Research Breakthrough

CHEMISTRY

New Directions for Old Drugs

Assistant Professor Martin J. Lear,
http://staff.science.nus.edu.sg/~chmlmj/index.htm
Associate Professor Yao Shao Qin
http://www.chemistry.nus.edu.sg/ourpeople/academic_staff/yaosq.htm

With the beneficial goal of generating new applications from known drugs, the chemistry and biology groups of Asst Prof Martin J. Lear and Assoc Prof Yao Shao Qin have teamed up to develop an anti-cancer agent out of the FDA-approved anti-obesity drug called Orlistat (also known as tetrahydrolipstatin, THL). The findings of their research have been published in the prestigious *Journal of the American Chemical Society* and will be featured in the November 2010 issue of *Chemical Communications*[1,2].

Their strategy combines the techniques of total synthesis and chemical proteomics to generate THL-probes capable of trapping off-target proteins (Figure 1). These probes were synthesized through the introduction of alkyne handles in the parental THL structure to maintain the native biological properties of Orlistat, while still providing the necessary functionality for target identification via bio-orthogonal click chemistry. With these probes, they were able to demonstrate for the first time that this chemical proteomic approach is suitable for the identification of previously unknown cellular targets, i.e., the off -targets of Orlistat.

Through their approach, several anticancer related proteins including HSP90 and three ribosomal proteins have been identified[1], as well as more specific THL-analogues against a validated anti-cancer target called fatty acid synthase (FAS)[2]. Some of these new targets

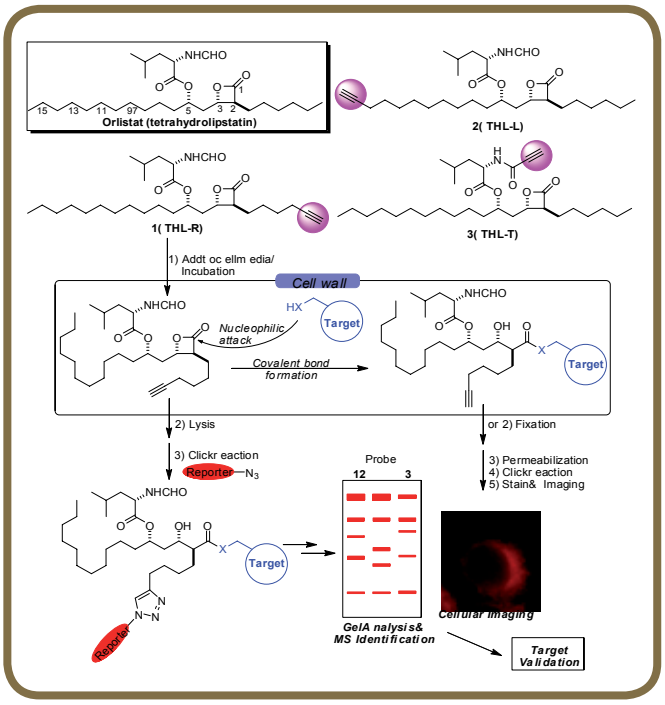

Fig. 1 Trapping off-target proteins

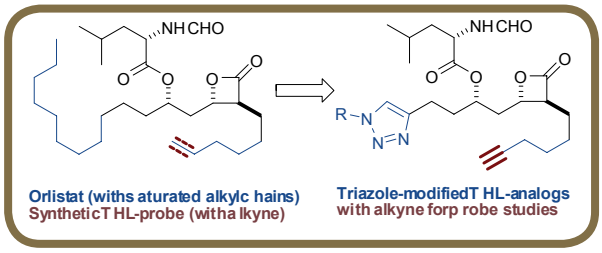

Fig. 2 Activity-based protein profiling

were further validated by experiments including Western blotting, recombinant protein expression and site-directed mutagenesis.

The chemical key to the success of their approach resides in the use of bio-compatible/bio-orthogonal "click" chemistry (between azides and alkynes) to not only rapidly diversify a compound library, but also to allow the activity-based protein profiling (ABPP) of cellular off-targets of lead compounds (Figure 2).

The findings of this research have important implications in the consideration of Orlistat as a potential anti-cancer drug at its early stage of development for cancer therapy. This strategy should be broadly useful for off-target identification against a number of existing drugs and/or candidates, which are known to covalently modify their biological targets. With this breakthrough, the future can now promise to reveal new directions for old drugs.

References: [1] Yang, P-Y.; Liu, K.; Ngai, M.H.; Lear, M.J..; Wenk, M.; Yao, S.Q. *J. Am. Chem. Soc.* 2010, 132, 656-666. [2] Ngai, M.H; Yang, P-Y.; Liu, K.;. Shen, Y.; Wenk, M.; Yao, S.Q.; Lear, M.J. *Chem. Commun.* 2010, DOI: 10.1039/c0cc01276a