

BIOGRAPHICAL SKETCH

NAME Robert A. Bonomo	POSITION TITLE Associate Professor, Department of Medicine (primary); Pharmacology and Molecular Biology and Microbiology (secondary)		
eRA COMMONS USER NAME RBONOMO			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Hamilton College, Clinton, New York	B.A.	May, 1976	Biology
New York University, Basic Medical Sciences		1977-1979	Histology
Case Western Reserve University, Cleveland, Ohio	M.D.	May, 1983	Medicine
University Hospitals of Cleveland, Cleveland, Ohio		1983-1986	Resident, Medicine
University Hospitals of Cleveland, Cleveland, Ohio		1990-1994	Fellowship, Infectious Diseases
University Hospitals of Cleveland, Cleveland, Ohio		1998	Certificate of Added Qualification, Geriatrics

A. Positions

1986-1990	Clinical Instructor, CWRU School of Medicine, Cleveland, Ohio
1986-1990	Physician, Internal Medicine, Cleveland Neighborhood Health Services, Inc.
1986-1991	Staff Physician, Cleveland Neighborhood Health Services
1989-1990	Chief of Medicine, Cleveland Neighborhood Health Services
1994-2001	Assistant Professor of Medicine, CWRU School of Medicine, Cleveland, Ohio
1997-present	Staff Physician, Division of Geriatrics, Cleveland Veterans Affairs Medical Center
2000-present	Section Chief, Infectious Diseases, Cleveland Veterans Affairs Medical Center
2000-present	Secondary appointment, Department of Pharmacology, CWRU School of Medicine
2001	Associate Professor of Medicine, CWRU School of Medicine, Cleveland, Ohio
2002	Award of Tenure, CWRU School of Medicine, Cleveland, Ohio
2003	Committee on Medical Education, CWRU School of Medicine, Cleveland, Ohio
2004	Secondary appointment, Department of Molecular Biology and Microbiology, CWRU SOM
2008	Director Cleveland VAMC Cleveland GRECC

Honors

1973	Curran Prize in Classical Languages, Hamilton College
1983	The Milton B. Schweid Memorial Award CWRU SOM for Excellence in Cardiovascular Disease
1994	MetroHealth Medical Center Scientific Contest for Residents and Fellows, Second Place
1994	American College of Physicians, Associate Clinical Vignette Competition, Winner
2004	Kaiser Permanente Excellence in Teaching Award for Basic Medical Sciences, CWRU SOM
2005	Alpha Omega Alpha Honor Medical Society
2005	Award from University Hospitals of Cleveland for Excellence in House Staff Teaching
2008	Distinguished Educator in Infectious Diseases, University of Pittsburgh
2008	Gender Equity Award for Excellence in Teaching

Professional Societies and Service

1990-present	Infectious Disease Society of America (IDSA)
1990-present	American Society for Microbiology (ASM)
1990-present	American Association for the Advancement of Science (AAAS)
2002-2003	National Institutes of Health, Study Section, Indian Health Service
2002 -2008	Editorial Board, Antimicrobial Agents and Chemotherapy
2005-2007	Protein Society, American Society for Biochemistry and Molecular Biology
2005-present	Program Committee, Interscience Conference on Antimicrobial Agents and Chemotherapy
2006 -2011	Editorial Board, <i>Journal of Biological Chemistry</i>

B. Selected peer-reviewed publications (40 recent papers chosen in chronological order).

- Hujer, A. M.; Hujer, K. M.; **Bonomo, R. A.**, Mutagenesis of amino acid residues in the SHV-1 beta-lactamase: the premier role of Gly238Ser in penicillin and cephalosporin resistance. *Biochim Biophys Acta* 2001, 1547, (1), 37-50.

2. Hujer, A. M.; Page, M. G.; Helfand, M. S.; Yeiser, B.; **Bonomo, R. A.**, Development of a sensitive and specific enzyme-linked immunosorbent assay for detecting and quantifying CMY-2 and SHV beta-lactamases. *J Clin Microbiol* 2002, 40, (6), 1947-57.
3. Hoyen, C. M.; Hujer, A. M.; Hujer, K. M.; Marshall, S. H.; Carias, L.; Toltzis, P.; Rice, L. B.; **Bonomo, R. A.**, A clinical strain of *Escherichia coli* possessing CMY-2 plasmid-mediated amp C beta-lactamase: an emerging concern in pediatrics? *Microb Drug Resist* 2002, 8, (4), 329-33.
4. Hujer, A. M.; Hujer, K. M.; Helfand, M. S.; Anderson, V. E.; **Bonomo, R. A.**, Amino acid substitutions at Ambler position Gly238 in the SHV-1 beta-lactamase: exploring sequence requirements for resistance to penicillins and cephalosporins. *Antimicrob Agents Chemother* 2002, 46, (12), 3971-7.
5. Helfand, M. S.; Bethel, C. R.; Hujer, A. M.; Hujer, K. M.; Anderson, V. E.; **Bonomo, R. A.**, Understanding resistance to beta-lactams and beta-lactamase inhibitors in the SHV beta-lactamase: lessons from the mutagenesis of SER-130. *J Biol Chem* 2003, 278, (52), 52724-9.
6. Nukaga, M.; Mayama, K.; Hujer, A. M.; **Bonomo, R. A.**; Knox, J. R., Ultrahigh resolution structure of a class A beta-lactamase: on the mechanism and specificity of the extended-spectrum SHV-2 enzyme. *J Mol Biol* 2003, 328, (1), 289-301.
7. Nukaga, M.; Abe, T.; Venkatesan, A. M.; Mansour, T. S.; **Bonomo, R. A.**; Knox, J. R., Inhibition of class A and class C beta-lactamases by penems: crystallographic structures of a novel 1,4-thiazepine intermediate. *Biochemistry* 2003, 42, (45), 13152-9.
8. Paterson, D. L.; Hujer, K. M.; Hujer, A. M.; Yeiser, B.; Bonomo, M. D.; Rice, L. B.; **Bonomo, R. A.**, Extended-spectrum beta-lactamases in *Klebsiella pneumoniae* bloodstream isolates from seven countries: dominance and widespread prevalence of SHV- and CTX-M-type beta-lactamases. *Antimicrob Agents Chemother* 2003, 47, (11), 3554-60.
9. Helfand, M. S.; **Bonomo, R. A.**, Beta-lactamases: a survey of protein diversity. *Curr Drug Targets Infect Disord* 2003, 3, (1), 9-23.
10. Pagan-Rodriguez, D.; Zhou, X.; Simmons, R.; Bethel, C. R.; Hujer, A. M.; Helfand, M. S.; Jin, Z.; Guo, B.; Anderson, V. E.; Ng, L. M.; **Bonomo, R. A.**, Tazobactam inactivation of SHV-1 and the inhibitor-resistant Ser130 -->Gly SHV-1 beta-lactamase: insights into the mechanism of inhibition. *J Biol Chem* 2004, 279, (19), 19494-501.
11. Venkatesan, A. M.; Gu, Y.; Dos Santos, O.; Abe, T.; Agarwal, A.; Yang, Y.; Petersen, P. J.; Weiss, W. J.; Mansour, T. S.; Nukaga, M.; Hujer, A. M.; **Bonomo, R. A.**; Knox, J. R., Structure-activity relationship of 6-methylidene penems bearing tricyclic heterocycles as broad-spectrum beta-lactamase inhibitors: crystallographic structures show unexpected binding of 1,4-thiazepine intermediates. *J Med Chem* 2004, 47, (26), 6556-68.
12. Sun, T.; Bethel, C. R.; **Bonomo, R. A.**; Knox, J. R., Inhibitor-resistant class A beta-lactamases: consequences of the Ser130-to-Gly mutation seen in Apo and tazobactam structures of the SHV-1 variant. *Biochemistry* 2004, 43, (44), 14111-7.
13. Rice, L. B.; Bellais, S.; Carias, L. L.; Hutton-Thomas, R.; **Bonomo, R. A.**; Caspers, P.; Page, M. G.; Gutmann, L., Impact of specific pbp5 mutations on expression of beta-lactam resistance in *Enterococcus faecium*. *Antimicrob Agents Chemother* 2004, 48, (8), 3028-32.
14. Bethel, C. R.; Hujer, A. M.; Helfand, M. S.; **Bonomo, R. A.**, Exploring the effectiveness of tazobactam against ceftazidime resistant *Escherichia coli*: insights from the comparison between susceptibility testing and beta-lactamase inhibition. *FEMS Microbiol Lett* 2004, 234, (1), 99-103.
15. Hujer, A. M.; Bethel, C. R.; **Bonomo, R. A.**, Antibody mapping of the linear epitopes of CMY-2 and SHV-1 beta-lactamases. *Antimicrob Agents Chemother* 2004, 48, (10), 3980-8.
16. Thomson, J. M.; **Bonomo, R. A.**, The threat of antibiotic resistance in Gram-negative pathogenic bacteria: beta-lactams in peril! *Curr Opin Microbiol* 2005, 8, (5), 518-24.
17. Hujer, A. M.; Kania, M.; Gerken, T.; Anderson, V. E.; Buynak, J. D.; Ge, X.; Caspers, P.; Page, M. G.; Rice, L. B.; **Bonomo, R. A.**, Structure-activity relationships of different beta-lactam antibiotics against a soluble form of *Enterococcus faecium* PBP5, a type II bacterial transpeptidase. *Antimicrob Agents Chemother* 2005, 49, (2), 612-8.
18. Hujer, K. M.; Hamza, N. S.; Hujer, A. M.; Perez, F.; Helfand, M. S.; Bethel, C. R.; Thomson, J. M.; Anderson, V. E.; Barlow, M.; Rice, L. B.; Tenover, F. C.; **Bonomo, R. A.**, Identification of a new allelic variant of the *Acinetobacter baumannii* cephalosporinase, ADC-7 beta-lactamase: defining a unique family of class C enzymes. *Antimicrob Agents Chemother* 2005, 49, (7), 2941-8.

19. Padayatti, P. S.; Helfand, M. S.; Totir, M. A.; Carey, M. P.; Carey, P. R.; **Bonomo, R. A.**; van den Akker, F., High resolution crystal structures of the trans-enamine intermediates formed by sulbactam and clavulanic acid and E166A SHV-1 beta-lactamase. *J Biol Chem* 2005, 280, (41), 34900-7.
20. Paterson, D. L.; **Bonomo, R. A.**, Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev* 2005, 18, (4), 657-86.
21. Helfand, M. S.; **Bonomo, R. A.**, Current challenges in antimicrobial chemotherapy: the impact of extended-spectrum beta-lactamases and metallo-beta-lactamases on the treatment of resistant Gram-negative pathogens. *Curr Opin Pharmacol* 2005, 5, (5), 452-8.
22. Sulton, D.; Pagan-Rodriguez, D.; Zhou, X.; Liu, Y.; Hujer, A. M.; Bethel, C. R.; Helfand, M. S.; Thomson, J. M.; Anderson, V. E.; Buynak, J. D.; Ng, L. M.; **Bonomo, R. A.**, Clavulanic acid inactivation of SHV-1 and the inhibitor-resistant S130G SHV-1 beta-lactamase. Insights into the mechanism of inhibition. *J Biol Chem* 2005, 280, (42), 35528-36.
23. Babic, M.; Hujer, A. M.; **Bonomo, R. A.**, What's new in antibiotic resistance? Focus on beta-lactamases. *Drug Resist Updat* 2006, 9, (3), 142-56.
24. Reynolds, K. A.; Thomson, J. M.; Corbett, K. D.; Bethel, C. R.; Berger, J. M.; Kirsch, J. F.; **Bonomo, R. A.**; Handel, T. M., Structural and computational characterization of the SHV-1 beta-lactamase-beta-lactamase inhibitor protein interface. *J Biol Chem* 2006, 281, (36), 26745-53.
25. Bethel, C. R.; Hujer, A. M.; Hujer, K. M.; Thomson, J. M.; Ruszczycky, M. W.; Anderson, V. E.; Pusztai-Carey, M.; Taracila, M.; Helfand, M. S.; **Bonomo, R. A.**, Role of Asp104 in the SHV beta-lactamase. *Antimicrob Agents Chemother* 2006, 50, (12), 4124-31.
26. Thomson, J. M.; Distler, A. M.; Prati, F.; **Bonomo, R. A.**, Probing active site chemistry in SHV beta-lactamase variants at Ambler position 244. Understanding unique properties of inhibitor resistance. *J Biol Chem* 2006, 281, (36), 26734-44.
27. Szabo, D.; Silveira, F.; Hujer, A. M.; **Bonomo, R. A.**; Hujer, K. M.; Marsh, J. W.; Bethel, C. R.; Doi, Y.; Deeley, K.; Paterson, D. L., Outer membrane protein changes and efflux pump expression together may confer resistance to ertapenem in *Enterobacter cloacae*. *Antimicrob Agents Chemother* 2006, 50, (8), 2833-5.
28. **Bonomo, R. A.**; Szabo, D., Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. *Clin Infect Dis* 2006, 43 Suppl 2, S49-56.
29. Helfand, M. S.; **Bonomo, R. A.**, Extended-spectrum beta-lactamases in multidrug-resistant *Escherichia coli*: changing the therapy for hospital-acquired and community-acquired infections. *Clin Infect Dis* 2006, 43, (11), 1415-6.
30. Totir, M. A.; Padayatti, P. S.; Helfand, M. S.; Carey, M. P.; **Bonomo, R. A.**; Carey, P. R.; van den Akker, F., Effect of the inhibitor-resistant M69V substitution on the structures and populations of trans-enamine beta-lactamase intermediates. *Biochemistry* 2006, 45, (39), 11895-904.
31. Hujer, K. M.; Hujer, A. M.; Hulten, E. A.; Bajaksouzian, S.; Adams, J. M.; Donskey, C. J.; Ecker, D. J.; Massire, C.; Eshoo, M. W.; Sampath, R.; Thomson, J. M.; Rather, P. N.; Craft, D. W.; Fishbain, J. T.; Ewell, A. J.; Jacobs, M. R.; Paterson, D. L.; **Bonomo, R. A.**, Analysis of antibiotic resistance genes in multidrug-resistant *Acinetobacter* sp. isolates from military and civilian patients treated at the Walter Reed Army Medical Center. *Antimicrob Agents Chemother* 2006, 50, (12), 4114-23.
32. Thomson, J. M.; Prati, F.; Bethel, C. R.; **Bonomo, R. A.**, Use of novel boronic acid transition state inhibitors to probe substrate affinity in SHV-type extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 2007, 51, (4), 1577-9.
33. Totir, M. A.; Helfand, M. S.; Carey, M. P.; Sheri, A.; Buynak, J. D.; **Bonomo, R. A.**; Carey, P. R., Sulbactam forms only minimal amounts of irreversible acrylate-enzyme with SHV-1 beta-lactamase. *Biochemistry* 2007, 46, (31), 8980-7.
34. Endimiani, A.; Luzzaro, F.; Migliavacca, R.; Mantengoli, E.; Hujer, A. M.; Hujer, K. M.; Pagani, L.; **Bonomo, R. A.**; Rossolini, G. M.; Toniolo, A., Spread in an Italian hospital of a clonal *Acinetobacter baumannii* strain producing the TEM-92 extended-spectrum beta-lactamase. *Antimicrob Agents Chemother* 2007, 51, (6), 2211-4.
35. Thomson, J. M.; Distler, A. M.; **Bonomo, R. A.**, Overcoming Resistance to beta-Lactamase Inhibitors: Comparing Sulbactam to Novel Inhibitors against Clavulanate Resistant SHV Enzymes with Substitutions at Ambler Position 244. *Biochemistry* 2007.
36. Perez, F.; Hujer, A. M.; Hujer, K. M.; Decker, B. K.; Rather, P. N.; **Bonomo, R. A.**, The Global Challenge of Multidrug Resistant (MDR) *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2007.

37. Kalp, M.; Sheri, A.; Buynak, J. D.; Bethel, C. R.; **Bonomo, R. A.**; Carey, P. R., Efficient inhibition of class A and class D beta-lactamases by Michaelis complexes. *J Biol Chem* 2007, 282, (30), 21588-91.
38. Ke, W.; Bethel, C. R.; Thomson, J. M.; **Bonomo, R. A.**; van den Akker, F., Crystal structure of KPC-2: insights into carbapenemase activity in class A beta-lactamases. *Biochemistry* 2007, 46, (19), 5732-40.
39. Perez, F.; Endimiani, A.; Hujer, K. M.; **Bonomo, R. A.**, The continuing challenge of ESBLs. *Curr Opin Pharmacol* 2007.
40. Leonard, D. A.; Hujer, A. M.; Smith, B. A.; Schneider, K. D.; Bethel, C. R.; Hujer, K. M.; **Bonomo, R. A.**, The role of OXA-1 beta-lactamase aspartate 66 in stabilization of the active site carbamate and substrate turnover. *Biochem J* 2008.

C. Research Support

ACTIVE

1RO1 AI072219 (Bonomo)

9/1/2007-8/30/2012

NIH/NIAID

Multidrug Resistant *Acinetobacter baumannii*

The major goals of this study are to examine cephalosporin resistance by determining the atomic structure of the class C (ADC-type) beta-lactamases and testing novel boronic acid and sulfone transition state inhibitors against this class of cephalosporinases. We will examine carbapenem resistance by random mutagenesis of the class D beta-lactamases, OXA-23 and OXA-58, and will perform mass spectrometry to determine the intermediates of inactivation by beta-lactamase inhibitors. Efflux pumps are a major component of antibiotic resistance. The genetic heterogeneity of the regulatory regions of the adeABC efflux pump will be determined and will be used to develop a novel PCR/ESI-MS method to predict the multidrug resistant phenotype in *Acinetobacter*.

1RO1 AI063517 (Bonomo)

2/1/2005 – 1/31/2010

NIH/NIAID

Understanding ceftazidime resistance in SHV beta-lactamases

In this proposal we will determine the atomic structures of boronic acid transition state analogue inhibitors that have R1 side chains of ceftazidime and cefotaxime in the SHV-1, -2, and -5 beta-lactamases. We will also study the evolution of ceftazidime resistance in isolates deficient in DNA mismatch repair proteins, determine if mutator phenotypes exist in *Klebsiella pneumoniae*, and develop a model of Extended-Spectrum beta-lactamase (ESBL) evolution in *mutS* deficient strains. We will also seek to determine if the SHV beta-lactamase possess mutations that stabilize the deleterious effects of other mutations (global suppressor).

Merit Review (Bonomo)

4/1/2005 – 3/31/2008

Department of Veterans Affairs

Understanding inhibitor resistant SHV beta-lactamases

The major goals of this project are to explore the genetic and amino acid determinants of inhibitor resistant beta-lactamase variants of the SHV-1 beta-lactamase, a class A enzyme. Crystallography, mass spectrometry, and site-directed mutagenesis have been undertaken. Novel compounds will be assessed. The search for peptide inhibitors specific for SHV will be undertaken using phage display.

1RO1AIO45626 (Rice)

3/1/2005 - 2/28/2010

NIH/NIAID

Regulation of ampicillin resistance in enterococci

This grant is to study the mechanisms by which expression of PBP5 and ampicillin resistance in *Enterococcus faecium* is regulated. Our goal is to perform site-directed mutagenesis of PBP5 and clone mutants of PBP5 into an expression system, pET 24a (+), to facilitate purification.

OVERLAP

There is no scientific overlap between the active grants and the application under consideration.