Curriculum Vitae-September 2015

Lizbeth Hedstrom

Professor of Biology and Chemistry
Brandeis University
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Postdoctoral Training

University of California, San Francisco	W.J. Rutter
University of California, San Francisco	C.C. Wang
Massachusetts Institute of Technology	W.H. Orme-Johnson (dec)

Education

Brandeis University	Ph.D.	Biochemistry R.H. Abeles (dec.)
University of Virginia	B.S.	Chemistry, with high distinction

Honors

AAAS Fellow, Louis Dembitz Brandeis Prize for Excellence in Teaching, Beckman Young Investigator, NSF Career Award, Searle Scholar

Research Interests

Small molecule strategies to modulate protein levels. Structure/function relationships in enzyme catalysis. Nucleotide metabolism. Antimicrobial drug discovery. Protein degradation. Proteases. Pathological mechanisms of retinitis pigmentosa.

Awards and Grants

Current

2011-16 IMPDH-targeted antibiotics for select agents (role: PI)
NIH/NIAID 5R01AI093459 total costs: $5,403,329
Brandeis direct costs: $1,812,188

1998-2016 IMP Dehydrogenase (role: PI)
NIH/NIGMS RO1GM054403 total costs current project period: $1,310,270
Brandeis direct costs: $647,094

2012-2016 Inhibitor mediated protein degradation (role: PI)
NIH/NIGMS 1R01GM100921 total costs: $1,222,936
Brandeis direct costs: $760,000

2015-2016 Optimizing IMPDH inhibitors for the treatment of Cryptosporidiosis (role: co-PI)
subaward of 1R56AI106743 (Greg Cuny, PI) total costs: $198,000
Brandeis direct costs: $122, 391

Publications (*undergraduate author)

127. Lawson, Ann P.; Long,Marcus J. C.; Coffey,Rory T.; Qian,Yu; Weerapana, Eranthie; El Oualid, Farid and Hedstrom, Lizbeth. *Naturally Occurring Isothiocyanates Inhibit Deubiquitinating Enzymes*. Submitted.

126. Makowska-Grzyska, Magdalena; Kim, Youngchang; Gorla, Suresh Kumar; Wei, Yang; Mandapati, Kavitha; Zhang, Minjia; Maltseva, Natalia; Modi, Gyan; Boshoff, Helena I.; Gu, Minyi; Aldrich, Courtney; Cuny, Gregory D.; Hedstrom, Lizbeth and Joachimiak, Andrzej. *Mycobacterium tuberculosis* IMPDH in complexes with substrates, products and antitubercular compounds. PLoS ONE in press.

125. Hedstrom, Lizbeth. *Cryptosporidium: a first step toward tractability.* Trends in Parasitology, in press.

124. Kim, Youngchang; Makowska-Grzyska, Magdalena; Gorla, Suresh Kumar; Gollapalli, Deviprasad R.; Cuny, Gregory D.; Joachimiak, Andrzej and Hedstrom, Lizbeth. *Structure of Cryptosporidium IMP dehydrogenase bound to an inhibitor with in vivo antiparasitic activity.* Acta Cryst. Sec. F, in press (2015).

123. Makowska-Grzyska , Magdalena; Kim, Youngchang; Maltseva, Natalia; Osipiuk, Jerzy; Gu, Minyi; Zhang, Minjia; Mandapati, Kavitha; Gollapalli, Deviprasad R.; Gorla, Suresh Kumar; Hedstrom, Lizbeth and Joachimiak, Andrzej. *A novel cofactor binding mode in bacterial IMP dehydrogenases explains inhibitor selectivity.* J. Biol. Chem. 290, 5893-911 (2015). PMC4342496

122. Sun, Zhuming; Khan, Jihan; Makowska-Grzyska, Magdalena; Zhang, Minjia; Cho, Joon Hyun; Suebsuwong, Chalada; Vo, Pascal; Gollapalli, Deviprasad R.; Kim, Youngchang; Joachimiak, Andrzej; Hedstrom, Lizbeth and Gregory D. Cuny. *Synthesis, in vitro evaluation and co-crystal structure of 4-oxo-[1]benzopyrano[4,3-c]pyrazole Cryptosporidium parvum inosine 5'-monophosphate dehydrogenase (CpIMPDH) inhibitors*. J. Med. Chem., in press (2015).

121. Kuang, Yi; Long, Marcus J. C.; Zhou, Ji; Shi, Junfen; Gao, Yuan; Xu, Chen; Hedstrom, Lizbeth and Xu, Bing. *Prion-like Nanofibrils of Small Molecules (PriSM) Selectively Inhibit Cancer Cells by Frustrating Cytoskeleton Dynamics*. J. Biol. Chem., in press (2014).

120. Mandapati, Kavitha; Gorla, Suresh Kumar; House, Amanda L.; McKenney, Elizabeth S.; Zhang, Minjia; Rao, Suraj Nagendra*; Gollapalli, Deviprasad R.; Mann, Barbara J.; Goldberg, Joanna B.; Cuny, Gregory D.; Glomski, Ian J. and Hedstrom, Lizbeth. *Repurposing Cryptosporidium Inosine 5'-monophosphate Dehydrogenase Inhibitors as Potential Antibacterial Agents*. ACS Med. Chem. Lett, 5, 846-850 (2014). PMC4137380 ACS Editors Choice

119. Checkley, William ; White Jr., A. Clinton; Jaganath, Devan; Arrowood, Michael J; Chalmers, Rachel M; Chen, Xian-Ming; Fayer, Ronald; Griffiths, Jeffrey; Guerrant, Richard L; Hedstrom, Lizbeth;

Huston, Christopher; Kotloff, Karen L; Kang, Gagandeep; Mead, Jan R; Miller, Mark; Petri Jr., William; Priest, Jeffrey W; Roos, David S; Striepen , Boris; Thompson, RC Andrew; Ward, Honorine D; Van Voorhis, Wesley; Xiao, Lihua; Zhu, Guan; Houpt, Eric R. *A Review of the Global Burden, Novel Diagnostics, Therapeutics and Vaccine Targets for Cryptosporidiosis*. The Lancet Infectious Diseases, 15, 85-89 (2015). PMC4342496

118. Wang, Junling; Han, Xuemei; Wong, Catherine C.L.; Cheng, Hong; Aslanian, Aaron; Xu, Tao; Leavis, Paul; Roder, Heinrich; Hedstrom, Lizbeth; Yates, III, John R. and Kashina, Anna. *Arginylation of intact proteins in vivo involves a novel type of Arg linkage to amino acid side chains*. Chem. Biol, 21, 331-7 (2014). PMC4010198

117. Gorla, Suresh Kumar; McNair, Nina N.; Yang, Guangyi; Gao, Song; Hu, Ming; Jala, Venkatakrishna R.; Haribabu, Bodduluri**;** Striepen, Boris; Cuny, Gregory D.; Mead, Jan R. and Hedstrom, Lizbeth. *Validation of IMP dehydrogenase inhibitors in a mouse model of cryptosporidiosis*. Antimicrob. Agents Chemother. 58, 1603-14 (2014). PMC3957894

116. Gorla, Suresh Kumar; Kavitha, Mandapati; Zhang, Minjia; *Chin, James En Wai; Liu, Xiaoping; Striepen, Boris; Makowska-Grzyska, Magdalena; Kim, Youngchang; Joachimiak, Andrzej; Hedstrom, Lizbeth and Cuny, Gregory D. *Optimization of benzoxazole-based inhibitors of Cryptosporidium parvum inosine 5'-monophosphate dehydrogenase*. J. Med. Chem., 56, 4028-43 (2013). PMC3756936

115. Johnson, Corey R.; Gorla, Suresh Kumar; Kavitha, Mandapati; Zhang, Minjia; Liu, Xiaoping; Striepen, Boris; Mead, Jan R.; Cuny, Gregory D. and Hedstrom, Lizbeth. *Phthalazinone Inhibitors of Inosine-5'-Monophosphate Dehydrogenase from Cryptosporidium parvum*. Bioorg. Med. Chem. Lett. 23, 1004-7 (2013). PMC3557747 PDF

114. Pan, Yue; Long, Marcus J. C.; Lin, Hsin-Chieh; Hedstrom, Lizbeth and Xu, Bing. *Magnetic Nanoparticles for Direct Protein Sorting inside Live Cells*. Chemical Science 3, 3495-9 (2012).

113. Gao, Yua, Long, Marcus J.C; Shi, Junfeng; Hedstrom, Lizbeth and Xu, Bing. *Using supramolecular hydrogel to discover the interactions between proteins and molecular nanofibers of small molecules.* Chem. Commun. (Camb) 48, 8404-6 (2012).

112. Gorla, Suresh Kumar; Kavitha, Mandapati; Zhang, Minjia; Liu, Xiaoping; Sharling, Lisa; Gollapalli, Deviprasad R; Striepen, Boris; Hedstrom, Lizbeth and Cuny, Gregory D. *Selective and potent urea inhibitors of Cryptosporidium parvum inosine 5'-monophosphate dehydrogenase.* J. Med. Chem. 55, 7759-71 (2012). PMC3635066

111. Makowska-Grzyska, M.; Kim, Y.; W., R.; Wilton, R.; Gollapalli, D.R.; *Wang, X.K.; Zhang, R.; Jedrzejczak, R.; Mack, J.C.; Maltseva, N.; Mulligan, R.; Binkowski, T.A; Gornicki, P.; Kuhn, M.; Anderson, W.F.; Hedstrom, L and Joachimiak, A. *Bacillus anthracis IMP Dehydrogenase in Action: Structures of Apoenzyme and in Complex with Substrate and Product.* Biochemistry 51, 6148-63 (2012). PMC3836674

110. Long, Marcus J. C. and Hedstrom, Lizbeth. *Mushroom Tyrosinase Oxidizes Tyrosine-rich Sequences, Allowing Selective Protein Functionalization*. ChemBiochem 13, 1818-25 (2012). PMC3516906

109. Long, Marcus J. C., Gollapalli, Deviprasad R. and Hedstrom, Lizbeth. *Inhibitor Mediated Protein Degradation.* Chemistry & Biology 19, 629-37 (2012). PMC3361691 *Nature News & Views*

108. Hedstrom, Lizbeth. *IMP dehydrogenase: the dynamics of reaction specificity*. Proceedings of the "5th International ESCEC Symposium on Experimental Standard Conditions of Enzyme Characterizations" (2012).

107. Hedstrom, Lizbeth. *The dynamic determinants of reaction specificity in the IMPDH/GMPR family of $(\beta/\alpha)_8$ barrel enzymes.* Critical Reviews In Biochemistry & Molecular Biology 47, 250-63 (2012). PMC3337344

106. Gorla, Suresh Kumar; Johnson, Corey; Khan, Jihan; Sun, Xin; Sharling, Lisa; Striepen, Boris and Hedstrom, Lizbeth. *Targeting prokaryotic enzymes in the eukaryotic pathogen* Cryptosporidium. chapter in Apicomplexan Parasites: Molecular Approaches toward Targeted Drug Development. Edited by Katja Becker. Wiley-Blackwell (2011). Second volume in book series *Drug Discovery in Infectious Diseases*, edited by Paul M. Selzer. Chapter 14, p 271-286.

105. Kirubakaran S, Gorla SK, Sharling L, Zhang M, Liu X, Ray SS, Macpherson IS, Striepen B, Hedstrom L, Cuny GD. *Structure-activity relationship study of selective benzimidazole-based inhibitors of Cryptosporidium parvum IMPDH.* Bioorg Med Chem Lett. 22, 1985-8 (2012). PMC3289519

104. Sun, Xin E.; Hansen, Bjarne G. and Hedstrom, Lizbeth. *Kinetically Controlled Drug Resistance: How* Penicillium brevicompactum *Survives Mycophenolic Acid.* J. Biol. Chem. 286, 40595-600 (2011). PMC3220510

103. Hansen, Bjarne G., Sun, Xin E., Genee, Hans J.; Kaas, Christian S.; Nielsen, Jakob B.; Mortensen, Uffe H.; Frisvad, Jens C. and Hedstrom, Lizbeth. *Adaptive evolution of drug targets in producer and non-producer organisms*. Biochemical Journal 441, 219-26 (2011).

102. McGrew, Dharia A. and Hedstrom, Lizbeth. *Towards a pathological mechanism for IMPDH1-linked retinitis pigmentosa*. Retinal Degenerative Diseases. M.M. LaVail et al., editors. Advances in Experimental Medicine and Biology 723, 539-45 (2011).

101. MacPherson, Iain S.; Temme, J. Sebastian; Habeshian, Sevan*; Felczak, Krzysztof; Pankiewicz, Krzysztof; Hedstrom, Lizbeth and Krauss, Isaac J. Multivalent glycocluster design through directed evolution. Angew. Chem. Int. Ed. 50, 11238-42 (2011). *Hot Paper.* PMC3900255

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99. Patton, Gregory C.; Stenmark, Pål; Gollapalli, Deviprasad R.; Sevastik, Robin; Kursula, Petri; Flodin, Susanne; Schuler, Herwig; Swales, Colin T.*; Eklund, Hans; Himo, Fahmi; Nordlund, Pär and Hedstrom, Lizbeth. *Cofactor mobility determines reaction outcome in the IMPDH/GMPR (ß/α)$_8$ barrel enzymes.* Nat. Chem. Biol. 7, 950-8 (2011).

98. Long, Marcus J. C.; Pan, Yue; Lin, Hsin-Chieh; Hedstrom, Lizbeth and Xu, Bing. C*ell Compatible Trimethoprim (TMP)-Decorated Iron Oxide Nanoparticles Bind Dihydrofolate Reductase (DHFR) for Magnetically Modulating Focal Adhesion of Mammalian Cells*. J. Am. Chem. Soc. 133, 10006-9 (2011). *Faculty of 1000*.

97. Pan, Yue; Long, Marcus J. C.; Li, Xinming; Shi, Junfeng; Hedstrom, Lizbeth & Bing Xu. *Glutathione (GSH)-decorated magnetic nanoparticles for binding glutathione-S-transferase (GST) fusion protein and manipulating live cells.* Chemical Science 2, 945-948 (2011).

96. Hedstrom, Lizbeth; Liechti, George; Goldberg, Joanna B. and Gollapalli, Deviprasad R. *The antibiotic potential of prokaryotic IMP dehydrogenase inhibitors.* Current Medicinal Chemistry 18, 1909-18 (2011).

95. Hoefler, B. Christopher; Gollapalli, Deviprasad R. and Hedstrom, Lizbeth. *Specific Biotinylation of IMP Dehydrogenase.* Bioorg. Med. Chem. Lett. 21, 1363-1365 (2010). PMC3044611

94. Josephine, Helen R.; *Ravichandran, Kanchana R. and Hedstrom, Lizbeth. *The Cys319 loop modulates the transition between dehydrogenase and hydrolase conformations in IMP dehydrogenase*. *Biochemistry 49, 10674-81 (2010).* PMC3005847

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92. Gollapalli, Deviprasad R.; MacPherson, Iain S.; Liechti, George; Goldberg, Joanna B. and Hedstrom, Lizbeth. *Structural Determinants of Inhibitor Selectivity in Prokaryotic IMP Dehydrogenases,* Chemistry and Biology 17, 1084-1091 (2010). featured in SciBX 3(44); doi:10.1038/scibx.2010.1327. PMC2991053

91. Sharling, Lisa: Liu, Xiaoping; Gollapalli, Deviprasad R.; Maurya, Sushil; Hedstrom, Lizbeth and Striepen, Boris. *A screening pipeline for antiparasitic agents targeting Cryptosporidium inosine monophosphate dehydrogenase.* PLoS Neglected Tropical Diseases, 4, e794 (2010). PMC2919388

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89. Sun, Xin E.; Sharling, Lisa; Muthalagi, Mani; Mudeppa, Devaraja G.; Pankiewicz, Krzysztof W.; Felczak, Krzysztof; Rathod, Pradipsinh K.; Mead, Jan; Striepen, Boris and Hedstrom, Lizbeth. *Prodrug activation by Cryptosporidium thymidine kinase.* J. Biol. Chem. 285, 15,916-15,922 (2010). PMC2871459

88. MacPherson, Iain S.; Kirubakaran, Sivapriya; Gorla, Suresh Kumar; Riera, Thomas V.; D'Aquino, J. Alejandro; Zhang, Minjia ; Cuny, Gregory D. and Hedstrom, Lizbeth. *The Structural Basis of Cryptosporidium-Specific IMP Dehydrogenase Inhibitor Selectivity.* J. Am. Chem. Soc., 132, 1230-1231 (2010). PMC2819028

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84. Hedstrom, L. *IMP dehydrogenase: structure, mechanism and inhibition*. Chemical Reviews 109, 2903-2928 (2009). PMCID: PMC2737513.

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72. Liu, Lu; Mushero, Nicole; Hedstrom, Lizbeth & Gershenson, Anne. *Conformational distributions of protease-serpin complexes: a partially translocated complex*. Biochemistry 45, 10865-72 (2006).

71. Rejman, Dominic; Olesiak, Magda; Chen, Liqiang; Patterson, Steven E.; Wilson, Daniel; Jayaram, Hiramagalur N.; Hedstrom, Lizbeth & Pankiewicz, Krzysztof W. *Novel Methylenoxybis(phosphonate) Analogues of Mycophenolic Adenine Dinucleotide (MAD) Inhibition of IMP Dehydrogenase.* J. Med. Chem. 49, 5018-5022 (2006).

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61. #Guillén Schlippe, Yollete V.; #Riera, Thomas V.; *Seyedsayamdost, Mohammad R. & Hedstrom, Lizbeth. *Substitution of the Conserved Arg-Tyr Dyad Selectively Disrupts the Hydrolysis Phase of the IMP Dehydrogenase Reaction*. Biochemistry 43, 4511-4521 (2004). (# co-first authors).

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Patents

Brandeis Case No. 2006-0303
Title: Compounds and Methods for Treating Mammalian Gastrointestinal Parasitic Infections
Inventors: Hedstrom, L. and Striepen, B.
Applications filed: US Provisional Application No.60/810,276 (Expired - Converted to PCT)
Filing Date: 6/2/2006
PCT/US07/070233
Filing Date: 6/1/2007
USA Utility Patent Application No. 12/302,600
Filing Date: 11/26/2008

Brandeis Case No. 1022
Title: Compounds and Methods for Treating Mammalian Gastrointestinal Microbial Infections
Inventors: Hedstrom, L., Maurya, S., Gollapalli, D., Cuny, G., Striepen, B., Kirubkaran, S., Johnson, C.R., Khan, J., Kavitha, M., Gorla, S.K.
USA Provisional Application No. 61/162,013 (Expired - Converted to PCT) Filing Date: 03/20/2009
PCT/US10/28178 Filing Date: 3/22/2010

Brandeis Case No. 1052
Title: Nucleotide-based Carbohydrate Vaccines
Inventors: Lizbeth Hedstrom, Isaac Krauss, Iain MacPherson and Sevan Habeshian
USA Provisional 61/353,857 filed 6/11/10
International PCT/US11/39949 filed 6/10/11

Brandeis Case No. 1053
Title: Small-Molecule-Targeted Protein Degradation
Inventors: Lizbeth Hedstrom, Marcus Long and Deviprasad Gollapalli
USA Provisional 61/360,257 filed 6/30/10
International PCT/US11/42535 filed 6/30/11

Brandeis Case No. 1115
Title: Compounds and Methods for Treating Mammalian Gastrointestinal Microbial Infections
Inventors: Hedstrom, L., Cuny, G., Kavitha, M. and Gorla, S.K.

USA Provisional 61/684,263 filed 8/17/12

Brandeis Case No. 1126
Title: Carbonate, Carbamate, and Thiocarbamate Inhibitors of Deubiquitinating Proteases
Inventors: Hedstrom, L.K., Long, M.J.C. and Baggio, R.F.
USA Provisional US 61/813,328 filed 4/18/13