SPOTTING THE WEAKEST BINDERS

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A NEW LEVEL OF PERFORMANCE AND FLEXIBILITY IN DRUG DISCOVERY

Employing our Grating-Coupled Interferometry (GCI)[1] technology to deliver superior sensitivity over traditional Surface Plasmon Resonance (SPR) technologies, researchers can reliably determine off-rates of up to $10 s^{-1}$, starting with just a crude reaction mixture. Combined with microfluidics that sustain a wide variety of solvents - including acetonitrile and high concentrations of DMSO -, the occurrence of false positives is minimized.

Screen, rank and characterize weak binders with off-rates up to 10 s^{-1}

Study binding kinetics even at large analyte:ligand MW ratios (up to 1:1000)

Experiment with crude mixtures, detergents and other additives without clogging

GRATING-COUPLED INTERFEROMETRY (GCI)

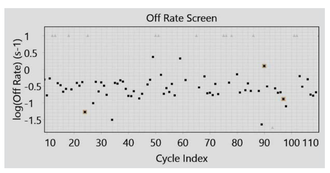
More information about GCI

GCI is a surface-based, label-free biosensing technique. When target molecules (e.g. proteins) are attached to the sensor surface, binding of analytes leads to an increase in mass and hence to a change in the refractive index within the evanescent field near the surface. In GCI, refractive index changes on a sensor surface are measured as time-dependent phase-shift signals. The long light-to-sample interaction length of the waveguide provides intrinsically high signal-to-noise levels for improved sensitivity.

With high sensitivity, the ability to resolve extremely rapid dissociating kinetics and innate compatibility with high molecular weight ratios, the Creoptix® WAVEsystem's GCI technology improves fragment-based screening and kinetic analysis of small molecules to accelerate drug development. Paired with no-clog WAVEchips®, a wide range of molecules can be immobilized using various chemistries.[2]

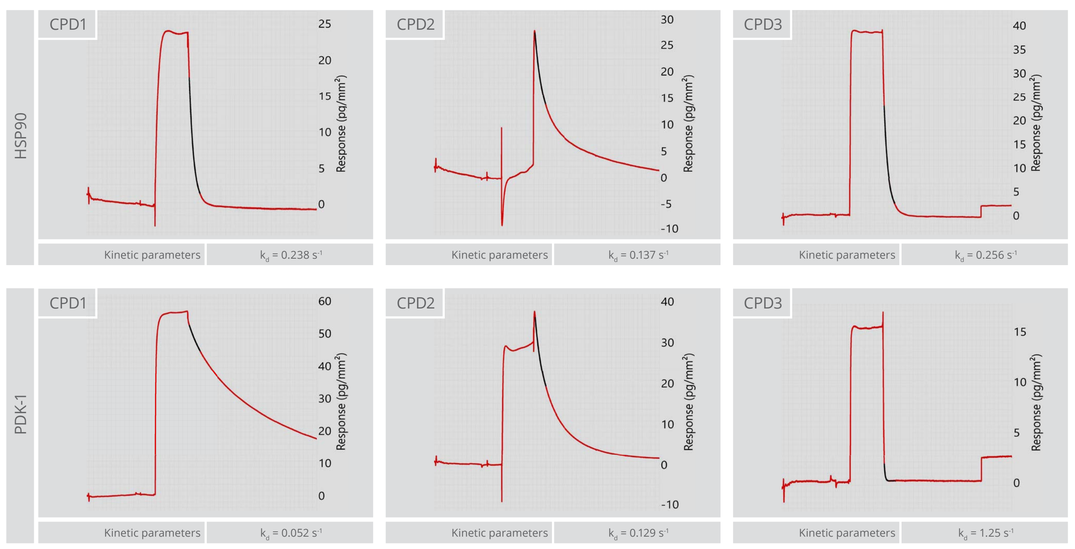
HITS WON'T BE MISSED

The Creoptix® WAVEsystem provides a versatile platform for fragment screening and analysis. Thanks to its ultra-fast transition times, excellent resolution for compounds with k_d's well above 1 s^{-1} can be achieved.



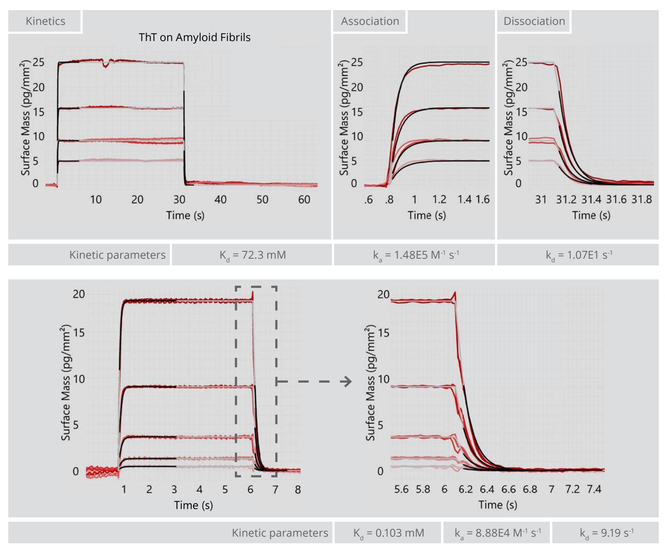
Selected HSP90 or PDK-1 hits (highlighted) are in good agreement with the reported literature[3-4]. Aberrant samples can be simply and automatically excluded based on the apparent k_d and the Chi^2 (grey triangles).

Sensorgrams of selected compounds of a 83 crude non-purified compounds[3-4] library-subset, screened against His-tagged Pyruvate Dehydrogenase Kinase (PDK-1) and captured on a PCH WAVEchip. Samples were injected at ~ 20 µM. His-tagged HSP90, captured on a different channel, served as negative control.



WEAK BINDERS, STRONG DATA

Weak binders such as those found in fragment-based screening are typically ranked by affinity rather than kinetics due to their very fast off-rates, which can not be resolved by traditional SPR instrumentation. Here we show that the Creoptix® WAVEsystem provides an outstanding resolution whereby very fast kinetics can be reliably determined at off-rates up to 10 s^{-1}.

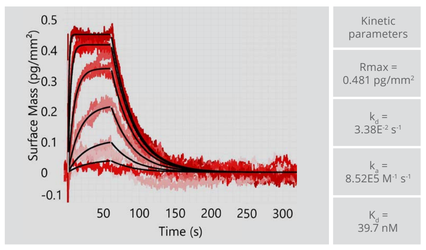


Self-assembled amyloid fibrils were immobilized via amine coupling on a 4PCZ WAVEchip® (zwitterionic surface). The small molecule thioflavin (ThT, 319 Da) was injected in four (4) concentrations (50 µM - 6.25 µM) for 30s at 400 µl/min. Raw data were double referenced and globally fit with a 1:1 binding model showing accurate determination of an off-rate around 10 s^{-1}.

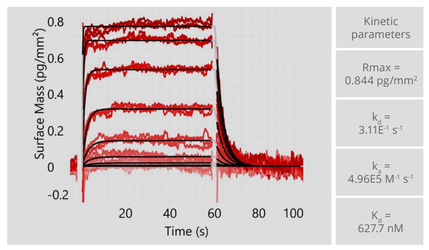
Sensorgrams of a 6-mer oligonucleotide (1.7 kDa) binding onto its complementary ssDNA (11 kDa biotinylated 34-mer) captured on streptavidin on a PCP-S WAVEchip. The interaction was measured at 25°C. Zoom into the dissociation shows excellent data fitting and an accurate determination of an off-rate around 10 s^{-1}.

SMALL MOLECULES CAN'T HIDE ANYMORE

Sensitivity is key and often limiting for accurate and reliable analysis of molecular interactions. The high-sensitivity of the Creoptix® WAVEsystem allows researchers to confidently analyze binding interactions at very low signal levels and high analyte-to-ligand molecular weight (MW) ratios.



Sensorgrams of acetazolamide (222 Da) binding to Carbonic Anhydrase II (29 kDa) immobilised at low density onto a PCH WAVEchip.



Sensorgrams of a small drug molecule (295 Da) binding to a target protein (110 kDa) immobilised at low density onto a PCH WAVEchip. Note the analyte-to-ligand MW ratio is > 300.

GCI IS FEATURED IN

PNAS — Mechanistic basis for the activation of plant membrane receptor kinases by SERK-family coreceptors

nature plants — LETTERS — The SERK3 *elongated* allele defines a role for BIR ectodomains in brassinosteroid signalling

eLIFE — RESEARCH ARTICLE — Dynamics of human protein kinase Aurora A linked to drug selectivity

REFERENCES

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2 Hohmann et al., "The SERK3 elongated allele defines a role for BIR ectodomains in brassinosteroid signalling.", Nature Plants, 4:345–351 (2018)
3 Brough et al., "Application of Off-Rate Screening in the Identification of Novel Pan-Isoform Inhibitors of Pyruvate Dehydrogenase Kinase", J. Med. Chem., 60 (6), pp 2271-2286 (2017)
4 Brough et al., "4,5-Diarylisoxazole Hsp90 Chaperone Inhibitors: Potential Therapeutic Agents for the Treatment of Cancer", J. Med. Chem., 51 (2), pp 196–218 (2008)

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