Project 4 Treatment of iron overload

Project 4 emphasizes the integration of basic science with the development of new therapeutic strategies for iron overload conditions.

1. Non-transferrin-bound iron

Non-transferrin-bound iron has been characterized and studied at King’s over the past 20 years. LC-ICP-MS based studies by the group in the Pharmacy Department has provided a basis for the understanding of the chemical nature of this important iron pool and underscores the importance of these iron species in haemochromatosis, thalassaemia, sickle cell anaemia and possibly diabetes. A new fluorescence-based method for NTBI quantification recently developed by the group will be more suitable for routine analysis in clinical laboratories. Non-transferrin bound iron (NTBI) appears in plasma when transferrin is saturated and may reach levels of 10μM. Its distribution is not limited to cells which express the transferrin receptor as NTBI can be absorbed by highly vascular tissue such as the endocrine organs and the heart. Removal of this iron is therefore essential for effective treatment of iron overloaded patients.

2. Intracellular iron pool

Iron speciation in intracellular compartments is also a central question in understanding iron toxicity. The nature of the intracellular labile iron pool is unknown, as is its intracellular distribution between cytoplasm, lysosome and mitochondrial compartments. The Hider group has recently produced a series of fluorescent probes capable of entering cells and being quenched in the presence of physiological levels of iron (10μM-10nM). These probes are being investigated for potential use with confocal microscopy, where it is intended to establish the intracellular distribution of labile iron in macrophages and hepatocytes. A clear knowledge and understanding of the size and dynamic nature of these iron pools will further assist in the design of clinically useful iron chelators.
3. Development of iron chelators.

Bob Hider’s interest in medicinal chemistry is focussed on the mechanics of the movement of iron both within cells and across membranes. He has worked with siderophore-based iron uptake processes in micro-organisms, plant root absorption of iron and the absorption of different molecular forms of iron by mammalian cells, including gastrointestinal enterocytes, hepatocytes, macrophages, myocytes and reticuloctyes. This work has led to the development of novel oral iron chelators for the treatment of iron overload. Hider synthesised a range of iron chelators, all designed to permeate cell membranes in both the iron-free and iron-complexed form. This systematic analysis took place in the early 1980’s and identified N-alkyl-3-hydroxypyridin-4-ones as having potential for clinical application. Initial studies with these molecules indicated high oral activity in normal and iron-overloaded animals. A series of such molecules were subjected to pre-clinical toxicity investigation with advice from Medicines Control Agency and one of the first generation compounds, deferiprone, was introduced into clinical trials. 1,2-dimethyl-3-hydroxypyridin-4-one (deferiprone) is becoming increasingly widely adopted by clinicians for the treatment of iron overload associated with the treatment of thalassaemia. Deferiprone received European Medicines Evaluation Agency-approval in 2000. Deferiprone is orally active whereas desferrioxamine, the current generally adopted drug, must be administered by continuous infusion over prolonged periods (6-8h). We have continued to develop orally active iron chelators, aiming to design more potent analogues of deferiprone. This work has led to the identification of more effective, second generation oral iron chelators. These compounds are the most powerful bidentate chelators of iron reported to date and are currently under investigation for a range of additional clinical applications including treatment of neurodegenerative diseases and photodynamic therapy of cancers.

Over the past 5 years there has been an increasing interest in the possibility of iron chelators having potential in the treatment of various forms of neurodegeneration. Following the success of deferiprone for the treatment of Friedriechs ataxia we have
designed other hydroxypyridinones which cross the Blood-Brain barrier more efficiently.