New PhD Projects- Dr Esther Woon

1. Development of small molecule probe of FTO to study the epigenetic basis for obesity

Mutations of the *FTO* (Fat Mass and Obesity associated) gene has recently been identified, through genome-wide association studies, to be associated with obesity in both children and adults, and across multiple ethnic groups. In addition, inactivation of *FTO* is found to protect from obesity; this is important given that obesity predisposes individuals to serious chronic conditions, such as diabetes, cardiovascular disease, hypertension and certain cancers, and is the leading cause of premature death worldwide. There is increasing evidence that the nucleic acid demethylase activity of FTO may regulate metabolic processes through epigenetic mechanisms. Currently there is no report of selective inhibitor of FTO. In this project, we seek to develop potent and selective probe for FTO, which will then be used for functional and mechanistic studies in cells and in animal model, to help us understand its physiological link to obesity. This work could also pave the way for obesity prevention drugs.

Related publication:

1. Woon, E. C. Y.; Demetriades, M.; Bagg, E. A. L.; Aik, W. S.; Krylova, S. M.; Ma, J. H. Y.; Chan, M. C.; Walport, L. J.; Wegman, D. W.; Dack, K. N.; McDonough, M. A.; Krylov, S. N.; Schofield, C. J. Dynamic combinatorial mass spectrometry leads to inhibitors of a 2-oxoglutarate dependent nucleic acid demethylase. ***J. Med. Chem.*, 2012, 55, 2173-2184.**

2. Novel boron-based dynamic chemistry for the discovery of anti-obesity drugs

To aid existing drug discovery effort, we are interested in developing novel methods of lead identification. We have recently employed Dynamic Combinatorial Mass Spectrometric (DCMS) technique to the rapid identification of several clinically important proteins, such as nucleic acid demethylases and JmjC histone demethylases. As an extension to this work, and for application to proteins that are not amenable to MS analysis, we are keen to explore the use of novel boron chemistry in combination with other biophysical detection techniques, such as differential scanning fluorimetry (DSF) and NMR. This strategy will initially be applied to the discovery of new anti-obesity drug.

Related publication:

1. Demetriades, M.; Leung, I. K. H.; Chowdhury, R.; Chan, M. C.; Yeoh, K. K.; Tian, Y-M.; Claridge, T. D. W.; Rgatcliffe, P. J.; Woon, E. C. Y.;* Schofield, C. J.* Dynamic combinatorial chemistry employing boronic acids/boronate esters leads to potent oxygenase inhibitors. ***Angew. Chem. Int. Ed.* 2012, 51, 6672-6675.**

2. Woon, E. C. Y.; Demetriades, M.; Bagg, E. A. L.; Aik, W. S.; Krylova, S. M.; Ma, J. H. Y.; Chan, M. C.; Walport, L. J.; Wegman, D. W.; Dack, K. N.; McDonough, M. A.; Krylov, S. N.; Schofield, C. J. Dynamic combinatorial mass spectrometry leads to inhibitors of a 2-oxoglutarate dependent nucleic acid demethylase. ***J. Med. Chem.*, 2012, 55, 2173-2184.**

3. Rose, N. R.; Woon, E. C. Y.; Kingham, G. L.; King, O. N. F.; Mecinovic, J.; Clifton, I. J.; Ng, S. S.; Talib-Hardy, J.; Oppermann, U.; McDonough, M. A.; Schofield, C. J. Selective inhibitors of the JMJD2 histone demethylases: combined nondenaturing mass spectrometric screening and crystallographic approaches. ***J. Med. Chem.*, 2010, 53, 1810-1818.**

3. Novel approach to obesity treatment through the induction of brown adipose tissue formation

One major contributing factor for the prevalence of obesity in the developed world is sedentary lifestyle, coupled with a ready supply of calorie-dense food. Conceivably, therapeutic strategy that promotes energy expenditure would be valuable in the treatment of obesity. In this regard, brown adipose tissue (BAT) is of tremendous medical interest. Unlike white adipose tissue (WAT), they serve primarily to generate heat (through burning fat) rather than storing it. Importantly, the conversion of WAT to BAT has been shown in animal studies to induce beneficial metabolic effects, such as reduced adiposity and increase insulin sensitivity. Our lab has recently developed several small molecules that could potentially turn 'nasty' WAT into 'good' BAT. In this project, we will optimise their potency and selective using modelling analyses and structure-based approach. Selected compounds will then be investigated for their 'browning effect' using a range of *in vitro* and cell-based assays, and eventually in animal model. This work could pave the way for novel anti-obesity treatment.

4. Investigation of epigenetic enzymes as therapeutic targets

Environmental factors such as diet and lifestyle can alter the way in which our genes are expressed. This is achieved primarily through chemical modifications on DNA, RNA and histones. The study of how these modifications bring about gene regulation is known as epigenetics. One such chemical modification involves the removal methyl group from histones by a class of enzymes called the histone demethylases. Since their discovery in 2006, they have been found to be associated with a wide range of human diseases, such as obesity, inflammatory disorders and cancer; and are currently being hotly pursued as potential therapeutic targets. In this project, we seek to identify potent and selective probes for currently less well-studied JmjC histone demethylases. The probes will then be used for subsequent functional and mechanistic studies.

Related publication:

1. Woon, E. C. Y.; Tumber, A.; Kawamura, A.; Hillringhaus, L.; Ge, W.; Rose, N. R.; Ma, J. H. Y.; Chan, M. C.; Walport, L. J.; Che, K. H.; Ng, S. S.; Marsden, B. D.; Oppermann, U.; McDonough, M. A.; Schofield, C. J. Linking of 2-oxoglutarate and substrate binding sites enables potent and highly selective inhibition of JmjC histone demethylases. ***Angew. Chem. Int. Ed.*** **2012, 51, 1631-1634.**

2. Rose, N. R.*, Woon, E. C. Y.*; Walport, L. J; Chowdhury, R.; Li, X. S.; King, O. N. F.; Lejeune, C.; Tumber, A.; Ng, S. S.; Krojer, T.; Chan, M. C.; Rydzik, A. M.; McDonough, M. A.; Oppermann, U.; Klose, R. J.; Schofield, C. J.; Kawamura, A. The Plant Growth Regulator Daminozide is a Selective Inhibitor of the KDM2/7 Histone Demethylases. ***J. Med. Chem.*** **2012, 55, 6639-6643.**

3. Chowdhury, R.; Yeoh, K. K.; Tian, Y. M.; Hillringhaus, L.; Bagg, E. A.; Rose, N. R.; Leung, I. K. H.; Li, X. S.; Woon, E. C. Y.; Yang, M.; McDonough, M. A.; King, O. N. F.; Clifton, I. J.; Klose, R. J.; Claridge, T. D. W.; Ratcliffe, P. J.; Schofield, C. J.; Kawamura, A. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. ***EMBO rep.,*** **2011, 12, 463-469.**

4. Chang, K. H.; King, O. N. F.; Tumber, A.; Woon, E. C. Y.; Heightman, T. D.; McDonough, M. A.; Schofield, C. J.; Rose, N. R. Inhibition of histone demethylases by 4-carboxy-2,2'-bipyridyl compounds. ***ChemMedChem,*** **2011, 6, 759-764.**

Join our group!

- You can expect to be **intellectually stimulated** in this new, yet important field of epigenetics
- You will benefit from learning **a variety of research skills and techniques** in a supportive lab environment
- Solid phase peptide synthesis, organic synthesis
- X-ray crystallography, molecular modelling, structure-based design
- Molecular biology, biochemical assays, cell-based assay
- Biophysical techniques, such as, mass spectrometry (non-denaturing ESI-MS, MALDI-TOF) and differential scanning fluorimetry (DSF)
- There will also be excellent opportunities to interact/ work on short attachment with our **local (ASTAR, NUS, NTU) and overseas collaborators (Oxford, Bath)**

I want to find out more!

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