When the DDO Came to Town.

Meeting 21 October 2011, The Drug Development Office (DDO) visit to ECMC Sheffield.

As a lay member of the ECMC, I was invited to attend this meeting, along with all the other members. I was hoping to see what excellence Sheffield had to offer, and I wasn't disappointed.

The purpose of the meeting was to enable the Sheffield Experimental Cancer Centre (ECMC) to showcase their talent and facilities to the Cancer Research UK DDO, who in turn would explain their organisational structure, drug development procedures, and display their portfolio of drugs in early trials.

Professor Penella Woll opened the meeting with an overview of the benefits of working in Sheffield, with its extensive University infrastructure and skills base, and very pleasant local National Park. Members of the DDO team were introduced who explained the different aspects of their organisation.

What is the DDO? The DDO is a body within the Strategy and Research Directorate of Cancer Research UK, and their role is to look at promising anti-cancer treatments which may not be otherwise developed by their parent companies for strategic or other reasons. The office was set up in 1982, and its focus is now development, not operational, as it once was. Further details of their work can be found on their website:
http://science.cancerresearchuk.org/research/drug-development/

The DDO does not market new drugs, but may license them out to industry. Industry may not wish to take up 'risky' projects, so the DDO will pick these up and 'derisk' them by funding part of the development process.

Within DDO itself, there are functions such as the Project and Portfolio Management Team who assign a project manager to each study; a Biotherapeutics Development Unit to develop methods to manufacture of biological agents for use in trials; a Formulation Unit to manufacture small molecule drugs.

The 100 staff of the Portfolio Management Team look after 36 agents (at the time of writing). Of these, 62% are small molecules, vaccines 15%, antibodies 10%, and the remainder are peptides, virus, and cell therapy agents. There is a broad range of indications, from paediatrics to bowel cancer. At the moment, the team are looking to increase throughput of development stages in exploratory, pre-clinical, and trial setup. They are continually trying to improve study timelines, bringing the time from development to recruiting for study down to 18 to 24 months, which is a difficult target.

New roles and responsibilities have recently been added to the DDO, including Operational Excellence who identify key areas of improvement on a continuing basis, the Medical Sciences Team of two people who bring medical advice and input to project strategies, the Drug Development Scientist who gets involved at an early stage to develop a target profile and identify key

success criteria, and a Protocol Safety and Review Board to make sure that patients are not harmed by trials. All is aimed at working smoothly with industry, and maximising safety and benefit for patients.

It was obvious that despite much of the work being far removed from the patient, the interests of the patient are foremost in the minds of the people involved: harnessing scientific creativity, management expertise, and industry power to develop and bring to use effective drugs and agents.

Sheffield ECMC aims to increase the number of rationally designed therapies being tested in the UK. The DDO are a neutral organisation and industry collaborators, smoothing the way to cooperation between industry and medicine. A collaboration was agreed in January 2011 with AstraZeneca, and plans are under way for the next one. Drug companies will fund trials, providing sums of money to fund necessary patient scans and investigations, and will often supply trial-ready agents at no cost.

Of course, it is not only industry which develops drugs. Academics do too, and there is a pathway for them to push *their* discoveries forward. The New Projects Review Team will evaluate an agent and advise on how to take it to the New Agents Committee (NAC), or the scientist may take it directly to the NAC. This process is very quick. Advice can be given on where to go next, or the agent (which must be a finished compound) can be pushed for development.

A member of ECMC asked whether it was possible to find what agents have been shelved by industry, but which may be interesting and effective. The DDO finds out about these when a company comes on board, and the information can then be disseminated to interested parties. The ECMC approach is to try promising agents in the laboratory first, to test the biological principles involved, rather than relying on using empirical combinations as we tend to do at present.

During 2010, Sheffield ECMC treated 1826 patients in 45 trials. New trials opening in 2011 include STOMP, which was named by the NTCRN CRP, and is of Olaparib as maintenance therapy for small cell lung cancer patients, the majority of whom have a poor prognosis. At present the median survival is 10.3 months and the team are looking to improve this. ECMC are also studying the effects of the treatment on circulating cancer cells, and plasma DNA from patients in the trial.

ECMC achievements in the development of treatment combinations for lung cancer, melanoma, genetics studies, and bone oncology were demonstrated. Dr Ingunn Holen is developing a range of system models for the investigation of the development of bone metastases in breast and prostate cancer, looking at their micro-environment and the molecules involved. Ingunn's work suggests that the micro-environment plays an important role in tumour development.

Professor Martin Paley spoke of the pioneering use In Sheffield of a radio-active isotope of Xenon to image lungs and tumours, and the use of MRI spectroscopy to look at metabolites of drugs in body fluids, along with many

other ventures. Imaging is an essential part of research, and last years acquisition of the MRI spectroscope was part of the plan to improve services.

Studies involving radioactive drugs (Alpharadin), macrophages which can be engineered to take a virus into the cancer cell which explodes under the strain, ruthenium compounds to complement the existing role of metals (eg cisplatin) in treatment, vascular biology of tumours, viruses, markers, magnetic nano-particles offering targeted drug therapy, and the wish to go to first-in-man studies were described. A full range of techniques are available and used to investigate their chosen areas of study, and the expertise on offer was demonstrated to good effect. Sheffield ECMC is pulling all the research strands together.

At lunch, I had a conversation with a biochemist based at the University of Sheffield, who said it was very difficult to predict how a drug will work and how effective they are, as there are so many confounding factors. My own impression of the science until now, was that metabolic pathways and rogue genes operating in cancers were identified and compounds formulated to deal with them but I learned this is not the case. This is an ideal that researchers are working towards. Herceptin (Trastuzumab) for example, was a drug which observation showed worked in a small group of breast cancer patients, and it was found to work by targeting the HER2 gene, not developed to specifically target the gene.

Metabolic pathways are being mapped on powerful computers by talented programmers, aberrant genes found, and uprated or down-regulated genes investigated and agents found to combat and re-regulate them. But, these are very early days. Stem cells are being found in many cancers, adding a new twist, as this view is an old idea, proposed in the early years of the 20th century by embryologist Professor John Beard of Edinburgh University, who was nominated for the Nobel Prize in medicine 1906. Of course, because a scientific idea is old doesn't mean it is a bad one. On the contrary, science works by continually making observation and re-evaluating previous hypotheses and theories and taking them forward. Stem cells develop on their own internal conversation, and a conversation with their surroundings and their neighbouring cells. We have only begun to explore their possibilities. Epigenetics, the study of the manipulation and regulation of genes by the macro environment in which we live and the cellular environment itself, adds yet another layer of complexity and interest. Research by Professor Wolf Reik, at the Babraham Institute in Cambridge, indicates that experiences of our parents and grandparents affect the development and life chances of their offspring as epigenetic changes to genetic structures are passed onward. So while we have discovered much, there is much more yet to discover, and I suspect that we are still a long way from a cure.

But we can begin to look forward to the day when a cancer is biopsied for its genetic and epigenetic characteristics, and a cocktail of treatment and drugs designed to correct all mis-regulation dispensed, and a cure obtained. Sheffield ECMC is working towards that.