Bound water molecules are very powerful.

They can protect biological drugs and also keep the surfaces of biomaterial implants and devices free of adsorbed proteins and cells.

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In this talk I will describe the early history of PEGylation, and introduce the scientist, Frank Davis (Rutgers Univ), who originally conceived of PEGylation to protect a circulating protein drug. The mechanism of this protective effect involves retention of (bound) water molecules by the PEG chain, which provides PEG the ability to repel circulating enzymes that might otherwise destroy the protein drug. The first papers on this novel concept were published in 1977 by Davis and his student, Abraham Aubuchowski.

The related, early history of non-fouling polymer surfaces (NFSs), will introduce the work of the pioneers in the late 1970s and 1980s working with PEGylation of biomaterial surfaces: Ed Merrill and his students at MIT, Shoji Nagaoka, and colleagues at the Toray Co. in Japan, and Milton Harris at Univ Alabama-Huntsville collaborating with Allan Hoffman and his student Wayne Gombotz at Univ Wash, Seattle. The various chemical and physical methods for PEGylating surfaces and biomolecules will be reviewed. The mechanism of non-fouling surfaces is similar to that of PEGylated biomolecules; it is based on the retention of bound water molecules by the surface.

The unique properties of PEG will be reviewed, including the interactions of its ether group with 2-3 water molecules to form a hydrate that has a melting point. We will show why thermodynamics and entropy tell us that retention of (bound) water molecules by the surface-attached PEG molecules is the major mechanism of non-fouling PEGylated surfaces.

I will follow with a brief mention of the evidence supporting the use of higher PEG molecular weights, bimodal MW distributions, and optimum PEG surface densities to achieve non-fouling behavior. I will relate it to the apparently contradictory work of Whitesides and coworkers with non-fouling self-assembled monolayers (SAMs) containing short chain oligo(ethylene oxides)$_6$. I will follow this with a proposal that links all of these results together into one generalized hypothesis.

I will conclude the talk by briefly commentlng on zwitterion surfaces that show promise as future non-fouling surfaces and long-circulating conjugates for biomolecular drugs.