Drug-drug interactions of human cytochrome P450s by a new electrochemical array

L.H. Mak, P. Panicco, S. Collins, S. Sadeghi, S. Ferrero, G. Gilardi

NanoBioDesign Ltd., Woodstock House, Winch Road, Kent Science Park, Sittingbourne, Kent ME9 8EF, UK

Email: s.collins@nanobiodesign.com

NanoBioDesign (NBD) has developed a new electrochemical array technology for analysing small samples of a drug candidate using immobilised human P450 enzymes.

Human P450s screening is particularly difficult due to their membrane-bound nature and their lack of stability. In nature, the electrons are supplied by NADPH via a favin-containing reductase [1].
The key idea in the NBD technology is based on the molecular lego principle [2], whereby the P450 enzymes are genetically fused to an artifical reductase to achieve optimal electrochemical contact on a gold electrode. The enzyme is covalently bound to the electrode via a self-assembled monolayer. The electrode supplies the reducing units for the P450 turnover, and the measurement of the current on the electrode (typically nA) allows to construct Michaelis-Menten-type of curves from which key enzymatic parameters such as V_{max} , K_M, K_I, IC50 are extracted.

NBD's technology provides a quick and reliable method of cost-effectively ascertaining the nature of a drug/P450 interaction *in vitro* using a 8-well arrays, i.e. one column of a 96 well plate. The array can determine whether a new chemical entity is a substrate or an inhibitor allowing the study of drug-drug interactions. Furthermore, the system is reagentless, fast and gives highly reproducible results.
The presentation will show the data obtained for a number of drugs with the major human P450s.

[1] Guengerich F. P., Kim D. H., Iwaski M., Chem. Res. *Toxicol*. **4** (1991) 168-179
[2] Gilardi G., Meharenna Y. T., Tsotsou G. E., Sadeghi S. J., Fairhead M. and Giannini S., *Biosensors and Bioelectronics* Volume **17**, Issues 1-2, January 2002, Pages 133-145
[3] Fantuzzi A., Fairhead M., Gilardi G., *J. Am. Chem. Soc.* **126** (2004) 5040-5041