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Protein Chip to Drug Discovery

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To date, well-based robotic systems equipped with 96- or 384-well plates have been extensively used for high-throughput screening (HTS) of drug candidates. However, conventional well-based screening systems are often limited in their ability to screen small molecule inhibitors because they require a huge amount of small molecules as well as target proteins. Therefore, protein chips have been recognized as a valuable tool for such tasks since they require only a nanoliter scale sample volume with a few picograms of the target proteins. In an attempt to develop a novel protein chip system for HTS, the surface plasmon resonance imaging (SPRI)-based system has been developed to detect protein-ligand interactions in an array format on the surface of two-dimensional gold thin film. The major advantage of the technique is to detect molecular interactions in a high-throughput mode without the use of labels. We have also developed various types of modified gold thin film surfaces that could detect affinity-tagged proteins. The affinity-tagged protein samples were spotted onto the affinity ligand-modified gold chip, and the protein-protein interactions were successfully detected with the SPR imaging system. And then, the SPR imaging-based protein chip system was applied to screen targeted drug candidates from chemical or natural product libraries.

To examine the potential applicability of SPR imaging-based protein arrays for the high-throughput screening of protein-protein interaction inhibitors, 1500 protein samples were spotted on a GST-E7-layered gold chip surface (10 X 5 mm) and were analyzed by SPR imaging (Fig. 1A). Bright spot images resulted

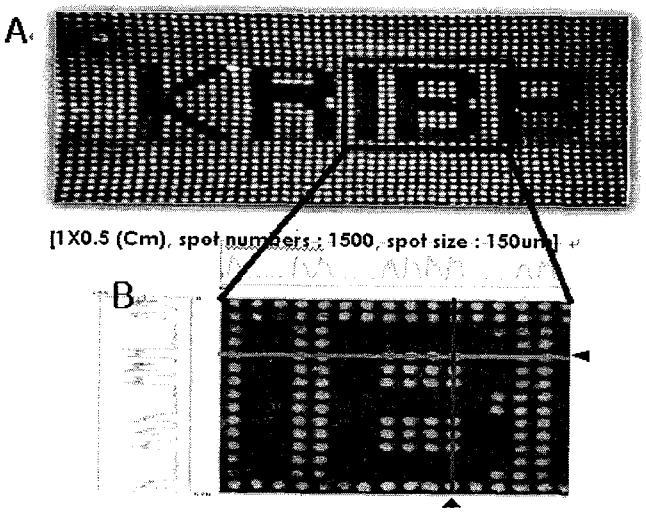

Fig. 1 SPR imaging analysis of a 1500 protein spot array.

(A) 1500 spots (50 X 30) were arrayed on a 10 X 5 mm of gold chip. Bright spots resulted from His_6-RB/GST-E7 interaction by spotting His_6-RB protein solution onto the GST-E7-layered gold chip surface. Empty spots marked by 'KRIBB' were made by spotting a mixture of His_6-RB/PepC onto the GST-E7-layered gold chip surface.

(B) An enlarged image of the spots.

from His_6-RB/GST-E7 interaction by spotting a His_6-RB protein solution onto the GST-E7-layered gold chip surface. Empty spots, marked by 'KRIBB', were made by spotting a mixture of His_6-RB and PepC onto the GST-E7-layered gold chip surface. This shows that PepC inhibits the His_6-RB/GST-E7 interaction by binding to His_6-RB competitively. Fig. 1B shows an enlarged image of 240 spots and the digitized relative SPR imaging intensities of the spot images on the solid line. The difference in SPR imaging intensity values enables researchers to distinguish the inhibitor-containing samples from an enormous number of unknown samples.

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