverted microscopes, a programmable thermal cycler, and various pieces of small equipment. Adjacent core space houses Sorvall RC centrifuges, Beckman ultracentrifuges, refrigerators, freezers, beta- and gamma counters, liquid nitrogen storage, an ELISA reader, balances, and a MASH cell harvester. There is a cold room with work and storage space, and a warm room with rotating shakers and equipment for suspension cell cultures. A state of the art Zeiss confocal microscope and fluorescence cell sorter is available on the third floor.

Dr. Finberg has a separate office in Room 227 of the University of Massachusetts Lazare Research Building. Next door are offices equipped with computers, printers, a typewriter, a Facsimile machine and a photocopy machine. A variety of MacIntosh computers, a SUN system computer, as well as IBM computers are available to the research team.

UMMS Animal Facilities

The animal care facility at UMMS provides a centralized animal care program with disease surveillance and vendor monitoring. It is fully accredited by the American Association for Accreditation of Laboratory Animal Care, as well as Federal and State agencies. The physical plant consists of approximately 50,000 sq. ft. as well as supporting services. The animal care provides centralized animal receiving, quarantine, isolation maintenance, breeding, surgical and necropsy facilities. Animal care facilities and procedural capabilities comply with all provisions described for the Good Laboratory Studies (*Federal Register)* of October 28, 1977, 42-FR-57699. A Quality Assurance Officer is available to respond to program requirements. Compliance with PHS standards through the NIH Office for Protection from Research Risks is recorded under assurance number A3306-01.

Other Facilities on UMMS Campus

In addition to assigned laboratory space, and adjacent core space, the laboratory has access to the fluorescence activated cell sorter, and access to the UMMS molecular biology core facility which includes oligonucleotide and peptide synthesis, peptide sequencing facility, automated DNA sequencer, and a Pharmacia Biacore device. The Proteomics core provides state of the art proteomic and mass spectrometric analyses that support the research, educational and clinical programs at UMMS. UMMS also houses several core facilities including a **Flow Cytometry Core** with access to four cell sorters (including BD FACSVantage DV-1, BD FACSAria II) and six analysis instruments (including BD LSR IIs, BD FACSCaliburs). The Flow Cytometry Core provides technical assistance and experimental consultation.

Equipment

Equipment in Yan Research Lab

- UV-Vis Spectrometer: Perkin Elmer Lambda 45
- FT-IR Spectrometers: Nicolet 6700, including diamond ATR and grazing angle reflectance accessories
- Fluorescence Spectrophotometer: Agilent Cary Eclipse
- Thermogravimetric Analyzer: TA Instruments Q50
- Microarray scanner: GenePix 4100A
- Microarrayer system: Array-It
- Balances (2): Metter Toledo 0.1 mg, Metter Toledo 0.01 mg
- Microscope: Zeiss
- Cell Counter: Invitogen countess
- Plate Reader: Epoch Biotek
- CO_2 Incubator: Fisher Scientific
- Shakers (3): VWR, Thermo Scientific, Lab-line
- Freezers (2): VWR -80 degree, Kenmore -20 degree
- Bio-safety Hoods (2): Baker Sterilgard III, Thermo Scientific 1300 A2
- Steam Sterilizer: Tuttnauer
- Air Clean Workstation: Air Clean 600
- Box Furnace: Thermo Lindberg blue M
- Photochemical Equipment (2 sets): Hanovia 450 W medium pressure mercury lamp with power supply
- Refrigerators (2): VWR
- Spin Coater: Specialty Coating System P6700
- Sonicators (4): Sonics with controller and power supply, Fisher FS60, Branson 2510 (2 sets)
- Centrifuges: Hermle Labnet Z326, Eppendorf 5415C, Labnet Spectrafuge 24D
- Vortex Mixer: Fisher Scientific
- pH-Meter: Metter Toledo
- Circulators (4): Thermo NESLab, VWR, Guu (2 sets)
- Lab Ovens (2): Fisher Scientific, Thermo Science
- Rotavapors (2): Buchi R3000, Ruchi RII
- Vacuum Pump: Buchi
- Oil Pump: Edwards

Equipment in Finberg Research Lab

All the major equipment required for the proposed work is available in the laboratory and adjacent core space. This includes laminar flow hoods for tissue culture, dual chamber CO_2 incubators, ultracentrifuges with rotors, medium speed refrigerated centrifuges, scintillation counters, gamma counter, automated HPLC equipment, column chromatography equipment, liquid N_2 storage tanks, -70°C Revco freezers, -20°C freezers, gel electrophoresis equipment for DNA and protein characterization. A programmable thermal cycler for PCR and an electroporation device were recently acquired. Polaroid photographic set-ups are available for photographing DNA or protein gels. There is also access to the FACS facility, and the automated DNA sequencing and oligonucleotide synthesis facilities. There is an ultrastructure/electron microscopy facility in the Biotech 2 Research building. NanoString nCounter™ multiplex system including Sample Preparation Station and nCounter Digital Analyzer is a shared instrument in the Department of Medicine.

Sample Characterization Equipment at UML CMCL:

- JEOL JSM7401F (unit A) Field-emission scanning electron microscope (FE-SEM) with EDS Microanalysis System (EDAX) and Nano-Pattern Generation System
- JEOL JSM7401F (unit B) Field-emission scanning electron microscope (FE-SEM) with EDS Microanalysis System (Oxford)
- Topcon SM-510 Scanning electron microscope (SEM)
- JEOL JSM6390 Scanning Electron Microscope (SEM)
- Philips EM400T Transmission electron microscope (TEM) with energy dispersive spectroscopy (EDS) system and CCD camera
- Philips CM12 Transmission electron microscope (TEM)
- Topcon 002B 200keV Transmission Electron Microscope with EDS and CCD camera attachments
- Park Systems XE-150 Atomic force microscope (AFM)
- Park Systems XE-100 Atomic force microscope (AFM)
- Veeco MultiMode w/Nanoscope IV Atomic force microscope (AFM)
- Veeco Dimension 3100 Atomic force microscope (AFM)
- Thermo-Vacuum Generators ESCALAB MKII X-ray photoelectron spectrometer (XPS)
- Waters Micromass Matrix-assisted laser desorption-ionization time-of-flight mass spectrometer (MALDI-TOF MS)
- Wyko NT2000 Optical 2D Profiling System
- Zeiss Auriga Focused Ion Beam-Scanning Electron Microscope; Ga liquid metal ion source; Multi-gas injection system; SE/BE/STEM detectors; Omniprobe nanomanipulator; Leica Cryo-Stage attachment
- Olympus FV300 Laser Scanning Confocal Fluorescence Microscope; Location OG-2B
- Olympus BX61 Fluorecence Microscope
- Zeiss Discovery V20 Stereo Microscope
- Horiba NanoPartica SZ-100 Dynamic Light Scattering Spectroscopy
- Surforce SFA 3 Surface Forces Analyzer
- Quantachrome PoreMaster Mercury Porosimeter
- Quantachrome Autosorb Nitrogen Sorption Porosimeter
- Illinois Instrument Oxygen Permeation Analyzer
- Scintag XDS2000 X-ray Diffractometer
- Rigaku R-Axis IV++/RU-H3R X-ray Crystallography System

Sample Preparation Equipment at UML CMCL:

- Leica EM UC6 FC6 Cryo-Ultramicrotome
- Tousimis SAMDRI-795 Critical Point Dryer
- Porter Blum MT-1 Ultramicrotome
- Gatan 691 Precision Ion Polishing System
- Fischione Ion Mill Model 1010
- VCR D500i Sample Dimpler
- Denton Vacuum DV-502 Thermal Evaporator (for metals coating)
- Denton Vacuum Desk IV Sputter Coater (for Au coating)
- Denton Vacuum Desk II Sputter Coater Carbon Accessory
- Struers DP-U4 Grinding and Polishing System
- Isomet 11-1180 Low Speed Saw
- Leica EM KMR2 Glass cutter

- Leica SCD500 Cryogenic Sample Coating System
- Branson 1510 Sonicator
- Napco Model 5831 Vacuum Oven
- Mettler A100 Analytical Balance

Instruments in UML ETIC Building

- Brucker Senterra R200-L Raman Microscope Spectrometer
- Woolam Alpha SE300 Spectroscopy Ellipsometer
- MA6B Mask Aligner
- Raith150 E-Beam Lithography
- Aixtron 4" CNT-Graphene
- CHA E-Beam Evaporator
- CD200CBX Spin Coater
- CD200CBX Spin Develop
- TIGI Flexus2320 Stress Measurement
- Filmetric F40-UV Thin Film Measurement
- K&S Dicing Saw
- Oxford Plasma Lab 80 Reactive Ion Etcher
- Plasma lab 100 PECVD

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: Mingdi | Middle Name:
* Last Name: Yan | Suffix:
Position/Title: | Department: Chemistry
Organization Name: University of Massachusetts Lowell | Division:
* Street1: One University Avenue
Street2:
* City: Lowell | County/ Parish: Middlesex
* State: MA: Massachusetts | Province:
* Country: USA: UNITED STATES | * Zip / Postal Code: 01854-3648
* Phone Number: 978 934-3467 | Fax Number: 978 934-3013
* E-Mail: Mingdi_Yan@uml.edu

Credential, e.g., agency login: eRA Commons User Name

*** Project Role:** PD/PI | **Other Project Role Category:**

Degree Type:
Degree Year:

***Attach Biographical Sketch** 000_01_Yan_Biosketch100442643 | Add Attachment | Delete Attachment | View Attachment
Attach Current & Pending Support | Add Attachment | Delete Attachment | View Attachment

PROFILE - Senior/Key Person 1

Prefix: | * First Name: Robert | Middle Name: W
* Last Name: Finberg | Suffix:
Position/Title: Professor | Department: Medicine
Organization Name: University of Massachusetts Medical School | Division:
* Street1: 364 Plantation Street, LRB 228
Street2:
* City: Worcester | County/ Parish: Worcester
* State: MA: Massachusetts | Province:
* Country: USA: UNITED STATES | * Zip/ Postal Code: 01605-0002
* Phone Number: 508-856-1886 | Fax Number: 508-856-6176
* E-Mail: robert.finberg@umassmed.edu

Credential, e.g., agency login: eRA Commons User Name

*** Project Role:** Co-Investigator | **Other Project Role Category:**

Degree Type:
Degree Year:

***Attach Biographical Sketch** 000_02_Finberg_Biosketch10044 | Add Attachment | Delete Attachment | View Attachment
Attach Current & Pending Support | Add Attachment | Delete Attachment | View Attachment

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Mingdi Yan	Professor
eRA COMMONS USER NAME eRA Commons User Name	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Science and Technology of China	BS	1988	Polymer Physics
University of Oregon	Ph.D.	1994	Organic Chemistry
University of Oregon	Postdoctoral	1995	Materials Chemistry

A. Personal Statement

My research focuses on functional surfaces and biointerfaces. It lies at the interface of synthesis, nanotechnology and bioanalysis. For the past 15 years, we studied the fundamental surface chemistry, developed new approaches to synthesize functional nanomaterials and investigated the impact of ligand presentation on the performance of the nanomaterials. Our research group has been at the forefront of the glyconanomaterial research. We have published numerous articles on the synthesis, characterization and applications of these novel glyconanomaterials. We found that the glycan ligands profoundly influence how the glyconanomaterials interact with the biological entities. In this project, we use maltoheptaose, a nutrient for bacteria, to enhance the uptake of therapeutic-encapsulated nanoparticles to bacterial cells. We expect that this strategy will lead to the development of new nanotherapeutics for treating drug-resistant bacterial infections. The project is the collaboration between my nanomaterials group and Dr. Robert Finberg's clinical laboratory at our medical school. The geographical proximity between the two groups and the close association with the hospitals will greatly facilitate the clinical translation of the technologies developed in this project.

B. Positions and Honors

Positions and Employment

1995-1998	Senior Research Scientist, Ikonos Corporation, Portland, OR
1998-2004	Assistant Professor, Department of Chemistry, Portland State University, Portland, OR
2001-2004	Assistant Professor, Department of Electrical and Computer Engineering, Oregon Health and Science University, Portland, OR
2004-2008	Associate Professor, Department of Chemistry, Portland State University
2008-2011	Professor, Department of Chemistry, Portland State University
2011-present	Professor, Department of Chemistry, University of Massachusetts Lowell, Lowell, MA

Other Experience and Professional Memberships

1994-present	Member, American Chemical Society
1998	Chair, Scientific Advisory Board, Ikonos Corporation
2003-2005	Consultant, National Security Directorate, Pacific Northwest National Laboratories
2003-2011	Consultant, Advanced Material Sciences, Inc.
April, 2002	Organizer, Symposium on "Molecularly Imprinted Materials," Materials Research Society (MRS) 2002 Spring National Meeting
2005	Book co-editor, *Molecularly Imprinted Materials*, Marcer Dekker Inc.
2006-07	Consultant, Vistakon (Johnson Vision Care, Inc.)
June, 2006	Ad-hoc reviewer and participant, NIH Synthetic and Biological Chemistry A (SBCA) Study Section
2006-present	Editorial board member, *Analytical Chemistry Insights*
2006-present	Scientific Advisory Board member, Society of Molecular Imprinting
May, 2009	Ad-hoc reviewer and participant, NIH Biomaterials and Biointerface (BMBI) Study Section
Feb., 2010	Ad-hoc reviewer and participant, NIH Biomaterials and Biointerface (BMBI) Study Section
2010	Consultant, Virogenomics, Inc.
2010-present	Associate Editor, *Journal of Nanoscience Letters*
2010-2011	Consultant, Grace Bio-Labs, Bend, OR
2011-2017	Permanent member, NIH Biomaterials and Biointerface (BMBI) Study Section

Honors, Awards, and Recognitions

2004	Outstanding Mentor of 2003/2004 Siemens Westinghouse Competition in Math, Science & Technology Winners
2006-07	Guest Professor, Department of Materials, ETH Zurich, Switzerland
2007	Outstanding Overseas Chinese Young Investigator Award, National Natural Science Foundation of China
2009	Outstanding Researcher Award, Columbia-Willamette Chapter of Sigma Xi
2011-15	Guest Professor, Department of Chemistry, School of Chemical Science and Engineering, KTH – Royal Institute of Technology, Sweden

C. Selected peer-reviewed publications (from 93)

1. Wang, X.; Liu, L.-H.; Ramström, O.; Yan, M. "Engineering Nanomaterial Surfaces for Biomedical Applications," *Exp. Biol. Med.* **2009**, *234*, 1128-1139. PMCID:**PMC19596820**.
2. Wang, X.; Ramström, O.; Yan, M. "A Photochemically Initiated Chemistry for Coupling Underivatized Carbohydrates to Gold Nanoparticles," *J. Mater. Chem.* **2009**, *19*, 8944-8949. PMCID:**PMC20856694**.
3. Tyagi, A.; Wang, X. Deng, L.; Ramström, O.; Yan, M. "Photogenerated Carbohydrate Microarrays for Studying Protein-Carbohydrate Interactions Using Surface Plasmon Resonance Imaging," *Biosens. Bioelectron.* **2010**, *26*, 344-350. PMCID:**PMC20800471**.
4. Wang, X.; Ramström, O.; Yan, M. "Glyconanomaterials: Synthesis, Characterization, and Ligand Presentation," *Adv. Mater.* **2010**, *22*, 1946-1953. PMCID:**PMC20301131**.
5. Liu, L.-H., Yan, M. "Perfluorophenyl Azides: New Applications in Materials Synthesis and Surface Functionalization," *Acc. Chem. Res.* **2010**, *43*, 1434–1443. PMCID:**PMC20690606**.
6. Liu, L.-H.; Lerner, M. M.; Yan, M. "Derivatization of Pristine Graphene with Well-defined Chemical Functionalities," *Nano Lett.* **2010**, *10*, 3754-3756. PMCID:**PMC20690657.** (Highlighted in *Nature*, **2010**, *466*, 904.)
7. Wang, X.; Ramström, O.; Yan, M. "Quantitative Analysis of Multivalent Ligand Presentation on Gold Glyconanoparticles and the Impact on Lectin Binding," *Anal. Chem.* **2010**, *82*, 9082–9089. PMCID:**PMC2094240**.
8. Wang, H.; Ren, J.; Hlaing, A.; Yan, M. "Fabrication and Anti-Fouling Properties of Photochemically and Thermally Immobilized Poly(ethylene Oxide) and Low Molecular Weight Poly(ethylene Glycol)," *J. Colloid Interface Sci.* **2011**, *354*, 160-167. PMCID:**PMID21044787**.
9. Norberg, O.; Deng, L.; Aastrup, T.; Yan, M.; Ramström, O. "Photo-Click Immobilization on Quartz Crystal Microbalance Sensors for Stereoselective Carbohydrate-Protein Interaction Analyses," *Anal. Chem.* **2011**, *83*, 1000-1007. PMCID:**PMID21162569**.
10. Wang, H.; Zhang, Y.; Yuan, X.; Chen, Y.; Yan, M. "A Universal Protocol for Photochemical Covalent Immobilization of Intact Carbohydrates for the Preparation of Carbohydrate Microarrays," *Bioconjugate Chem.* **2011**, *22*, 26-32. PMCID:**PMID21138274**.
11. Wang, X.; Matei, E.; Deng, L.; Ramström, O.; Gronenborn, A.; **Yan, M.** "Multivalent Glyconanoparticles with Enhanced Binding to Anti-Viral Lectin Cyanovirin-N," *Chem. Commun.* **2011**, *47*, 8620 – 8622. **PMID: 21720651.**
12. Wang, X.; Ramström, O.; **Yan, M.** "Dynamic Light Scattering as an Efficient Tool to Study Glyconanoparticle-lectin Interactions," *Analyst* **2011**, *136*, 4174 – 4178. **PMID: 21858301.**
13. Sensors Produced by Thiol-Ene/Yne Photo-Click Chemistry in Aqueous Solution," *Biosens. Bioelectron.* **2012**, *34*, 51 – 56. **PMID: 22341757.**
14. Tong, Q.; Wang, X.; Wang, H.; Kubo, T.; Yan, M. "Fabrication of Glyconanoparticle Microarrays," *Anal. Chem.* **2012**, *84*, 3049 – 3052. **PMID: 22385080.**
15. Zeng, Z.; Patel, J.; Lee, S.-H.; McCallum, M.; Tyagi, A.; **Yan, M.**; Shea, K. J. "Synthetic Polymer Nanoparticle-Polysaccharide Interaction: A Systematic Study," *J. Am. Chem. Soc.* **2012**, *134*, 2681 – 2690. PMCID: **PMC3275679 PMID: 22229911.**
16. Wang, X.; Matei, E.; Gronenborn, A.; Ramström, O.; Yan, M. "Direct Measurement of Glyconanoparticles and Lectin Interactions by Isothermal Titration Calorimetry," *Anal. Chem.* **2012**, *84*, 4248 – 4252. **PMID: 23116448/**
17. Park, J.; Yan, M. "Covalent functionalization of Graphene with Reactive Intermediates," *Acc. Chem. Res.* **2013**, *46*, 181–189. **PMID: 23116448.**
18. Wang, H.; Tong, Q.; Yan, M. "Antifouling Surfaces for Proteins Labeled with Dye-doped Silica Nanoparticles," *Anal. Chem.* **2013**, *85*, 23–27. **PMID: 23236953.**
19. Jayawadena, H. S. N.; Jayawadana, K.; Chen, X.; **Yan, M.** "Maltoheptaose Promotes Internalization of Nanoparticles by *E. coli*," *Chem. Commun.* **2013**, *49*, 3034 – 3036.

D. Research Support

Ongoing Research Support

1R01 GM080295-01 (Yan) 4/01/08-3/31/14
NIH/NIGMS
Photogenerated Carbohydrate Microarrays
The goal of this project is to develop strategies for creating efficient carbohydrate microarrays, and use them for probing carbohydrate-binding proteins, high-throughput ligand screening and bacterial/toxin analysis.

1R01 GM080295-01S1 (Yan) 4/01/08-3/31/14
NIH/NIGMS
Characterization of Photogenerated Carbohydrate Microarrays
The goal of this grant is to collaborate with Professor David Castner, University of Washington, to characterize carbohydrate microarrays with XPS and TOF-SIMS.

1R01 CA136491 (Brard) 7/01/09-6/30/14
NIH/NCI
Development of an Assay for the Early Detection of Ovarian Cancer
The goal of this project is to develop simple and reliable methods for the routine LPA (lysophosphatidic acid) screening for the early detection of ovarian cancer.

NSF (CHE-1112436) (Yan) 10/1/2011-9/30/2014
Derivatization of Pristine Graphene with Well-Defined Chemical Functionalities
The goal of this grant is to develop a new chemistry to derivatize pristine graphene, and to study the fundamental reaction mechanism.

DOD/ARO (DURIP) (La Rosa) 9/2012-10/2013
Self-Assembled Polymer Nanostructures with Responsive Characteristics
The goal of this project is to develop a femtosecond laser system for the fabrication and characterization of stimuli-responsive, self-assembled polymer nanostructures.

Completed Research Support (Since 2009)

ONAMI/ONR (Ramstrom) 1/1/10-12/31/10
Oregon Nanoscience and Microtechnology Institute
Glyconanoparticles for Tumor Imaging
The goal of this project is to synthesize carbohydrate-functionalized nanoparticles that can be used for imaging tumor cells

NSF SBIR Phase I (Clare) 7/1/10-12/31/10
Electronic, multiplexed allergy diagnostics
The goal of this project is to develop a point-of-care device for the fast and low-cost diagnosis of allergy.
Role: **academic partner** (Industrial collaborator: Virogenomics, Inc.)

Private Source (Yan) 12/15/10-6/15/11
Development of new coating materials for microarray applications
The goal of this contract research is to develop robust, low fluorescence background, and high porosity coating materials for microarray applications.

2R15 GM066279-02 (Yan) 4/01/05-6/30/11
NIH/NIGMS
Surface Chemistry for Immobilization of Ultrathin Films
The goal is this project is to investigate how the surface and interface affect the yield and efficiency of the photochemically initiated immobilization chemistry.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Robert W. Finberg, MD	Professor of Medicine Chair, Dept. of Medicine
eRACOMMONS USER NAME eRA Commons User Name	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Chicago	A.B.	1971	Biology
Albert Einstein College of Medicine	M.D.	1974	Medicine

A. Personal Statement

My research is in the area of prevention and treatment of infectious diseases, and in finding new ways to provide preventive healthcare to all populations. I have designed and participated in numerous antibiotic trials in humans (including trials with anti-bacterial, anti-fungal, and anti-viral drugs) and worked on animal models of bacterial and virus infection. In addition I have characterized the pathogenesis of infection in animals as well as studying the effects of anti-infective agents on human and mouse cells. As a clinician my expertise is the use of anti-infective agents to treat patients with infections and I have recently completed a book on the use of anti-infective agents. Having extensively studied the use of anti-bacterial agents in vitro and in animal models (as well as in human disease), I feel well qualified to work on this grant concerning the new development of anti-bacterial agents and to oversee all the animal studies.

B. Positions and Honors

Postdoctoral Training:

1974-1977 Intern and Resident in Medicine, Bellevue Hospital, New York
1977-1980 Research Fellow in Pathology and Medicine, Harvard Medical School, Boston, MA

Professional Experience:

1980-1985 Assistant Professor of Medicine, Harvard Medical School
1985-1995 Associate Professor of Medicine, Harvard Medical School
1996-1999 Professor of Medicine, Harvard Medical School
1999-present Professor of Medicine, University of Massachusetts Medical School
1999-present Chair, Department of Medicine, University of Massachusetts Medical School

Honors:

1973 Alpha Omega Alpha
1980-1983 Hartford Foundation Award for the support of faculty in scientific research
1983-1988 Scholar of the Leukemia Society

Editorial Boards:

1982-1985 Infection and Immunity
1984-2003 Journal of Immunology, Section Editor
1999- Viral Immunology

Government Committees:

1984-1989 Reviewer, Experimental Immunology Study Section
2007- Reviewer, Immunity and Host Defense (IHD) Study Section, Chair, 2009-2011

C. Selected peer-reviewed publications (from a total of 228, in chronological order)

1. Onderdonk AB, Kasper DL, Shapiro ME, Finberg RW. Role of the capsular polysaccharide of *Bacteroides fragilis* in pathogenicity. Microbiology. 1982;335-7.
2. Ambrosino DM, Siber GR, Chilmonczyk BA, Jernberg JB, Finberg RW. An immunodeficiency characterized by impaired antibody responses to polysaccharides. N Engl J Med. 1987;316:790-3. PMID: 3493431
3. Onderdonk AB, Cisneros RL, Crabb JH, Finberg RW, Kasper DL. Intraperitoneal host cellular responses and *in vivo* killing of *Bacteroides fragilis* in a bacterial containment chamber. Infect Immun. 1989;57:3030-7. PMCID: PMC260766
4. Haregewoin A, Soman G, Hom RC, Finberg RW. Human γδ+ T cells respond to mycobacterial heat-shock protein. Nature. 1989;340:309-12. PMID: 2473405
5. Lew MA, Kehoe K, Ritz J, Antman KH, Nadler L, Takvorian T, Mayer R, Kalish L, Finberg R. Prophylaxis of bacterial infections with ciprofloxacin in patients undergoing bone marrow transplantation. Transplantation. 1991; 51:630-6. PMID: 2006519
6. Heagy W, Crumpacker C, Lopez PA, Finberg RW. Inhibition of immune functions by antiviral drugs. J Clin Invest. 1991; 87:1916-24. PMCID: PMC296943
7. Talcott JA, Whalen SMA, Clark J, Rieker PP, Finberg R. Home Antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. J Clin Oncol 1994;12:107-114. PMID: 8270967
8. Lew MA, Kehoe K, Ritz J, Antman KH, Nadler L, Kalish LA, Finberg R. Ciprofloxacin versus trimethoprim/sulfamethoxazol for prophylaxis of bacterial infections in bone marrow transplant recipients: a randomized, controlled trial. J Clin Onc 1995;13(1):239-250. PMID: 7799026
9. Kurt-Jones, EA., Popova, L,. Kwinn, L, Haynes, LM, Jones, LP, Tripp, RA, Walsh, EE, Freeman, MW, Golenbock, DT, Anderson, LJ, Finberg, RW. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. Nature Immunol., 2000; 1:398-401. PMID: 11062499
10. Webb IJ, Coral FS, Anderson JW, Elias AD, Finberg RW, Nadler LM, Ritz J, Anderson KC. Sources and sequelae of bacterial contamination of hematopoietic stem cell products: Implications for safety of hematotherapy and graft engineering. Transfusion 1996;36:782-788. PMID: 8823450
11. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz D, Bodensteiner D, Pappas P, Seibel N, Greenberg RN, Dummer S, Schuster M, Holcenberg JS, Dismukes WE, NIAID-Mycoses Study Group. Liposomal Amphotericin B for Empirical Therapy in Patients with Persistent Fever and Neutropenia. New Engl J Med. 1999; 340(10):764-71. PMID: 10072411
12. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J, Yanovich S, Stiff P, Greenberg R, Donowitz G, Lee J, Schuster M, Reboli A, Wingard J, Arndt C, Reinhardt J, Hadley S, Finberg R, Laverdiere M, Perfect J, Garber G, Fioritoni G, Anaissie E for the NIAID Mycoses Study Group. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. New Engl J Med. 2002;346(4):225-34. PMID: 11807146.
13. Finberg RW, Moellering R, Tally F, Craig W, Pankey GA, Dellinger EP, West M, Joshi M, Linden P, Rolston K, Rotschafer JC, Rybak MJ. The importance of bactericidal drugs: Future directions in infectious disease. Clin Inf Dis. 2004; 39:1314-20. PMID: 15494908
14. Li J, Wang JP, Ghiran I, Cerny A, Szalai AJ, Briles DE, Finberg RW. Complement receptor 1 expression on mouse erythrocytes mediates clearance of Streptococcus pneumoniae by immune adherence. Infect Immun. 2010 Jul;78(7):3129-35. PMCID: PMC2897369
15. Finberg, RW and Guharoy, R. *Clinical Use of Anti-Infective Agents* A guide to how to prescribe drugs used to treat infections. New York, Springer US, (2012).

D. Research Support

Ongoing

DARPA-BAA-10-93 (R. Finberg) 09/16/11-03/15/14
Algorithms to Limit Viral Epidemics (ALiVE) Project Director

The ALiVE project is a multidisciplinary team approach to develop algorithms to predict in advance how the influenza virus evolves in response to specific environmental pressures. The goal is to generate a set of algorithms that can specifically predict how viruses escape selective pressures. These algorithms will initially be tested in aclosed in vitro system, but can eventually be used to analyze clinical viral isolates.

The set of algorithms will have broad applicability and will be able to be trained for use on viruses other than Influenza.

U19 AI057319 (R. Finberg) 09/30/03-03/31/14
NIH/NIAID PI
Cellular Immunity to Category A-C Viruses in Humans
The UMMS Center for Translational Research on Human Immunology and Biodefense (CTRHIB) is a broad-based interdepartmental program to address, as its overall scientific theme, the role of T lymphocytes in the immunopathogenesis of and protection from category A-C viral pathogens in humans.

U54 AI057159 (D. Kasper) 09/01/03-02/28/14
NIH/NIAID PI
New England Center for Excellence in Biodefense and Emerging Diseases
Project 17 (R. Finberg)- Innate Immunity and Hemorrhagic Fever Viruses
The major goals are to define the mechanisms that lead to the high mortality rate of the hemorrhagic fever viruses and develop methods to prevent these diseases. Using core resources, purified proteins wil be produced and compounds will be screened for their ability to inhibit this activity.

R01 DK0980756-01A1 (J. Kim) 09/10/08-08/31/13
NIH Co-PI
Interleukin-10 and Regulation of Skeletal Muscle Insulin Action
A study of the role of cytokines (particularly IL-10) on fat deposition and the development of type 2 diabetes and obesity.

DARPA-BAA-09-43 (S. Sundaram) 08/1/10-09/20/14
The Charles Stark Draper Laboratories/DARPA Co-PI
Engineered Nanotraps for Virus Elimination via Opsonization
This grant is an investigation into using virus receptors as "decoys" to prevent virus infection. Using liposomes as a base, glycan residues will be conjugated to form synthetic receptors capable of binding influenza virus. The ability of these "decoy receptors" will be tested in vitro in plaque assays and in in vivo animal models (using mice infected with different strains of influenza).

U19 AI057234 (Y. Liu) 05/1/12-4/30/13
Baylor Univ/NIH PI
Characterization of Innate Immune Response to Influenza
This project will focus on key issues pertaining to the human immune response to influenza. The goal is to define the cell subpopulation in primary human respiratory epithelium in which influenza virus replicates. Then within the specific respiratory epithelial cell subpopulation, we will identify protein receptors involved in influenza binding and infection.

Completed

R01 AI49309 PI
NIH 2002-2008
TLRs in Innate Immunity to Bacterial and Viral Infection
To study TLR-CD14 interactions in RSV and Newcastle disease and polyoma virus.

R01 AI64349 PI
NIH 2005-2010
Innate Immunity and Herpes Simplex Pathogenesis
To study the role of TLR2 and other TLRs in the immunity and pathogenesis of herpes viruses in animal models and in human populations.

Research Grant - Innate Immunity (R. Finberg) PI
Private Source 2008-2011
Role of Coxsackievirus Infection and MDA5 in Type 1 Diabetes

This is a study of the role of genetic polymorphisms in MDA-5 and how that predisposes to the development of juvenile diabetes.

P01 AI083215-01 (R. Finberg) PI
NIH 2009-2011
Project 4 – Human Innate Immune Responses to HSV
The goal is to study the multitude of pattern recognition receptor (PRR)-driven pathways and responses regulated by herpes simplex (HSV) and the means by which HSV evades these responses.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
* First Name: Mingdi
Middle Name:
* Last Name: Yan
Suffix:

2. Human Subjects

Clinical Trial? ☐ No ☐ Yes

* Agency-Defined Phase III Clinical Trial? ☐ No ☐ Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix:
* First Name: Linda
Middle Name:
* Last Name: Concino
Suffix:

* Phone Number: 978-934-4723
Fax Number: 978-934-2027
Email: Linda_Concino@uml.edu

* Title: Dir, Grants and Contract Admin

* Street1: Office of Research Administration
Street2: 600 Suffolk Street, 2nd Floor South
* City: Lowell
County/Parish: Middlesex
* State: MA: Massachusetts
Province:
* Country: USA: UNITED STATES
* Zip / Postal Code: 01854-3648

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

PHS 398 Modular Budget

OMB Number: 0925-0001

Budget Period: 1

Start Date: 12/01/2013 End Date: 11/30/2014

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium F&A	125000
Consortium F&A	16,729.00
Total Direct Costs	141,729.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate(%)	Indirect Cost Base($)	Funds Requested ($)
1.	Research on Campus _Provisional_ MTDC	51.00	125,000.00	63,750.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, Ryan McCarthy, 212-264-2069

Indirect Cost Rate Agreement Date: 07/01/2009

Total Indirect Costs: 63,750.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($): 205,479.00

Budget Period: 2

Start Date: 12/01/2014 End Date: 11/30/2015

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium F&A	150000
Consortium F&A	57,375.00
Total Direct Costs	207,375.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate(%)	Indirect Cost Base($)	Funds Requested ($)
1.	Research on Campus _Provisional_ MTDC	51.00	65,000.00	33,150.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, Ryan McCarthy, 212-264-2069

Indirect Cost Rate Agreement Date: 07/01/2009

Total Indirect Costs: 33,150.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($): 240,525.00

PHS 398 Modular Budget

Cumulative Budget Information

1. Total Costs, Entire Project Period

Section A, Total Direct Cost less Consortium F&A for Entire Project Period	$	275,000.00
Section A, Total Consortium F&A for Entire Project Period	$	74,104.00
Section A, Total Direct Costs for Entire Project Period	$	349,104.00
Section B, Total Indirect Costs for Entire Project Period	$	96,900.00
Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period	$	446,004.00

2. Budget Justifications

?	Personnel Justification	006_Personnel_Justification1CU	Add Attachment	Delete Attachment	View Attachment
?	Consortium Justification	007_Consortium_Justification1C	Add Attachment	Delete Attachment	View Attachment
?	Additional Narrative Justification		Add Attachment	Delete Attachment	View Attachment

Personnel Justification

Mingdi Yan, Ph.D., Principal Investigator, (effort = EFFORT month). Dr. Yan is a Professor of Chemistry at the University of Massachusetts Lowell. Dr. Yan has over 15 years of experience in the synthesis and functionalization of nanomaterials especially glyconanomaterials that are the focus of this application. She will be responsible for the design and execution of the overall project especially the design of nanotherapeutics, the characterization and the *in vitro* studies. She will be responsible for personnel hiring, supervising the postdoctoral associate and the Ph.D. student, preparing progress reports and publications. She will also set up and oversee the regular monthly research meeting with Dr. Finberg's group at the medical school.

Other Personnel

TBD, Ph.D., Postdoctoral Associate, (effort = 6 month calendar). The postdoctoral associate will conduct the *in vitro* experiments evaluating the antimicrobial properties of the G7-functionalized liposomes and micelles against *P. aeruginosa*. He/she will carry out the assays described in Aim 2 to determine the uptake of antibiotics by *P. aeruginosa*, MIC values, time-kill studies, and mammalian cell cytotoxicity experiments. He/she will work under the direct supervision of Dr. Yan, and will work closely with the Ph.D. student and Dr. Finberg's research group to provide feedback on optimizing the nanotherapeutic formations. The postdoctoral associate will report the research progress on our regular group meetings, in research reports, and at conferences. He/she will analyze results and prepare manuscripts for publications.

Madanodaya Sundhoro, Ph.D. student, (effort = EFFORT calendar). Madanodaya Sundhoro is a second-year Ph.D. student in Dr. Yan's lab. He is a synthetic chemist experienced in organic and polymer synthesis, nanoparticle synthesis and characterization. He will work under the supervision of Dr. Yan on the synthesis and characterization of liposomes and micelles, encapsulation of antibiotics and characterization of antibiotic encapsulation yields. He will work closely with the postdoctoral associate and Dr. Finberg's research group to optimize the liposome and micelle formulations based on the feedback from the *in vitro* and *in vivo* studies. He will report the research progress on our regular group meetings, in research reports, and at conferences. He will analyze results and prepare manuscripts for publications.

Budget Justification (UMass Medical School)

Personnel

Robert W. Finberg, M.D., (Year 1: EFFORT months)

Dr. Finberg has extensive experience in both the study of anti-bacterial agents and in the use of animal models to study bacterial pathogenesis, and in the use of anti-infective agents in humans. He will work with Dr. Yan to define the optimal bacterial targets and their in vitro testing. He will also oversee all animal experiments.

Charles Carlton-Smith, Post Doctoral Fellow (Year 1: EFFORT calendar months)

Dr. Charles Carlton-Smith is a post-doctoral fellow with experience in animal handling and the use of infectious agents in animals. He will conduct all animal experiments and contribute to the experimental design.

Please note: The funds requested are based on the current salary limitation for DHHS grants. PII PII

OMB Number: 0925-0001

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application (for RESUBMISSION or REVISION only)		Add Attachment	Delete Attachment	View Attachment
2. Specific Aims	008_Specific_Aims100442694	Add Attachment	Delete Attachment	View Attachment
3. *Research Strategy	009_Research_Strategy100442	Add Attachment	Delete Attachment	View Attachment
4. Inclusion Enrollment Report		Add Attachment	Delete Attachment	View Attachment
5. Progress Report Publication List		Add Attachment	Delete Attachment	View Attachment

Human Subjects Sections

6. Protection of Human Subjects		Add Attachment	Delete Attachment	View Attachment
7. Inclusion of Women and Minorities		Add Attachment	Delete Attachment	View Attachment
8. Targeted/Planned Enrollment Table		Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Children		Add Attachment	Delete Attachment	View Attachment

Other Research Plan Sections

10. Vertebrate Animals	010_Vertebrate_Animals10044	Add Attachment	Delete Attachment	View Attachment
11. Select Agent Research		Add Attachment	Delete Attachment	View Attachment
12. Multiple PD/PI Leadership Plan		Add Attachment	Delete Attachment	View Attachment
13. Consortium/Contractual Arrangements	Letter of Intent UMMS100442	Add Attachment	Delete Attachment	View Attachment
14. Letters of Support	014_Letter_of_Support_Finbe	Add Attachment	Delete Attachment	View Attachment
15. Resource Sharing Plan(s)		Add Attachment	Delete Attachment	View Attachment

16. Appendix Add Attachments | Remove Attachments | View Attachments

Specific Aims

Antimicrobial resistance has become a major public health risk where drugs are no longer effective against microorganisms. In the report "Global Risks 2013" by the World Economic Forum, antibiotic-resistant bacteria are considered "the greatest risk of hubris to human health". The annual cost to the US health care system of antibiotic-resistant infections is already estimated at $22–34 billion. None of the drugs currently in the development would be effective against certain killer bacteria, which have newly emerging resistance to the strongest antibiotics. As a consequence, there exist a serious scenario in which all antibiotics would be rendered ineffective for treating even the common infections.

The objective of this application is to develop a new strategy for targeting multidrug-resistant bacterial infection, composed of therapeutics-encapsulated nanoparticles having maltoheptaose (G7), a maltodextrin that is the largest carbon source for metabolic activity, as the targeting agent. The ***key hypothesis is that G7 will greatly facilitate the uptake of nanotherapeutics by bacterial cells whereas the multivalent nanoparticles will deliver high local doses of therapeutics to achieve significantly enhanced potency than that of free therapeutics***. In addition, we hypothesize that ***G7-tagged nanotherapeutics will be effective in treating multidrug-resistant bacterial infections and will have minimal impact on mammalian cells***. Preliminary studies on streptomycin-resistant *E. coli* showed that nanoparticles conjugated with G7 and streptomycin effectively killed the bacteria whereas the bacteria cells were intact when treated with the free streptomycin at concentrations at least 5 times higher than that on the nanoparticles.

The hypothesis will be tested in the following three Specific Aims.

Aim 1. Synthesis of antibiotic-encapsulated, G7-conjugated liposomes and micelles. Nanotherapeutics have been proven to achieve higher therapeutic efficacy and lower off-target toxicity by altering the biodistribution of therapeutics. We choose liposomes and polymeric micelles as the delivery systems because drugs based on these systems such as DOXIL and Genexol-PM are already on the market, and therefore, our new nanotherapeutics, if successfully developed, can be readily adopted, greatly facilitating the clinical translation of the technology.

Aim 2. Antibacterial studies of antibiotic-encapsulated G7-liposomes and G7-micelles against *Pseudomonas aeruginosa in vitro*. We choose *P. aeruginosa* because it is a leading Gram-negative opportunistic pathogen at most medical centers. It has low outer membrane permeability, which forms a critical barrier preventing therapeutics to be effective. It also exhibits intrinsic resistance to many different types of antibiotics and disinfectants.

Aim 3. Evaluation of the *in vivo* efficacy of antibiotic-encapsulated G7-liposomes and G7-micelles. The animal studies will be conducted using a mice model to evaluate the efficacy of the nanotherapeutics in treating antibiotic-resistant bacterial infections.

The completion of these experiments will demonstrate that maltodextrin-based antibiotic delivery systems will significantly improve the therapeutic efficacy of common antibiotics and revive their effectiveness in treating multidrug-resistant bacterial infections. The proposal is innovative because it represents a *new strategy* using a bacteria nutrient to target drug-resistant bacteria, and is specific towards bacterial cells without affecting mammalian cells. The project is significant because it will develop an *enabling technology* that can be adapted to other antimicrobial therapeutics in addition to antibiotics. Results from these studies can be readily applied to other drug-resistant bacteria including antibiotic-resistant *Mycobacterium tuberculosis* (TB), methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE), thus a universal platform can be envisioned for the effective treatment of multidrug-resistant bacterial infections.

A. Significance

In the report "Global Risks 2013" by the World Economic Forum, antibiotic-resistant bacteria are considered "the greatest risk of hubris to human health".[1] In the US, the annual health care cost of antibiotic-resistant infections is already $21-34 billion.[2] None of the drugs currently in the development would be effective against certain killer bacteria, which have newly emerging resistance to even the strongest antibiotics.[3,4] In the meantime, the drug development pipeline for new antibiotics has been drying out, and there have been no successful discoveries of new classes of antibiotics since 1987.[5] As a consequence, there exist a serious scenario in which all antibiotics would be rendered ineffective for treating even the common infections.

Nanomaterial-based therapeutics uses nanomaterials to carry and deliver therapeutic agents to the disease sites.[6] Compared to small molecule drugs that generally have poor pharmacokinetic profiles and broad mechanisms of action, nanotherapeutics have been proven to achieve higher therapeutic efficacy and lower off-target toxicity by altering the biodistribution of therapeutics.[7-11] Multifunctional nanoparticles have been devised with stealth like features including protective layers to prevent the degradation of cargos and to control drug release, imaging agents to assess cargo delivery, and intracellular targeting moieties to direct drugs to specific intracellular compartments.[12,13] There are more than 40 nanotherapeutics that have reached the clinic, and over 200 new candidates are under clinical trial.[14-18]

Multifunctional nanotherapeutics carrying targeting ligands have shown to improve targeting specificity and cellular uptake. The increased uptake into target cells leads to higher intracellular drug concentrations, higher therapeutic efficacy and lower systemic toxicity. In addition, it has been shown that nanotherapeutics are able to overcome multidrug resistance because the glycoprotein efflux pumps are unable to remove drug-nanoparticle complexes that have entered via receptor-mediated events.[19]

In this application, we propose a new approach to nanotherapeutics using maltoheptaose (G7) as the targeting agent to greatly facilitate the delivery of antibiotics to drug-resistant *P. aeruginosa*. Unlike conventional targeting agents that are biomarker-based, G7 is a maltodextrin that is the nutrient for metabolic activity of bacteria. On the outer membrane of Gram-negative bacteria resides maltoporin, a membrane protein that facilitates the diffusion of maltodextrins from the extracellular medium to the periplasmic space and has a sugar-binding site with a dissociation constant of 10^{-4} M.[20-24] We choose *P. aeruginosa* as the target bacteria because it is a leading Gram-negative opportunistic pathogen at most medical centers, carrying a 40-60% mortality rate and complicating 90% of cystic fibrosis deaths.[25] *P. aeruginosa* thrives on many critical body organs as well as on medical devices including catheters, causing widespread cross-infection and chronic infection especially for immunocompromised patients and the elderly.[26-28] Moreover, *P. aeruginosa* exhibits intrinsic resistance to many different types of antimicrobial agents including antibiotics and disinfectants, making it one of the most difficult organism to treat and to remove from the hospital environment.[29] The reason for the low antibiotic susceptibility of *P. aeruginosa* is several folds: 1) low outer membrane permeability (8% of that of *E. coli*) and large exclusion limit; 2) periplasmic β-lactamase that hydrolyzes β-lactam; 3) an efflux system that actively pumps antibiotics outside the cell.[30-32] In all cases, the outer membrane of *P. aeruginosa* is the critical barrier causing slow uptake of antibiotics, facilitating efflux kinetics and thus severely diminishing the therapeutic efficacy of antibiotics.[33]

We have demonstrated that the conjugation of G7 on nanoparticles resulted in significantly increased surface binding and internalization of nanoparticles to *E. coli*. This applies to different nanoparticles of varying sizes, and to different *E. coli* strains with or without the maltodextrin transport channel. Unfunctionalized nanoparticles and nanoparticles functionalized with β-cyclodextrin, a cyclic analogue of G7, showed no particle internalization. Built on these

preliminary results, we propose to develop nanotherapeutics using G7 as the targeting ligand to treat *P. aeruginosa* infection. We expect that G7 will greatly accelerate the penetration of the bacterial outer membrane, and thus significantly enhancing the uptake of the nanotherapeutics by *P. aeruginosa*. Antibiotics encapsulated inside a drug delivery system will be released at high local doses, disfunctioning the efflux system and recovering the therapeutic efficacy of antibiotics. This strategy is general, and if successful, can be applied to antimicrobial therapeutics other than antibiotics. Additionally, the system is selective towards bacterial cells, and mammalian cells will be minimally impacted making this strategy highly effective for treating drug-resistant bacterial infections.

B. Innovation

The proposed research has several innovative aspects. The key novelty is the use of a bacterial nutrient, maltodextrin in this case, to promote membrane penetration and thus the uptake of the nanotherapeutics. The ability to overcome the membrane barrier in Gram-negative bacteria in general and *P. aeruginosa* in particular is a critical first step for many antimicrobial agents to be effective in treating bacterial infection. In addition, maltodextrin is non-toxicity and non-immunogenicity, and is therefore an attractive ligand facilitating the translocation of nanomaterials. Secondly, the high selectivity of G7 for bacterial cells over mammalian cells minimizes side effects. Thirdly, the general strategy developed here can be applied to other antimicrobial agents. In conjunction with clinically-established nanotherapeutic delivery systems of liposomes and micelles, which have demonstrated advantages of enhanced therapeutic efficacy, prolong circulation and controlled release, the systems developed in this proposal can be readily adapted, thus greatly facilitating the translation of the technology into clinical settings.

C. Approach

Preliminary Studies

We have demonstrated that conjugation of G7 on nanoparticles (G7-NPs) promoted the internalization of NPs by *E. coli* (**Fig. 1a**).[34] This applies to various NPs including quantum dots, silica and iron oxide NPs, as well as four different strains of *E. coli* (ATCC33456, JW3392-1, ORN178 and ORN208). In the experiment, G7-NPs was incubated with bacteria grown to 0.5 OD_{600} at 37 °C for 2 h. Cell wall crossing and internalization were observed for all G7-NPs and all four strains of *E. coli* including JW3392-1 which lacks the maltodextrin transport channel. TEM thin section sample showed the presence of nanoparticles inside the cytoplasm as well as throughout the cell walls.[34]

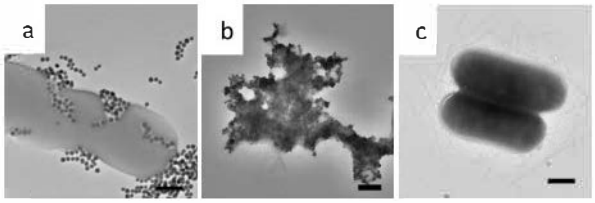


Figure 1. Streptomycin-resistant *E. coli* ORN208 treated with nanoparticles functionalized with G7 (a), both G7 and streptomycin (b). c) *E. coli* ORN208 treated with free streptomycin. Scale bars: 500 nm.

We also showed that the facilitated uptake was G7 specific. When the ligand was changed to β-cyclodextrin or D-mannose, no internalization was observed, and the same was true for unfunctionalized NPs. In addition, the cellular uptake was minimal for mammalian cells, demonstrating the high selectivity of G7 towards bacterial cells.

We then conjugated both G7 and streptomycin on nanoparticles and treated the resulting particles with streptomycin-resistant *E. coli* strain ORN208. Results showed that nanoparticles conjugated with G7 and streptomycin effectively killed the bacteria (**Fig. 1b**), whereas the bacteria cells were intact when treated with the free streptomycin at concentrations at least 5 times higher than that on the nanoparticles (**Fig. 1c**).

These preliminary studies confirmed that the ***G7 facilitated the internalization of nanoparticles by bacterial cells***. More importantly, ***G7-conjugated nanoparticles effectively reverted the bacterial resistance of antibiotics***.

Research Design

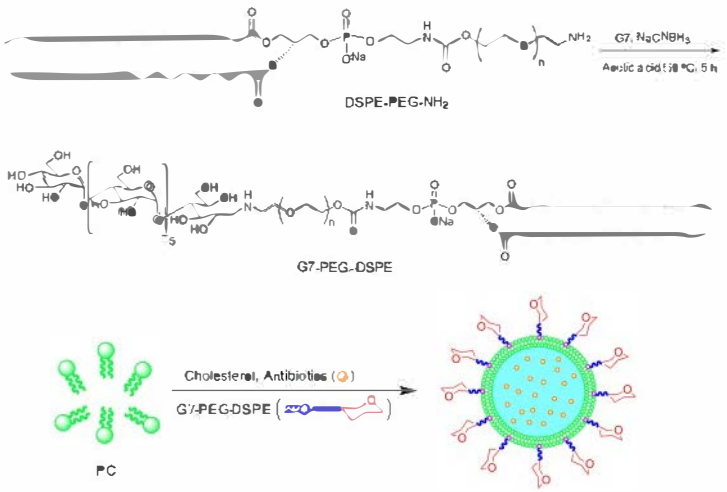
The objective of this application is to test our hypothesis that G7 will greatly facilitate the uptake of nanotherapeutics by bacterial cells, and the multivalent nanoparticles will deliver high local doses of therapeutics into bacterial cells to achieve significantly enhanced antibiotic potency thus reverting the bacterial resistance of antibiotics. In Aim 1, we will synthesize antibiotic-encapsulated, G7-conjugated liposomes and micelles. In Aim 2, the cellular uptake and antibacterial activities will be tested against *P. aeruginosa in vitro*. In Aim 3, the antibacterial activities of these nanotherapeutics will be tested *in vivo* in a mice model.

Aim 1. Synthesis of antibiotic-encapsulated, G7-conjugated liposomes and micelles

We choose liposomes and micelles as the delivery systems for the following reasons. a) Both liposomes and micelles are biocompatible and biodegradable, and have been extensively investigated as drug carriers.[35-43] b) Liposome and micelle-based formulations improve the pharmacokinetics and biodistribution of the drug. It can further achieve higher intracellular drug concentrations while reducing drug concentration in normal tissues.[44] c) Micelles are effective in entrapping hydrophobic drugs in its non-polar core, and liposomes can encapsulate polar drugs in the aqueous core and non-polar drugs in the lamellae shell. Therefore, a large library of therapeutics can be encapsulated including hydrophobic and hydrophilic small molecules, proteins, and nucleic acids. d) Drugs based on these materials are already on the market. In fact, the vast majority of clinically approved nanoparticle-based therapeutics are liposome- or micelle-based formulations.[6,13] Therefore, therapeutics based on these materials can be readily adapted to minimize the risk and facilitate clinical translation.

Synthesis of G7-functionalized liposomes and encapsulation of antibiotics

G7-functionalized liposomes will be prepared by incorporating G7-funcitonalized lipid, G7-PEG-DSPE, into the liposome formulation (Scheme 1). Specifically, G7-PEG-DSPE will be synthesized by reductive amination of DSPE-PEG-NH_2 and G7 following a literature procedure.[45] Note that one glucose unit will be opened after the reaction, however, this will not impact the uptake because the maltohexaose in the product has the same function as maltoheptaose as the bacteria nutrient. Antibiotic-encapsulated liposomes will be prepared by the standard extrusion technique that produces homogeneously-sized liposomes.[46] Briefly, L-α-phosphatidylcholine (PC), cholesterol and G7-PEG-DSPE will be mixed at varying weight ratio in chloroform. After drying under vacuum, the lipid film will be rehydrated with a solution of antibiotic in sterile PBS buffer. The suspension will be sonicated, and extruded through polycarbonate membranes for at least 10 times each to give antibiotic-encapsulated liposomes. Alternatively, G7-PEG-DSPE can be incorporated into the antibiotic-encapsulated PC liposomes by a postmodification protocol to minimize DSPE-PEG-G7 in the inner leaflets.[47] The size of the liposomes

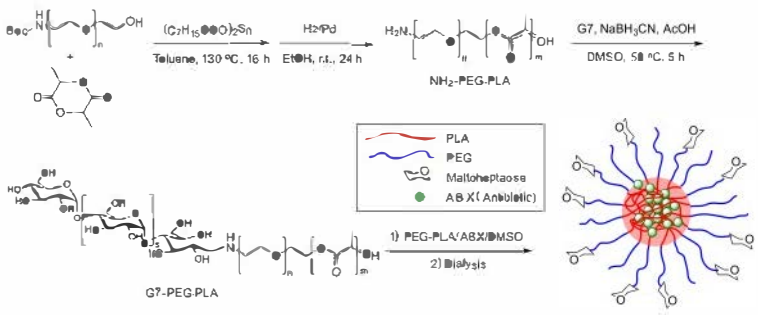


Scheme 1. Synthesis of G7-functionalized lipid and antibiotic-encapsulated liposome

will be controlled by the pore size of the membranes. Un-encapsulated antibiotics will be removed by dialysis. The particle size and size distribution of the liposomes will be characterized by TEM, DLS and fluorescence microscopy by staining with a lipid dye.

Synthesis of G7-functionalized polymer micelles and encapsulation of antibiotics

G7-functionalized micelles will be prepared as shown in Scheme 2. Ring opening polymerization of D,L-lactide from Boc-NH-PEG-OH (3 kDa PEG) followed by deprotection of Boc gives NH_2-PEG-PLA.[48,49] G7 will be conjugated by reductive amination to afford G7-PEG-PLA.[45] Each synthetic intermediate will be characterized by NMR, IR, and GPC (for molecular weight). The PEG/PLA ratio in the copolymer will be determined by NMR. The molecular weight of PLA will be varied (3–110 kDa) to control the size of the micelles, and the antibiotic loading capacility.[50]



Scheme 2. Synthesis of G7-functionalized PEG-PLA and antibiotic-encapsulated micelles.

To prepare antibiotic-encapsulated micelles, PEG-PLA, G7-PEG-PLA and antibiotic will be dissolved in DMSO. The ratio of each component will be varied to control the density of G7 on the micelles and antibiotic loading concentration. The solution will then be dialyzed against D.I. water, after which, the solution will be filtered through a 200 nm membrane to remove unencapsulated antibiotic.[51,52] The micelles will be characterized by TEM and DLS to determine the particle size and size distribution.

Encapsulation yield. The amount of encapsulated antibiotics will be determined using the Kirby-Bauer disk-diffusion method.[53] Liposomes or micelles will be disrupted with Triton X-100 (0.1%) and sample will be transferred to the holes of an agar plate prepared with the standard *E. coli* (ATCC25922) or *P. aeruginosa* (ATCC27853) bacterial culture. Plates will be incubated at 37 °C for 24 h and the inhibition zones will be measured. Results will be compared with a standard calibration curve prepared in the same manner from the free antibiotic. Encapsulation efficiency will be calculated as the percentage of encapsulated antibiotic vs. the antibiotic initially added.

Anticipated outcome and alternative approaches. We follow the well-documented protocols in the literature to synthesize precursors and prepare antibiotic-encapsulated liposomes and micelles. We do not anticipate major problems in the synthesis. The encapsulation efficiency may vary, and in case that the yield is low, liposomes and micelles of larger sizes will be prepared. We will test various antibiotics, which can be easily accomplished since *P. aeruginosa* is resistance to many antibiotics.

Aim 2. Evaluation of antibacterial properties of antibiotic-encapsulated G7-liposomes and G7-micelles *in vitro*

In Aim 2, we will treat *P. aeruginosa* with antibiotic-loaded G7-liposomes and G7-micelles, and study the antibacterial properties of these new nanotherapeutics. A sensitive laboratory strain (ATCC10145) will be used in the initial study. Highly resistant clinical strains will also be acquired and tested. The hypothesis guiding this Aim is that G7 will greatly facilitate the uptake and thus enhancing the therapeutic efficacy of antibiotics *in vitro*. In all studies, free antibiotic, and antibiotic-loaded liposomes and micelles without conjugated G7 will serve as positive

controls, while G7-liposomes and G7-micelles (without antibiotic), and PBS buffer will serve as negative controls.

Uptake of antibiotics. The sample will be incubated with *P. aeruginosa* (10^8 CFU/ mL) in sterile PBS buffer or Mueller–Hinton broth at 37 °C for various length of time (0.5–24 h). Free antibiotics will be separated by filtration. The amount of antibiotics in the filtrate will be quantified by the Kirby-Bauer disk-diffusion method, UV-vis spectroscopy or HPLC. The antibiotic uptake profile for each sample will be plotted and compared.

Minimum Inhibitory Concentration (MIC). The MIC will be determined following the standard broth dilution assay using the serial dilutions of each sample.[54] MIC, the lowest concentration that inhibits the growth of *P. aeruginosa*, will be calculated. We anticipate that the new nanotherapeutics will have significantly lower MICs than the free antibiotics or antibiotic-loaded nanoparticles without G7.

Time-kill studies. The sample will be added to bacterial cultures (10^5 - 10^8 CFU/mL) at 1, 2 or 4 times the MICs. Time-kill studies will be performed over a period of 24 h. Samples will be harvested at different time intervals and CFU will be determined following the standard protocol. We anticipate that the new nanotherapeutics will have prolonged antibacterial activities against the antibiotic-resistant *P. aeruginosa*.

Mammalian cell toxicity. The cytotoxicity of synthesized materials will be evaluated using *in vitro* cytotoxicity assay in cell lines including A549 (Human lung carcinoma epithelial, ATCC CCL-185) and a primary epithelial cell line (ATCC PCS-301-010). Cells will be incubated with varying concentrations of the nanotherapeutic samples, and the cell grown will be quantified by the WST-8 assay by measuring the absorbance at 450 nm.[55] The results will be compared to those of untreated cells to evaluate the cytotoxicity of the nanotherapeutics.

Characterization of nanotherapeutic-bacteria interactions. The interactions of the nanotherapeutics with bacteria will be analyzed by TEM. Thin section samples will also be prepared and examined, by TEM, to confirm the intracellular uptake of the nanotherapeutics. In addition, flow cytometry will be conducted to study the binding kinetics and to quantify the uptake of the nanotherapeutics by bacterial cells. We expect that the G7 conjugation will greatly enhance the interactions of liposomes and micelles with bacteria, promoting membrane fusing and facilitate the uptake of the nanotherapeutics.

Anticipated results and alternative approaches. We anticipate that G7 conjugation will greatly enhance the interactions of nanoparticles with *P. aeruginosa*, promoting membrane penetration and facilitating the uptake of the nanotherapeutics. The density of G7 on liposomes and micelles will be varied to study the impact on cell penetration. In case that the nanoparticles cannot penetrate *P. aeruginosa*, we will test durg-resistant Gram-positive pathogens such as MRSA, or use pathogenic *E. coli* which have shown excellent membrane pentration in our preliminary studies. The success on any of these pathogenic bacteria will be a significant achievement in treating drug-resistant bacterial infections.

Aim 3. Antibacterial studies of antibiotic-encapsulated G7-conjugated liposomes and micelles *in vivo*

The hypothesis guiding Aim 3 is that G7 will greatly enhance the therapeutic efficacy of antibiotics *in vivo*. A mice model will be used to test this hypothesis. In all studies, antibiotic-loaded nanoparticles without conjugated G7 and free antibiotics will serve as positive controls, while G7-nanoparticles (without antibiotics) and PBS buffer will serve as negative controls.

We will choose antibiotics based on the results of Specific Aims 1 and 2. Ideally we would like to use antiobiotics that are clinically useful, that have a spectrum of activity including organisms

that are difficult to treat such as carbapenem resistant enterobacteriaciae, and that demontstrate dramatic increases in activity after formulation as liposomes or micelles.

To mimic human disease, we will use two types of assays: a bacteremia model, and an abscess model. Dr. Finberg's laboratory has experience with both of these assays. Dr. Finberg's laboratory also has extensive experience in mouse models and has a large collection of mice with different host genes deleted. The availibility of knock-out mice will allow future experiments to define what host genes might be important in microbial clearance and if the nanotherapeutic formulations would lead to more or less dependance on given host genes. We will use two types of quantitative assays to measure the effect of the nanoparticle formulations.

To investigate the activity of the nanoparticles against blood stream infections caused by Gram-negative organisms, we will use an immunocompromised mouse model.[56] In this model, mice are treated with cyclophosphamide to render them neutropenic and then challenged with Gram-negative intra-peritoneally followed by delivery of nanotherapeutics given ip, iv, or po (using gastric lavage) two hours later. The effects of the nanotherapeutics will be determined by measuring bacteremia in the blood as we have described previously.[57] This model simulates a neutropenic host (such as humans receiving chemotherapy for cancer) and is currently in use in Dr. Finberg's laboratory.

In order to mimic disease caused by skin breakdown, we will use a subcutaneous abscess model. Two different models will be employed. One model employs the use of an implanted pump and allows for the quantitation of bacteria within the pump cavity.[58] Another assay involves the quantitation of efficacy by measuring subcutaneous abscess dimensions.[56,59] In all cases, group sizes will be calculated based on the *in vitro* efficacy and will be designed to test whether the nanoparticle formulation is superior to the conventional antibiotic. As outlined previously,[57] all power calculations and determinations of efficacy are done in collaboration with the University of Massachusetts Medical School (UMMS) Biostat core to minimize the use of animals and make clear determinations of efficacy using quantitative methods.

In addition to using the dimensions of the abscesses as a measure of efficacy, the infected tissues will be analyzed by histology and samples will be prepared as follows. The abscess tissues will be excised from euthanized mice, fixed in 10% formalin for 24 h, processed, and embedded in paraffin. Vertical sections (4 μm) will be fixed to glass slides and subjected to H&E, Gram, Gomori's trichrome, or CD34 staining. The slides will be examined under optical microscope for tissue morphology, bacteria, collagen deposition, or vascularization.

Numbers of mice will be calculated separately for each agent based on *in vitro* determinations and previous experience with *in vivo* challenges from the literature. All power calculations will be made with the help of the UMMS Biostat group as we have done previously.[57] Untreated, infected and non-infected mice will be used as additional controls.

Anticipated results and alternative approaches. We hypothesize that the G7-conjugated nanotherapeutic formulations will have statistically significant superiority compared to antibiotics alone. As noted above, our experience with *in vitro* assays indicates that this should be easy to demonstrate and we are using animals already in use in our laboratory. Since we have *in vitro* data with streptomycin, we will do our initial *in vivo* tests with aminoglycoside antibiotics. However, we recognize that these may not be the most useful agents for Gram-positive pathogens such as MRSA, and these formulations may work better with certain antibiotics as opposed to others. For these reasons we will consider testing the effects of the G7 formulation on cell wall active antibiotics such as colistin as well as DNA gyrase active agents such as ciprofloxacin. Such studies, using antibiotics that have entirely different mechanisms of action, will allow us to determine under what circumstances the G7-conjugation is useful and to define the mechanism(s) or action.

Vertebrate Animals

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work:

Mice: Up to 400 per year, 0.5 to 3 months of age of both sexes from various inbred strains (e.g. C57BL/6). Animals will be infected with *Pseudomonas* or *Staphylococcus* bacteria by intravenous injection. Following these procedures the mice will be followed clinically or humanely euthanized at various times post-infection, and tissues will be collected for analysis of bacterial titers and *ex vivo* studies. These procedures have been approved by the University of Massachusetts Medical School (UMMS) Institutional Animal Use and Care Committee as protocol A-1220, Dr. Robert W. Finberg, PI. All animal experiments will be conducted by postdoctoral associate Dr. Carlton-Smith, supervised by Dr. Finberg, and assisted by the staff members of the animal facilities at UMMS.

2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers:

This research is directed at investigating the mechanisms by which bacteria cause disease. An animal model is essential as we need to study this process as these events only occur *in vivo*. For these studies the mouse is the species of choice because there are well-established and unique mutant models available. The number of animals used will be the minimum to establish significance and reproducibility, to generate and validate experimental models, to give adequate material to achieve the scientific objectives.

3. Provide information on the veterinary care of the animals involved:

The University of Massachusetts Medical Center is accredited by the American Association for the Accreditation of Laboratory Animal Care, meets National Institutes of Health standards as set forth in the "Guide for the Care and Use of Laboratory Animals (Publication No. NIH 86-23, revised 1985), the Animal Welfare Act, and other relevant Federal laws. The Institute accepts as mandatory the NIH "Principles for the Use of Animals", an existing research protocol involving animals to assure compliance with the law and good laboratory practice. Veterinary and diagnostic services are provided through Jerald Silverman, D.V.M and his veterinary staff.

4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.

We will attempt to minimize discomfort to the animals. Anesthesia and analgesia will be administered as is appropriate. The principal investigator, laboratory personnel and animal technicians involved in anyway in the proposed research have had instruction or demonstrated their competence in the care, use and handling of laboratory animals. We give assurance of humane practice in animal use.

5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations:

Mice will be euthanized using lethal doses of carbon dioxide followed by cervical dislocation. The method is consistent with the AVMA recommendations, and the procedures have been approved by the UMMS Institutional Animal Use and Care Committee.

D. References

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Research Funding Services

STATEMENT OF INTENT TO ESTABLISH A CONSORTIUM AGREEMENT

APPLICATION TITLE: Nanotherapeutics for Targeting Multidrug-Resistant Bacteria

PRIME SPONSOR: National Institute of Health (NIH)

APPLICANT PRINCIPAL INVESTIGATOR: Dr. Mingdi Yan

APPLICANT INSTITUTION: University of Massachusetts Medical School - Lowell

COOPERATING INSTITUTION: University of Massachusetts Medical School - Worcester

DUNS number: 603847393

Congressional District: MA-002

UMMS INVESTIGATOR: Dr. Robert Finberg

TOTAL PROJECT COSTS: 184,104

PROPOSED PROJECT PERIOD: 12/01/2013 – 11/30/2015

In signing below and offering to participate in this research program, UMMS certifies that to the extent applicable under the law neither they nor their principals are presently debarred, suspended, proposed for debarment, declared ineligible or voluntarily excluded from receiving funds from any federal department or agency and are not delinquent on any federal debt; they are in compliance with the Drug Free Workplace Act of 1988; they are in compliance with the U.S. Code, Section 1352, restrictions on the use of federal funds for the purpose of lobbying; they have filed annually with the Office of Scientific Integrity a PHS form 6349 governing Misconduct in Science; they have filed with DHHS compliance offices certification forms governing Civil Rights (441), Handicapped Individuals (641), Sex Discrimination (639-A), and Age Discrimination (680); they are in compliance with PHS policy governing Program Income; they have established policies in compliance with 45 CFR Part 46, Subpart A (protection of human subjects); the Animal Welfare Act (PL-89-544 as amended) and the Health Research Exchange Act of 1985 (Public Law 99-158); and that they are in compliance with applicable federal and/or sponsor guidelines regarding human pluripotent stem cell research, transplantation of fetal tissue, recombinant DNA and human gene transfer research, and inclusion of women, children & minorities in research.

The appropriate programmatic and administrative personnel of each institution involved in this grant application are aware of the PHS-NIH consortium grant policies and are prepared to establish the necessary inter-institutional agreement(s) consistent with those policies. In signing below, the UMMS certifies that it has implemented and is enforcing the new PHS regulations on Conflict of Interest as of August 1,2012 and is in compliance with the updated provisions of 42 CFR Part 50, Subpart F & 45 CFR Subtitle A, Part 94. UMMS will notify the prime applicant of any determination of a positive conflict of interest before entering into a subagreement should this application be funded. UMMS confirms that it participates in the FDP Clearinghouse of PHS-COI Compliant Institutions (http://sites.nationalacademies.org/PGA/fdp/PGA_070596).

APPLICANT INSTITUTION — **University of Massachusetts Medical School - Worcester**

Principal Investigator	Date	UMMS Investigator	Date: 04/02/2013
Authorized Institutional Official Name, Title	Date	Authorized Institutional Official Janice Lagace, Assistant Director Grants, Research Funding	Date: 04/02/2013

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Robert W. Finberg MD
Richard M. Haddock Professor of Medicine
Professor, Molecular Genetics and Microbiology
Chair, Department of Medicine

April 3, 2013

Mingdi Yan, Ph.D., Professor
Department of Chemistry
University of Massachusetts Lowell
One University Avenue
Lowell, MA 01854

Dear Mingdi,

I am happy to write this letter of support for your R21 grant application submission titled, **"Nanotherapeutics for Targeting Multidrug-Resistant Bacteria".** The goal of developing nanotherapeutics to treat antibiotic resistant-bacterial infections is an innovative and exciting approach to an urgent problem. As a physician who sees patients, I am well aware of the increasing problem posed by antibiotic-resistant bacteria, and novel approaches to treating these infections is something that I am very interested in helping to advance. My laboratory will characterize the *in vivo* efficacy of these nanotherapeutics in mouse models of antibiotic-resistant infections. As you know my laboratory has extensive experience using *in vivo* models of infection with various pathogens. UMass Medical School is an excellent environment to conduct these studies as it has a state-of-the-art animal facility as well as a Flow Cytometry Core. I look forward to working with you on these exciting and innovative studies.

Sincerely,

Robert W. Finberg, M.D.

PHS 398 Checklist

OMB Number: 0925-0001

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

Federal Identifier:

2. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:
* First Name:
Middle Name:
* Last Name:
Suffix:

☐ Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes ☐ No ☐

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes ☐ No ☐

4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

5. * Disclosure Permission Statement

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes ☐ No