Scientific Contributions Summary 20180713

1. Improved formulation and drug delivery of peptides: This research area is aimed at improving the delivery of peptides molecules by understanding the physicochemical properties of the drug and subsequent drug stability modification through formulation. In particular, the role of variables such as viscosity, cosolvents, surfactants, lipids and polymers in liquid formulations, on both stability and release from the injection site, are examined and modulated. In solid lyophilized peptide formulations, the impact of water on the plasticization of the amorphous glassy systems, and enhanced drug mobility within those systems, is determined and contrasted to increased chemical reactivity of water. Prolonged delivery of polypeptides (eg. growth releasing factor), as described in the patent, are evidence of taking this knowledge to the implementation stage for an injectable product.

a. Li R, Hageman MJ, Topp EM. Effect of Viscosity on the Deamidation Rate of a Model ASN-Hexapeptide. *J Peptide Res.* 59, 211-220 (2002).
b. Foster TP, Moseley WM, Caputo JF, Hageman MJ. Aqueous Prolonged Release Parenteral Formulation. (for a polypeptide) Granted as U.S. Patent 6,429,195 on August 6, 2002.
c. Lai MC, Hageman MJ, Schowen RL, Borchardt RT, Laird BB, Topp EM. Chemical Stability of Peptides in Polymers. II. Discriminating Between Solvent and Plasticizing Effects of Water on Peptide Deamidation in Poly(vinyl pyrrolidone). *J Pharm Sci*. 88, 1081-1089 (1999).
d. Lai MC, Hageman MJ, Schowen RL, Borchardt RT, Topp EM. Chemical Stability of Peptides in Polymers. I. Effect of Water on Peptide Deamidation in Poly(vinyl alcohol) and Poly(vinyl pyrrolidone) Matrices. *J Pharm Sci*. 88, 1073-1080 (1999).

2. Drug delivery and stability of proteins with emphasis on moisture in lyophilized proteins: This research area is focused on understanding and improving formulation and processing variables for the stability of proteins as is relevant to drug delivery and long term storage. The role of moisture, either as a plasticizer of the formulation or as a chemical reactant itself, is explored extensively and applied to formulate and stabilize lyophilized proteins. The characterization of instability and subsequent strategies for the mitigation thereof, require careful characterization of both chemical and physical decomposition pathways for the proteins, with particular attention to aggregation and interactions of the protein with the components of formulation or overall delivery system. Through such as understanding, aqueous prolonged release formulations of proteins, as demonstrated in the patent, can be developed.

a. Hageman MJ, Possert ML. Aqueous Prolonged Release Formulation", (for a protein) Granted U.S. Patent 6,699,490 on March 2, 2004.
b. Miller BL, Hageman MJ, Thamann TJ, Barròn LB, Schöneich C. Solid State Photodegradation of Bovine Somatotropin (Bovine Growth Hormone): Evidence for Tryptophan-mediated Photo-oxidation of Disulfide Bonds. *J Pharm Sci*. 92(8), 1698-1709 (2003).
c. Sarciaux JM, Hageman MJ. Effects of Bovine Somatotropin (rbSt) Concentration at Different Moisture Levels on the Physical Stability of Sucrose in Freeze-Dried rbSt/Sucrose Mixtures. *J Pharm Sci.* 86, 365-371 (1997).
d. Bell LN, Hageman MJ, Bauer JM. Impact of Moisture on Thermally Induced Denaturation and Decomposition of Lyophilized Bovine Somatotropin. *Biopolymers*. 35, 201-209 (1995).

3. Facilitate oral drug absorption via enhanced dissolution of solid dispersions and generation of supersatured solutions: The bioperformance of amorphous solid dispersions are highly dictated by the physicochemical properties of the drug, the properties of the polymers used, and the media to which they are being delivered. The dissolution of the solid dispersion is also impacted by the

effective surface area provided through the dosage form and the rate at which the polymer excipients themselves can dissolve. Similarly, the rate of subsequent drug precipitation, and hence supersaturation, is also impacted by the excipients, the drug, constituents of the dissolution media and the complex nature in which they interact with one another. This research aims to dissect and understand these phenomena at a fundamental level so that drug delivery can be optimized and developable or patented formulations can be generated.

a. Chen Y, Wang S, Wang S, Liu C, Su C, Hageman M, Hussain M, Haskell R, Stefanski K, Qian F. Sodium Lauryl Sulphate Competitively Interacts with HPMC-AS and Consequently Reduces Oral Bioavailability of Posaconazole / HPMC-AS Amorphous Solid Dispersion. *Mol Pharm.* 13(8):2787-95 (2016).
b. Chen Y, Wang S, Wang S, Liu C, Su C, Hageman M, Hussain M, Haskell R, Stefanski K, Qian F. Initial drug release from amorphous solid dispersions controlled by polymer release and drug-polymer interaction. *Pharm Res*. 33(10):2445-58 (2016).
c. Vickery RD, Stefanski KJ, Su CC, Hageman MJ, Vig BS, Betigeri S, Bioavailable Compositions of Amorphous Piperidinyl Compounds, Granted as Patent US 9,095,585 on August 4, 2015.
d. Chen XQ, Stefanski K, Shen H, Huang C, Caporuscio C, Yang W, Lam P, Su C, Gudmundsson O, Hageman M. Oral Delivery of Highly Lipophilic Poorly Water-Soluble Drugs: Spray-Dried Dispersions to Improve Oral Absorption and Enable High Dose Toxicology Studies of a P2Y1 Antagonist. *J Pharm Sci*. 103: 3924–3931 (2014).

4. Enabled oral delivery of poorly water soluble drugs through solubilized dosage forms: This research area focuses on the utility of solubilized formulation strategies (pH modulation, cosolvents, cyclodextrins, sub-micron emulsions, self-emulsifying drug delivery systems(SEDDS), lipids/phospholipids, liposomes), modification of the solid form of the drug (nanoparticles, amorphous drug solids, amorphous solid dispersions with polymers, salt selection, cocrystals, coprecipitates) or direct molecular modification through prodrugs and softdrugs. The specialized nature of these delivery systems often requires extended efforts to mitigate instability of the drug. These approaches are applied to both small molecule NCEs and peptide drugs for oral delivery.

a. Rautio J, Meanwell NA, Di L, Hageman MJ. The expanding role of prodrugs in contemporary drug design and development. Nat Rev Drug Discov. 2018 Apr 27. doi: 10.1038/nrd.2018.46. [Epub ahead of print]
b. Morgen M, Gudmundsson O, Haskell R, Kumar A, Rao A, Su C, Goodwin A, Holenarsipur V, Cape J, Hageman M, Saxena A, Chowan GS, Chen X, Miller W, Nkansah R. Lipophilic Salts of Poorly Soluble Compounds to Enable High-Dose Lipidic SEDDS Formulations in Drug Discovery. Eur. J. Pharm. Biopharm. 117 (2017) 212-223.
c. Chen XQ, Gudmundsson O, Hageman M. Application of Lipid-Based Formulations in Drug Discovery.
J Med Chem. 55(18):7945-56 (2012).
d. Gao P, Rush BD, Pfund WP, Huang T, Bauer JM, Morozowich W, Kuo M, Hageman MJ. Development of a supersaturatable formulation of paclitaxel with improved oral bioavailability. *J Pharm Sci.* 92(12), 2386-2398 (2003).

5. Enabling the suceessful transition of drugs from discovery into development: Significant efforts have been employed to incorporate “developability” into the molecules that we design and select for clinical development. The end result is a mitigation of development risks and reduction in attrition of molecules during later phase development. We have actively developed stage-appropriate tools which can be used in discovery with minimal drug, limited time and on a higher

throughput basis. These tools are designed as surrogate measures to assess later phase development risk. The pharmaceutical properties resulting from molecular design include the deliverability of the molecule and a potential marriage of molecular properties to a given formulation strategy.

a. Chen XQ, Ziemba T, Huang C, Chang M, Xu C, Qiao JX, Wang TC, Finlay HJ, Salvati ME, Adam LP, Gudmundsson O, Hageman MJ. Oral Delivery of Highly Lipophilic, Poorly Water-Soluble Drugs: Self-Emulsifying Drug Delivery Systems to Improve Oral Absorption and Enable High-Dose Toxicology Studies of a Cholesteryl Ester Transfer Protein Inhibitor in Preclinical Species. *J Pharm Sci*.107(5):1352-1360 (2018).
b. Foster KA, Fancher RM, Proszynski M, Dixon G, Ford K, Cornelius G, Gudmundsson O, Hageman MJ. Utility of Gastric Retained Alginate Gels to Modulate PK Profiles in Rats. *J Pharm Sci*. 102(8):2440-9 (2013).
c. Amidon GE, He X, Hageman MJ. Physicochemical characterization and oral dosage form selection based on the biopharmaceutics classification system. In: Vol. 3, *Burger's Medicinal Chemistry, Drug Discovery and Development*, Seventh Edition. Abraham DJ, Rotella DP, eds.; John Wiley & Sons, Inc., October 2010.

Hageman MJ. Preformulation Designed to Enable Discovery and Assess Developability. *Combin Chem High Throughput Screening.* 13(2):90-100 (2010).