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Research Interests: NMR spectroscopy, molecular structure and dynamics, protein-carbohydrate complexes, pulse sequence development



High-resolution NMR spectroscopy is a powerful and rapidly developing technique which is widely used in many branches of chemistry, biology and medicine. Using NMR spectroscopy we can obtain information about the structure and dynamics of small organic molecules, oligo- and polysaccharides, proteins, DNAs and biomolecular complexes. Our research deals with the application of NMR to interesting biological problems as well as with the development of new techniques for biomolecular NMR spectroscopy.

Our applied research is focusing on studies of protein-carbohydrate interactions. The carbohydrates we are interested in are glycosaminoglycans (GAGs) – a large family of anionic polymers. The GAG-protein interactions have many biological functions. We are studying GAG complexes of two proteins, hepatocyte growth factor/scatter factor (HGF/SF) and factor H. Besides NMR we use ITC, Biacore and are working towards using FRET and EPR.

HGF/SF is a plasminogen-related multifunctional growth factor that primarily controls migration, proliferation and morphogenesis of epithelial/endothelial cells. There is now extensive evidence of HGF/SF involvement in the growth, invasiveness and metastasis of both carcinomas and sarcomas. HGF/SF forms a ternary complex with its Met2 receptor and GAGs and all three components are required for signalling. Disruption of the activation of Met2 by HGF/SF through the action of GAG-mimetics is thus a good potential target for anti-cancer therapy. As the first step, we are characterizing HGF/SF-GAG complexes.

Factor H is a crucial regulator of the alternative pathway of complement. It is through binding to negatively charged carbohydrates that fH discriminates between self and non-self cell-surfaces, and thus protects host-tissue from damage. A failure to bind leads to an autoimmune attack and severe diseases such as hemolytic uremic syndrome (HUS) and age-related macular degeneration (AMD). By studying factor H-GAG complexes we are investigating the mechanisms of these diseases at a molecular level.

In the area of NMR methodology we are developing new approaches for studies of protein-GAG complexes involving paramagnetic tagging. We are also developing NMR experiments for the conformational analysis of carbohydrates in particular measurement of residual dipolar coupling constants and long-range ^{13}C - ^{13}C coupling constants. Our NMR facility is superbly equipped; we have two cryoprobes at 600 and 800 MHz instruments.

SELECTED RECENT PUBLICATIONS

1. Herbert, A.P., Uhrin, D, Lyon, L. Pangburn, M.K. Barlow, P.N. Disease-associated Sequence Variations Congregate in a Polyanion Recognition Patch on Human Factor H Revealed in Three-dimensional Structure. *J. Biol. Chem.*, **281**, 16512 - 16520 (2006).
2. Jin, L., Barran, P.E., Deakin, J, A., Lyon, M., Uhrin, D Conformation of Glycosaminoglycans by Ion Mobility Mass Spectrometry and Molecular Modelling, *Chem Phys.Pys.Chem.*, 2005, **7(19)**, 3464-3471
3. Pham, T.N, Kövér, KE, Jin, L and Uhrin, D. ^1H -Detected Double-J-Modulated INEPT-INADEQUATE for simultaneous determination of one-bond and long-range carbon-carbon connectivities and the measurement of all carbon- carbon coupling constants *J. Magn. Reson.*, **176**, 199-206 (2005).
4. Pham, T.N., Hinchley, S.L., Rankin, D.W.H., Liptaj, T. and Uhrin, D, *J. Am. Chem. Soc.* **126**, 13100-13110 (2004): "Determination of sugar structures in solution from residual dipolar coupling constants: methodology and application to methyl $^{2\text{L}}$ -D-xylopyranoside".
5. Brisson J.-R, Sue S.C, Wu W.G., McManus G., Nghia T.N., Uhrin, D in *NMR of Glyco-Conjugates* Jimenez-Barmbero and Peters (Eds.), Wiley-VCH, Weinheim (2002): "NMR of Carbohydrates: 1D Homonuclear Selective Methods".