NEW ANION RECEPTORS AND TRANSPORTERS

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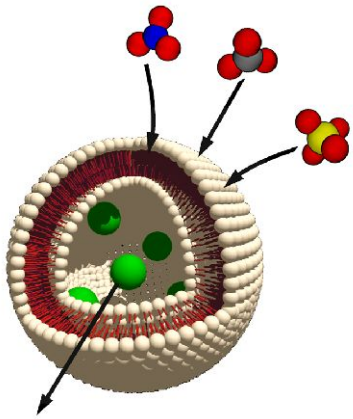
Diseases or “channelopathies”, such as cystic fibrosis, are caused by mis-regulation of anion transport across epithelial cell membranes. A number of research groups including our own are developing synthetic compounds to mediate anion and hence replace the functionality of the faulty anion channels. Additionally disruption of chemical potentials within cells can lead to apoptosis hence such compounds may have anti-cancer activity.

By studying structurally simple systems and varying their properties to change the degree of preorganisation, affinity for anions or lipophilicity we have begun to rationalize why particular anion transport mechanisms (co-transport or antiport processes) occur in particular cases.

We have used quantitative structure-activity relationship (QSAR) analysis to show that the anion binding abilities of the mono-thioureas are dominated by the (hydrogen bond) acidity of the thiourea NH function. Furthermore, mathematical models show that the experimental transmembrane anion transport ability is mainly dependent on the lipophilicity of the transporter (partitioning into the membrane), but smaller contributions of molecular size (diffusion) and hydrogen bond acidity (anion binding) are also present.



Most recently, we have shown that small molecules are capable of transporting sulfate across lipid bilayers. We have developed a new technique based on ^{33}S NMR that can be used to monitor sulfate transport, using ^{33}S-labelled sulfate and paramagnetic agents such as Mn^{2+} and Fe^{3+} to discriminate between intra- and extravesicular sulfate. Reasonable sulfate transport abilities were found for the reported for tren-based tris-ureas and tris-thioureas, providing a starting point for the development of more powerful synthetic sulfate transporters that can be used in the treatment of certain channelopathies or as a model for biological sulfate transporters.

Recent publications:

N. Busschaert, L.E. Karagiannidis, M. Wenzel, C.J.E. Haynes, N.J. Wells, P.G. Young, D. Makuc, J. Plavec, K.A. Jolliffe and P.A. Gale, *Chem. Sci.* 2014, DOI:10.1039/C3SC52006D; N. Busschaert, S.J. Bradberry, M. Wenzel, C.J.E. Haynes, J.R. Hiscock, I.L. Kirby, L.E. Karagiannidis, S.J. Moore, N.J. Wells, J. Herniman, G.J. Langley, P.N. Horton, M.E. Light, I. Marques, P.J. Costa, V. Félix, J.G. Frey and P.A. Gale, *Chem. Sci.,* 2013, 4, 3036-3045; Busschaert and P.A. Gale, *Angew. Chem. Int. Ed.* 2013, 52, 1374-1382; S.J. Moore, C.J.E. Haynes, J. González, J.L. Sutton, S.J. Brooks, M.E. Light, J. Herniman, G. J. Langley, Vanessa Soto-Cerrato, R. Pérez-Tomás, I. Marques, P.J. Costa, V. Félix and P.A. Gale, *Chem. Sci.* 2013, 4, 103-117; N. Busschaert, I.L. Kirby, S. Young, S.J. Coles, P.N. Horton, M.E. Light and P.A. Gale, *Angew. Chem. Int. Ed.* 2012, 51, 4426-4430; P.A. Gale, *Acc. Chem. Res.* 2011, 44, 216-226; N. Busschaert, M. Wenzel, M.E. Light, P. Iglesias-Hernández, R. Pérez-Tomás and P.A. Gale, *J. Am. Chem. Soc.,* 2011, 133, 14136-14148; M. Wenzel, M.E. Light, A.P. Davis and P.A. Gale, *Chem. Commun.* 2011, 47, 7641-7643; S.J. Moore, M.G. Fisher, M. Yano, C.C. Tong and P.A. Gale, *Chem. Commun.* 2011, 47, 689-691; N.J. Andrews, C.J.E. Haynes, M.E. Light, S.J. Moore, C.C. Tong, J.T. Davis, W.A. Harrell Jr. and P.A. Gale, *Chem. Sci.,* 2011, 2, 256-260; C.J.E. Haynes and P.A. Gale, *Chem. Commun.* (invited Highlight article), 2011, 47, 8203-8209; P.A. Gale, C.C. Tong, C.J.E. Haynes, O. Adeosun., D.E. Gross, E. Karnas, E. Sedenberg, R. Quesada, and J.L. Sessler, *J. Am. Chem. Soc.* 2010, 132, 3240-3241; J.T. Davis, P.A. Gale, O.A. Okunola, P. Prados, J.C. Iglesias-Sanchez, T. Torroba and R. Quesada, *Nature Chem.* 2009, 1, 138-144.