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RESEARCH INTERESTS

The Biology and Function of Sulfation

The research focus of my laboratory centres around sulfation, and the enzyme families that participate in the addition and removal of sulfate to a host of endogenous and environmental chemicals - the sulfotransferases (SULT) and sulfatases, respectively. Our work is directed towards understanding a) the function of the sulfation system in the "normal" human being and b) the mechanisms and consequences of its disruption for human disease. To achieve these goals, our fundamental studies on the molecular and cell biology of sulfation is complemented by strong interactions with clinical researchers in Dundee and elsewhere.

We are continuously exposed to a host of toxic or potentially toxic chemicals from our environment, both internal and external, and this represents a serious threat to health. To combat this threat, we have evolved a complex and effective chemical defence system comprising, among other components, a series of enzyme families whose main function is generally accepted to be the detoxification of xenobiotics and endogenous toxins. These so-called drug (or xenobiotic) metabolising enzymes classically act upon toxic or potentially toxic chemicals to reduce their biological activity and increase their water solubility, thereby facilitating removal from the body and achieving detoxification. This textbook view, however, masks many practical aspects of the way our bodies respond to chemical challenge, and does not reveal the central importance of many of these enzymes in the homeostasis and regulation of key body functions. Of particular importance is the fact that sulfation of many dietary and environmental chemicals actually renders them more reactive, and indeed sulfation is a key step in the bioactivation of many carcinogens.

Sulfation has a well-established role in drug metabolism and chemical defence, but it is in the area of hormone and neurotransmitter homeostasis that the most exciting possibilities lie, since reversible sulfation can provide an exquisitely sensitive and specific means of regulating the biological activity of these compounds in target and non-target cells. Current projects in the laboratory include:

Role of Sulfation and Glucuronidation in Drug Metabolism and Drug Interactions

Many drugs are excreted from the body conjugated with sulfate or glucuronic acid. A collaborative project with Brian Burchell (Dundee), funded by an international consortium of pharmaceutical companies, is examining the role of individual sulfotransferase and UDP-glucuronosyltransferase enzymes in key human tissues in the metabolism of commonly used drugs. We have also recently acquired an LC-MS-MS system (funded by the Wellcome Trust) for the analysis of drug and hormone conjugates.

Sulfation in human development

Steroid and thyroid hormones play key roles in human development, and we have shown that sulfation of these compounds is widespread, and under tight regulation, in the developing human. In collaboration with **Robert Hume** (Dundee) and **Theo Visser** (Rotterdam) we are trying to understand the contribution of sulfation to regulation of the biological activity of these potent compounds in key organs during development, through the use of in vitro and in vivo model systems. It is hoped that our investigations will identify novel therapeutic targets for the prevention of mortality and long-term morbidity associated with the extremely premature infant.

Structure and function of human catecholamine sulfotransferase

Catecholamines circulate predominantly as their sulfate conjugates (e.g. more than 95% of circulating dopamine is in the form of dopamine sulfate), and these sulfates are also found in substantial amounts in the brain. We have shown that migraine sufferers have reduced activity for the SULT enzyme responsible for the sulfation of catecholamines, which is expressed at high levels in the gastrointestinal tract, in the brain and in platelets. This enzyme also sulfates numerous drugs and dietary xenobiotics, and thus the potential for drug-endogenous compound interactions exists. In collaboration with **Rob Cooke** and **Gary Manchee** (Glaxo Wellcome) we have solved the 3-dimensional structure of this protein – the first human SULT structure to be solved. Molecular modelling of substrate interactions, also in collaboration with Jyrki Taskinen (Helsinki), will afford a major step forward towards the predictive metabolism of new pharmaceuticals.



X-ray crystal structure of human dopamine sulfotransferase, SULT1A3

Sulfation in chemical carcinogenesis - a risk factor for cancer susceptibility?

Many chemicals to which we are exposed are rendered more biologically active following metabolism, and this bioactivation is central to the mechanism of action of numerous chemical carcinogens, including those in the diet. Sulfation is the terminal step in the bioactivation of numerous mutagenic/carcinogenic aromatic amines and benzylic alcohols, and in collaboration with **Hansruedi Glatt** (Potsdam) and we are investigating the role of individual SULT isoenzymes in this process. Genetic polymorphisms are known to exist in the SULT enzymes responsible, and these may represent novel risk factors in cancer of the bladder and colon - target tissues for aromatic amines in particular. We have devised genotyping assays for different allelic variants of SULT, and are now applying these assays in molecular epidemiology studies of SULT genotype in human cancer, in collaboration with **Dick Strange** and **Tony Fryer** (Keele).

Our work is currently funded by: the Commission of the European Communities, The Wellcome Trust, Tenovus Scotland and the pharmaceutical industry.

Current Laboratory Staff:

Sheila Sharp, Senior Scientific Officer
 Lesley Wilson, Technician
 Emma Stanley, Postdoctoral Researcher
 Nickie Rose, PhD Student
 Victoria Butler, PhD Student

Recent Publications:

Papers:

Kester MH, Bulduk S, van Toor H, Tibboel D, Meinel W, Glatt H, Falany CN, Coughtrie MW, Schuur AG, Brouwer A, Visser TJ. Potent inhibition of estrogen sulfotransferase by hydroxylated metabolites of polyhalogenated aromatic hydrocarbons reveals alternative mechanism for estrogenic activity of endocrine disrupters. *J Clin.Endocrinol.Metab* **87** (3), 1142-1150 (2002).

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