Dr n. biol. Anna GRZEGORZEWICZ – informacja biograficzna

Address 1682 Campus Delivery
Colorado State University
Dept. Microbiology, Immunology, and Pathology
Fort Collins, CO 80523-1682
Phone: 970 491 4067
Fax: 970 491 10603
e-mail: agrzeg@colostate.edu

Education

Ph.D. (2003) Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Dept. of Immunology of Infectious Diseases, Laboratory of Medical Microbiology;,
Thesis: Surface components of actinobacterial cell wall.
Supervisor: Prof. Andrzej Gamian Ph.D

M.Sc. (1995) University of Wroclaw, Faculty of Natural Sciences, Biotechnology,
Thesis: Studies of phospholipase A2 activity in nuclear matrix and its protein components.
Supervisor: Prof. Arkadiusz Kozubek, Ph.D

Research experience

03/1997 – 01/1998	technical assistant, Institute of Immunology, Polish Academy of Sciences, Wroclaw, Poland
01/1998 – 09/2004	research assistant, Institute of Immunology, Polish Academy of Sciences, Wroclaw, Poland
2000–2001	multiple scientific stays at Lund University, Chemical Center, Dept. Pure and Applied Biochemistry, Lund, Sweden
10/2004 – 07/2008	post-doctoral fellow, Colorado State University, Fort Collins, USA Supervisor: Michael McNeil, Ph.D.
07/2008 – 08/2011	post-doctoral fellow, Colorado State University, Fort Collins, USA Supervisor: Mary Jackson, Ph.D.
08/2011 – present	research scientist/scholar I, Colorado State University, Fort Collins, USA Supervisor: Mary Jackson, Ph.D.

Professional experience

microbiology of actinobacteria
structural studies on actinobacterial glycolipids
studies on biological activities and location of actinobacterial glycolipids in the cell
investigation of the antitubercular drugs mode of action
development of high throughput assays

studies on the function of the mycobacterial proteins involved in the cell wall synthesis (enzymes and transporters)
studies on mycobacterial epoxide hydrolases

Current Research Interest

My research focuses on the elucidation of the mode of action of antitubercular drugs. The increasing prevalence of multidrug resistant tuberculosis highlights the need for drugs with bactericidal mechanism different from those of presently available agents. My work involves elucidating the molecular mechanism of action of new and well-established antitubercular drugs as an aid in developing new therapeutic agents with greater potency, improved pharmacokinetics and reduced toxicity.

I'm particularly interested in finding inhibitors affecting the synthesis of the mycobacterial cell envelope lipids, which form a hydrophobic barrier that prevents the entry of potential antibiotics. I'd like to mention two groups of compounds we've been working on: adamantyl urea and thiocarbamide compounds.

It was established in our laboratory that the bactericidal activity of adamantyl urea compounds on *Mycobacterium tuberculosis* result from the abolition of translocation of trehalose monomycolate across the plasma membrane. Further studies shown that the inner membrane transporter, MmpL3, carries out trehalose monomycolate transport. As a result of MmpL3 inhibition by adamantyl urea the cell envelope outer membrane is not formed. MmpL3 protein is a new promising target for antitubercular drugs.

The Isoxyl and thiacetazone are thiocarbamide-containing prodrugs, which have been used in the clinical treatment of tuberculosis, but theirs clinical use has been restricted due to low bioavailability or toxicity.

It has been known for the long time that these drugs inhibit *Mycobacterium tuberculosis* growth through the inhibition of mycolic acid synthesis but their targets in this pathway have remained unknown. Our recent studies have shown that isoxyl and thiacetazone inhibit the dehydration step of the type II fatty acid synthase cycle. The detailed understanding of the inhibition mechanism of dehydratases by thiacetazone and isoxyl would allow for rational development of optimized inhibitors of *Mycobacterium tuberculosis* growth.

Awards

Medical Sciences PAN Department's Group Award for studies on immunochemistry human pathogens actinobacteria – Warszawa, 2005

Memberships

2000 – Member of Polish Society for Biochemistry

Publications

1. Hidri N., Farina C., Mordarska H., Szponar B., Paściak M., **Grzegorzewicz A.**, Gamian A., Boiron P. *Nocardia,* nocardiosis and nocardiomycosis. Mikrobiologia Medycyna. (in Polish) 2000, 3, 4 (24, 25): 10–17.

2. Hidri N., Farina C., Boiron P., Mordarska H., Szponar B., Paściak M., **Grzegorzewicz A**., Gamian A. *Nocardia* and human nocardiosis.. Mikologia Lekarska. 2000, 7(4) 1–6.
3. Hidri N., Farina C., Mordarska H., Szponar B., Paściak M., **Grzegorzewicz A**., Gamian A., Boiron P. *Nocardia* and human nocardiosis. Pneumol. Alergol. Pol., (in Polish) 2001, 69, 11–12, 667–676.
4. Paściak M., Ekiel I., **Grzegorzewicz A.**, Mordarska H., Gamian A. Structure of the major glycolipid from *Rothia dentocariosa*. Biochim. Biophys. Acta. 2002, 1594, 199–205.
5. **Grzegorzewicz A.**, Gamian A. Atomic force microscope a new investigation tool in microbiology. Post. Mikrobiol. (in Polish) 2003, 42(4): 419–436.
6. Paściak M., Holst O., Lindner B., Mierzchała M., **Grzegorzewicz A.**, Mordarska H., Gamian A. Structural and serological characterization of the major glycolipid from *Rothia mucilaginosa*. Biochim Biophys Acta. 2004, 1675(1–3):54–61.
7. Novik G.I., Astapovich N.I., **Grzegorzewicz A.**, Gamian A. Isolation and comparative analysis of glycolipid fractions in bifidobacteria. Mikrobiologiia. (in Russian) 2005, 74(6):772–80.
8. **Grzegorzewicz A.E.**, Ma Y., Jones V., Crick D., Liav A., McNeil MR. Development of a microtitre plate-based assay for lipid-linked glycosyltransferase products using the mycobacterial cell wall rhamnosyltransferase WbbL. Microbiology. 2008, 154:3724–30.
9. Birch H.L., Alderwick L.J., Rittmann D., Krumbach K., Etterich H., **Grzegorzewicz A.**, McNeil M.R., Eggeling L, Besra G.S. Identification of a terminal rhamnopyranosyltransferase (RptA) involved in *Corynebacterium glutamicum* cell wall biosynthesis. J Bacteriol. 2009, 191(15):4879–87.
10. Sivendran S., Jones V., Sun D., Wang Y., **Grzegorzewicz A.E.**, Scherman M.S., Napper A.D., McCammon J.A., Lee R.E., Diamond S.L., McNeil M. Identification of triazinoindol--benzimidazolones as nanomolar inhibitors of the Mycobacterium tuberculosis enzyme TDP-6-deoxy-d-xylo-4-hexopyranosid-4-ulose 3,5-epimerase (RmlC). Bioorg Med Chem. 2010,18(2):896–908.
11. Gil F., **Grzegorzewicz A.E.**, Catalão M.J., Vital J., McNeil M.R., Pimentel M. Mycobacteriophage Ms6 LysB specifically targets the outer membrane of *Mycobacterium smegmatis*. Microbiology. 2010, 156(Pt 5):1497–504.
12. Brown J.R., North E.J., Hurdle J.G., Morisseau C., Scarborough J.S., Sun D., Korduláková J., Scherman M.S., Jones V., **Grzegorzewicz A.**, Crew R.M., Jackson M., McNeil M.R., Lee R.E. The structure-activity relationship of urea derivatives as anti-tuberculosis agents. Bioorg Med Chem. 2011, 19(18):5585–95.
13. **Grzegorzewicz A.E.**, Pham H., Gundi V.A., Scherman M.S., North E.J., Hess T., Jones V., Gruppo V., Born S.E., Korduláková J., Chavadi S.S., Morisseau C., Lenaerts A.J., Lee R.E., McNeil M.R., Jackson M. Inhibition of mycolic acid transport across the *Mycobacterium tuberculosis* plasma membrane. Nat Chem Biol. 2012, 8(4):334–41.
14. Scherman M.S., North E.J., Jones V., Hess T.N., **Grzegorzewicz A.E.**, Kasagami T., Kim I.H., Merzlikin O., Lenaerts A.J., Lee R.E., Jackson M., Morisseau C., McNeil M.R. Screening a library of 1600 adamantyl ureas for anti-*Mycobacterium tuberculosis* activity in vitro and for better physical chemical properties for bioavailability MR. Bioorg Med Chem. 2012, 20(10):3255–62.
15. **Grzegorzewicz A.E.**, Korduláková J., Jones V., Born S.E., Belardinelli J.M., Vaquié A., Gundi V.A., Madacki J., Slama N., Laval F., Vaubourgeix J., Crew R.M., Gicquel B., Daffé M., Morbidoni H.R., Brennan P.J., Quémard A., McNeil M.R., Jackson M. A common mechanism of inhibition of the *Mycobacterium tuberculosis* mycolic acid biosynthetic pathway by isoxyl and thiacetazone. J Biol Chem. 2012, 287(46):38434–41.

16. **Grzegorzewicz A.E.**, Jackson M.: Subfractionation and analysis of the cell envelope (lipo)polysaccharides of *Mycobacterium tuberculosis*. Methods Mol Biol. 2013; 966:309–24.
17. North E.J., Scherman M.S., Bruhn D.F., Scarborough J.S., Maddox M.M., Jones V., **Grzegorzewicz A**., Yang L., Hess T., Morisseau C., Jackson M., McNeil M.R., Lee R.E. Design, synthesis and anti-tuberculosis activity of 1-adamantyl-3-heteroaryl ureas with improved in vitro pharmacokinetic properties. Bioorg Med Chem. 2013, 21(9):2587–99.
18. Favrot L., **Grzegorzewicz A.E.**, Lajiness D.H., Marvin R.K., Boucau J., Isailovic D., Jackson M., Ronning D.R. Mechanism of inhibition of *Mycobacterium tuberculosis* antigen 85 by ebselen. Nat Commun. 2013, 4:2748.
19. Li W., Upadhyay A., Fontes F.L., North E.J., Wang Y., Crans D.C., **Grzegorzewicz A.E.**, Jones V., Franzblau S.G., Lee R.E., Crick D.C., Jackson M. Novel Insights into the Mechanism of Inhibition of MmpL3, a Target of Multiple Pharmacophores in *Mycobacterium tuberculosis*. Antimicrob Agents Chemother. 2014 Aug 18 (in print).

Communications

1. Paściak M., Mordarska H., **Grzegorzewicz A.** Glycolipid markers of *Propionibacterium propionicum* – the application in serodiagnosis of actinomycete-like infections. IX Meeting of Polish Society of Experimental & Clinical Immunology, Warsaw, Poland,16–18.09.1998.
2. Paściak M., **Grzegorzewicz A.**, Szponar B., Mordarska H., Gamian A. Identification of actinomycete-like clinical isolate by chemical markers using analytical methods. 4. International Symposium on the Interface between Analytical Chemistry and Microbiology. Tregastel, France, 4–7.06.2000.
3. Paściak M., Szponar B., Mordarska H., **Grzegorzewicz A.** Application of chemiotaxonmic methods in diagnosis of actinomycete like diseases. XXIV Congress of the Polish Society of Microbiologists. Bialystok, Poland, 12–15.09.2000.
4. ***Grzegorzewicz A.,*** Mordarska H., Gamian A., Paściak M. Location of major glycolipds in the cell of *Propionibacterium propionicum*. XXIV Congress of the Polish Society of Microbiologists. Bialystok, Poland, 12–15.09.2000.
5. Paściak M., **Grzegorzewicz A.**, Szponar B., Mordarska H., Gamian A. Application of GC-MS for identification of an actinomycete-like clinical isolate. Summer course on mass spectrometry in biotechnology and medicine. Dubrovnik, Croatia, 16–21.09.2001.
6. Bednarz I., **Grzegorzewicz A.**, Szponar B., Paściak M., Mordarska H., Gamian A. Polar lipids of *Oerskovia xanthineolytica* characterized by GC-MS and MALDI-TOF. Summer course on mass spectrometry in biotechnology and medicine. Dubrovnik, Croatia, 16–21.09.2001.
7. **Grzegorzewicz A.**, Szponar B., Paściak M., Gamian A. Cell envelope of *Gordonia bronchialis*. XXXVIII Meeting of Polish Biochemical Society, Wroclaw, Poland, 18–22.09.2002.
8. **Grzegorzewicz A.**, Gamian A., Paściak M., Szponar B. Location of the major glycolipids of *Rhodococcus equi* and *Saccharopolyspora hirsuta* in the bacterial cell. Xth International Congress of Bacteriology and Applied Microbiology. Paris, France, 27.07–01.08.2002.
9. **Grzegorzewicz A.**, Gamian A., Budashov I., Danielsson B. Studies on Actinobacteria characteristics by atomic force microscope image. Xth International Congress of Bacteriology and Applied Microbiology. Paris, France, 27.07–01.08.2002.
10. Paściak M., Szponar B., **Grzegorzewicz A.**, Niekrasz E., Gamian A. Actinobacterial phospholipid composition of total and purified cell wall lipids fractions analyzed by HPLC approach.

Xth International Congress of Bacteriology and Applied Microbiology. Paris, France, 27.07–01.08.2002.

11. Paściak M., **Grzegorzewicz A.**, Szponar B., Mordarska H., Gamian A. Identification of mycolic acid-containing actinomycetal clinical strain isolated from a cardiosurgery patient by the analysis of chemical markers. Xth International Congress of Bacteriology and Applied Microbiology. Paris, France, 27.07–01.08.2002.
12. Paściak M., Szponar B., **Grzegorzewicz A.**, Mordarska H., Gamian A. Application of GC-MS for the identification of a mycolic acid-containing actinomycete, isolated from a cardiosurgery patient. International Conference on Indoor Enviroment Quality in Hospitals. Prag, Czechy, 10–11.10.2002.
13. Korzeniowska-Kowal A., **Grzegorzewicz A.**, Szponar B., Kaczyński Z., Lindner B., Holst O., Gamian A. Structure and immunological activity of glycolipids from *Nocardiopsis dassonvillei*, The Carbohydrate Workshop, Borstel, Germany, 17–20.03.2004.
14. Tweedy T., **Grzegorzewicz A.**, Jackson M., Skovierova H., and McNeil M. Determining the Function of the Proteins Encoded by Rv0228 and Rv0225 as Possible Drug Targets for Tuberculosis. Celebrate Undergraduate Research and Creativity, Fort Collins, April 2008.
15. **Grzegorzewicz A.**, Kurosu M., Jones V., Ma Y., McNeil M. Towards development of a high throughput assay for rhamnosyl transferase. Keystone Symposia, Vancouver, Canada, 20–25.03. 2007.
16. **Grzegorzewicz A.E.**, Ma Y., Jones V., Crick D., Liav A., McNeil MR. Characterization of a mycobacterial rhamnosyl transferase and development of a microtiter plate based assay for its activity. Keystone Symposia, Keystone, USA, 25–30.01.2009.
17. Gil F., **Grzegorzewicz A.**, Catalão M.J., Vital J., Pimentel M., McNeil M**.** LysB: a new phage protein with lipolytic activity that hydrolyses mycobacterium lipids. Keystone Symposia, Keystone, USA, 25–30.01.2009.
18. **Grzegorzewicz A.E.**, Pham H., Gundi V., Scherman M.S., North J., Hess T., Jones V., Gruppo V., Born S., Morisseau C., Lenaerts A.J., Lee R.E., McNeil M.R., Jackson M**.** Identification of an inner membrane transporter required for the translocation of mycolic acids across the plasma membrane. Gordon conference, Italy, June 3–8, 2011.
19. **Grzegorzewicz A.E.**, Korduláková J., Jones V., Born S.E., Belardinelli J.M., Vaquié A., Gundi V.A., Madacki J., Slama N., Laval F., Vaubourgeix J., Crew R.M., Gicquel B., Daffé M., Morbidoni H.R., Brennan P.J., Quémard A., McNeil M.R., Jackson M. A Common Mechanism of Inhibition of the *Mycobacterium tuberculosis* mycolic acid biosynthetic pathway by isoxyl and thiacetazone. Gordon Conference, Italy, July 21–26, 2013.