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PROFESSIONAL TRAINING AND EMPLOYMENT HISTORY

- B. S. Biochemistry - April 1993, Brigham Young University, Provo, Utah.
- Ph. D. Biochemistry - July 23, 1998, University of Wisconsin-Madison, Madison Wisconsin, with Inorganic Chemistry Minor, Dissertation: The nickel processing system involved in the insertion of nickel into CO-dehydrogenase of Rhodospirillum rubrum. Dissertation Advisor; Paul W. Ludden.
- Postdoctoral Research - August 1998-August 2000, Princeton University, Department of Chemistry, Princeton New Jersey, Research areas: Photosynthesis, Biochemistry, Biophysical Chemistry, and Inorganic Chemistry. Postdoctoral advisor: G. Charles Dismukes.
- Assistant Professor - August 2000-May 2006, The University of New Mexico, Department of Chemistry, Albuquerque, NM. Bioinorganic chemistry.
- Assistant Professor - July 2006-2012, Brigham Young University, Department of Chemistry and Biochemistry, Provo, UT. Bioinorganic chemistry
- Associate Professor – August 2012-Present, Brigham Young University, Department of Chemistry and Biochemistry, Provo, UT. Bioinorganic chemistry

SUMMARY OF RESEARCH

Biological Research.

Biological systems require trace amounts of transition metal ions to sustain life. Transition metal ions are required at the active sites of many enzymes for catalytic activity. In fact, transition metals catalyze some of the most energetically demanding reactions in biology. Unfortunately, these highly reactive metal ions also catalyze reactions that are dangerous for biological systems, especially if the metal ion is free in solution. For this purpose biology has evolved elaborate transition metal ion handling systems to bind and sequester transition metal ions in non-reactive environments to prevent these dangerous reactions from occurring. The Watt lab focuses on how iron is properly moved throughout the body.

A healthy individual possesses iron trafficking systems to absorb iron from the diet, transport iron in the bloodstream and deliver iron to cells that require iron. The failure or inhibition of these iron trafficking systems results in free iron that is a potent catalyst to form reactive oxygen species or oxidative stress.

The Watt lab studies diseases where iron trafficking is disrupted and oxidative stress is elevated. Such conditions include Alzheimer's disease, Parkinson's disease, kidney disease, Diabetes along with other conditions.

Anemia of Chronic Inflammation Caused by Hepcidin.

Hepcidin is an iron regulatory hormone induced by inflammation that degrades the iron transport protein ferroportin. Hepcidin causes a condition known as anemia of chronic inflammation. Ferroportin is required to transport iron into the bloodstream from the intestinal cells that absorb iron from the diet. Ferroportin also exports iron from the liver, and spleen into the bloodstream where transferrin binds iron and delivers iron to the bone marrow for red blood cell synthesis. The Watt lab has identified hepcidin inhibitors that prevent hepcidin production and stabilize ferroportin. Studies in rats show that iron delivery to the bone marrow is restored using these hepcidin inhibitors

Inhibitors of Iron Binding Proteins

The Watt lab has focused on metabolites that build up in diseases with oxidative stress. We identified metabolites that disrupt iron loading into ferritin and transferrin. In Chronic kidney disease, serum phosphate levels increase because the kidneys are not properly filtering phosphate from the bloodstream. We demonstrated that elevated phosphate inhibits iron loading into ferritin and transferrin by forming insoluble iron phosphate complexes. We are now focusing on other elevated metabolites to determine if they also disrupt normal iron loading or release of iron from ferritin or transferrin.

Alzheimer's Disease

Iron dysregulation is intimately connected to Alzheimer's disease (AD) but the direct connections are not clear. A new hypothesis relating to homocysteine disrupting iron loading into ferritin might explain the elevated cytosolic iron and oxidative stress. The inability to load iron into ferritin results in elevated cytosolic iron which upregulates expression of the Amyloid Precursor Protein (APP). Homocysteine also inhibits the phosphatase that dephosphorylates tau leading to elevated hyper-phosphorylated tau and tau tangles. In collaboration with Dr. Jonathan Wisco in the BYU PDBio department, we are testing this hypothesis.

Diagnostics

For each of the situations outlined above, we are developing point of care diagnostic methods to evaluate known biomarkers. The goals of the diagnostics research are two-fold. First, we are modifying and developing new methods related to antibody detection methods to provide increased sensitivity for this type of analysis. We also focus on particular biomarkers that give diagnostic information to aid clinical practitioners identify the most beneficial and effective treatment.

Materials Research.

Artificial Photosynthesis. The iron mineral core of ferritin has been characterized as ferrihydrite, hematite and magnetite. Such minerals possess semi-conductor properties. The protein shell of ferritin allows these semi-conductors to be soluble in aqueous solutions and provides a unique nano-cage for solution phase catalysis. Ferritin is photo chemically active and can photo-oxidize organic molecules and store the high-energy electrons in the conduction band of the mineral, making a stable electron donor. Our laboratory has used ferritin to photo-reduce metal cations to

form ~10 nm nanoparticles of gold, platinum, palladium and silver. We are expanding this initial work to study electron donors, photo-catalysts inside ferritin and electron acceptors. Carboxylates, aldehydes, alcohols, amines and sulfur containing molecules act as electron donors for the ferritin photo-oxidation reaction (source of electrons as fuel). In addition, we are examining ferritin with different mineral cores as photo-catalysts to determine if they are more efficient catalysts and if they utilize different wavelengths of light. Active catalysts inside ferritin include metal oxides of Fe, Fe and phosphate, Mn and Co. Finally we have attached ferritin to electrodes and successfully used the electrode as an electron acceptor to store the harvested electrons.

PUBLICATIONS

Articles in Refereed Journals:

1. Watt, R. K., Frankel, R. B., Watt, G. D., Redox Reactions of Apo Mammalian Ferritin, (1992) Biochemistry 31, 9673-9679.
2. Heqing, H., Watt, R. K., Frankel, R. B., Watt, G. D., Role of Phosphate in Fe2+ Binding to Horse Spleen Holoferritin, (1993) Biochemistry 32, 1681-1687.
3. Watt, R. K., Ludden, P. W., The Identification, Purification and Characterization of CooJ: A Nickel-Binding Protein that is Co-Regulated with the Nickel-Containing CO-Dehydrogenase from Rhodospirillum rubrum, (1998) J. Biol. Chem. 273, 10010-10025.
4. Johnson, J. L., Cannon, M., Watt, R. K., Frankel, R. B., Watt, G. D., Forming the phosphate layer in reconstituted horse spleen ferritin and the role of phosphate in promoting core surface redox reactions, (1999) Biochemistry, 38, 6706-6713.
5. Watt, R. K., Ludden, P. W., Nickel Transport in Rhodospirillum rubrum (1999) The Journal of Bacteriology 181, 4554-4560.
6. Büchel, C., Barber, J., Ananyev, G., Eshaghi, S., Watt, R., Dismukes, C., Photoassembly of the manganese cluster and oxygen evolution from monomeric and dimeric CP47-reaction centre photosystem II complexes, (1999) Proc. Natl. Acad. Sci. 96, 14288-14293.
7. Watt, R. K., Ludden, P. W., Nickel Binding Proteins. Cellular and Molecular Life Sciences (1999) 56, 604-625.
8. Song, Y. J., Challa, S. R., Medforth, C, J., Qiu, Y., Watt, R.K., Pena, D., Miller, J.E., van Swol, F. Shelnutt, J.A., Synthesis of peptide-nanotube platinum-nanoparticle composites. Chemical Communications; (2004), no.9, p.1044-1045.
9. Polanams, J., Ray, A. D., Watt R. K., Nanophase Iron Phosphate, Iron Arsenate, Iron Vanadate and Iron Molybdate Minerals Synthesized within the Protein Cage of Ferritin, Inorganic Chemistry, (2005) 44, 3204-3209.
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11. Zhang, B., Watt, R. K., Galvez, N., Dominguez-Vera, J. M., Watt, G. D., Rate of Iron Transfer through the Horse Spleen Ferritin Shell Determined by Formation of Prussian Blue and Fe-Desferrioxamine in the Ferritin Cavity. Biophysical Chemistry (2006) 120, (2) 96-105.
12. Tyryshkin, A. M., Watt, R. K., Baranov, S. V., Dasgupta, J., Hendrich, M. P., Dismukes, G. C., Spectroscopic evidence for Ca2+ involvement in the assembly of the Mn4Ca cluster in the photosynthetic water-oxidizing complex. Biochemistry (2006) 45, (43) 12876-12889.

(Articles in Refereed Journals while at BYU.)

13. Zhang, F., Gates, R. J., Smentkowski, V. S., Natarajan, S., Gale, B. K., Watt, R. K., Asplund, M. C., Linford, M. R., Direct Adsorption and Detection of Proteins, Including Ferritin, onto Microlens Array Patterned Bioarrays, J. Am. Chem. Soc. (2007), 129, 9252-9253.
14. Shin, K. M., Watt, R. K., Watt, G. D., Choi, S. H., Kim, H. H., Kim, S. I., Kim, S. J., Characterization of ferritin core on redox reactions as a nanocomposite for electron transfer. Electrochimica Acta (2010), 55, (10) 3486-3490.
15. Watt, R.K., Hilton, R. J., Graff, D. M., Oxido-Reduction is not the Only Mechanism Allowing Ions to Traverse The Ferritin Protein Shell (Invited Review), Biochim. Biophys. Acta (2010), 1800, 745-759.
16. Johnson J. Kenealey, J., Hilton, R.J., Bronsahan, D., Watt, R.K., Watt, G.D., Non-reductive iron release from horse spleen ferritin using desferoxamine chelation, J. Inorg. Biochem. (2011), 105, 202-207.
17. Watt, R.K., The many faces of the octahedral protein ferritin (Invited Review), BioMetals, (2011) 24 (3), 489-500.
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19. Keyes, J. D., Hilton, R. J., Farrer, J., Watt, R. K., Ferritin as a Photocatalyst for Gold Nanoparticle Synthesis, Journal of Nanoparticle Research (2011) 13, 2563-2575.
20. Snow, C., Martineau, L. N., Hilton, R. J., Brown, S., Farrer, J., Boerio-Goates, J., Woodfield, B. F., Watt, R. K., Ferritin iron mineralization proceeds by different mechanisms in MOPS and imidazole buffers, J. Inorg. Biochem. (2011) 105, 972-977.
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22. López-Castro, J. D., Delgado, J. J., Perez-Omil, J. A., Gálvez, N., Cuesta, R., Watt R. K., Domínguez-Vera, J. M. A New Approach to the Ferritin Iron Core Growth: The Core Shape is a Fingerprint of the Protein Capsid Composition. Dalton Trans. (2012) **41**, 1320–1324.

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24. Hilton, R. J., Zhang, B., Watt, G. D., L. Naomi Martineau, Watt, R. K., Anion Deposition into Ferritin. J. Inorg. Biochem. (2012) 108, 8-14.
25. Hilton, R. J., Seare, M. C., Andros, N. D., Kenealley, Z., Watt, R. K., Phosphate Inhibits In Vitro Fe3+ Loading into Transferrin by Forming a Soluble Fe(III)-Phosphate Complex: A Potential Non-Transferrin Bound Iron Species. J. Inorg. Biochem. (2012) 110, 1-7.
26. Watt, R. K., A Unified Model for Ferritin Iron Loading by the Catalytic Center: Implications for Controlling "Free Iron" during Oxidative Stress. ChemBioChem (2013), 14, 415-419.
27. Watt, R. K., Petrucci, O. D., Smith, T., Ferritin as a model for developing 3rd generation nano architecture organic/inorganic hybrid photo catalysts for energy conversion, Catalysis, Science & Technology (2013) 3, 3103-3110.
28. Petrucci, O. D., Buck, D. C., Farrer, J. K., Watt, R. K., A ferritin mediated photochemical method to synthesize biocompatible catalytically active gold nanoparticles: size control synthesis for small (similar to 2 nm), medium (similar to 7 nm) or large (similar to 17 nm) nanoparticles. RSC Advances (2014) 4, (7) 3472-3481.
29. Colton, J. S., Erickson, S. D., Smith, T. J., Watt, R. K., Sensitive detection of surface- and size-dependent direct and indirect band gap transitions in ferritin. Nanotechnology (2014), 25, (13) Article number 135703.
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34. Swensen, A. C., Finnell, J. G., Matias, C, Gross, A. J., Prince, J. T., Watt, R. K., Price, J. C., Whole blood and urine bioactive Hepcidin-25 determination using liquid chromatography mass spectrometry. Analytical Biochemistry (2017), 517, 23-30.
35. Matias, C., Belnap, D. W., Smith, M. T., Stewart, M. G., Torres, I. F., Gross, A. J., Watt, R. K., Citrate and albumin facilitate transferrin iron loading in the presence of phosphate, J. Inorg. Biochem., 168 (2017) 107–113

Chapters Appearing in Edited Volumes:

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2. Dismukes, G. C., Ananyev, G. M., Watt, R. K., The Assembly of the Inorganic Core and "Inorganic Mutants" of the Water Oxidizing Complex of Photosystem II: The Water/Plastoquinone Oxido-Reductase In Photosynthesis, T Wydrzynski and K. Satoh Editors; (2005), Springer, The Netherlands. Ch 30. Pp. 683-695.

Conference Proceedings:

1. Hilton, R. J., Keyes, J. D., Watt, R. K., Photoreduction of Au(III) to form Au(0) nanoparticles using ferritin as a photocatalyst. Nanosensors, Biosensors, and Info-Tech Sensors and Systems, Proceedings of SPIE (2010), 7646, 764607.
2. Hilton, R. J., Keyes, J. D., Watt, R. K., Maximizing the photocatalytic properties of ferritin as a photocatalyst in an artificial photosynthesis system. Nanosensors, Biosensors, and Info-Tech Sensors and Systems, Proceedings of SPIE (2010), 7646, 76460J.