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DISSERTATION TITLE: *Engineering of the albumin-FcRn interaction*

In this thesis, Bern demonstrates that albumin, the most abundant protein in the blood, is actively transported across mucosal layers. Efficient transport is dependent on the binding to a specific mucosal expressed receptor, the neonatal Fc receptor (FcRn). This mechanism may serve as a gateway for mucosal delivery of albumin conjugated to a therapeutic molecule or a drug without the usage of needles. Needle-free drug delivery or vaccination is a major goal to minimize risk of secondary infections. FcRn also is known to also bind IgG antibodies, and receptor binding ensures high abundance and long half-life of both IgG and albumin in the blood. The unique half-life of albumin is currently exploited to extend duration, as well as reducing dosing regimen of several short-lived drugs such as diabetes medications or coagulation factors used by patients suffering from hemophilia. A hallmark of the interaction between FcRn and its ligands is that it is strictly pH-dependent with binding at acidic pH, and no binding at neutral pH. FcRn resides predominantly in acidified endosomes inside cells, which allow binding to its ligands that enter through pinocytosis. FcRn binding rescues albumin and IgG from intracellular degradation by transport to the cell surface in a process called recycling or transcytosis, and the neutral pH at the surface will trigger release.
Bern has also investigated the interaction interface between albumin and FcRn in great detail to understand which amino acids on albumin that are essential for optimal binding, as well as which have a more modulatory role. Such knowledge is crucial when designing novel engineered albumin molecules with altered binding properties to FcRn. Several albumin variants were generated, and improved binding at acidic pH resulted in enhanced transport across mucosal epithelial cells. Such novel albumin molecules may be utilized therapeutically to increase efficacy of drugs or vaccines. Mice are the most common used pre-clinical animal model, and knowledge about cross-species differences in the albumin-FcRn interaction is crucial when evaluating albumin-based therapeutics in mice. Important differences were discovered in binding properties between the human and mouse albumin-FcRn binding pairs that must be considered in future development and *in vivo* evaluation of albumin based drugs.