

## rapifleX MALDI PharmaPulse

- Label-free mass spectrometry  
The universal tool for drug discovery

# rapifleX MPP for HTS and hit confirmation



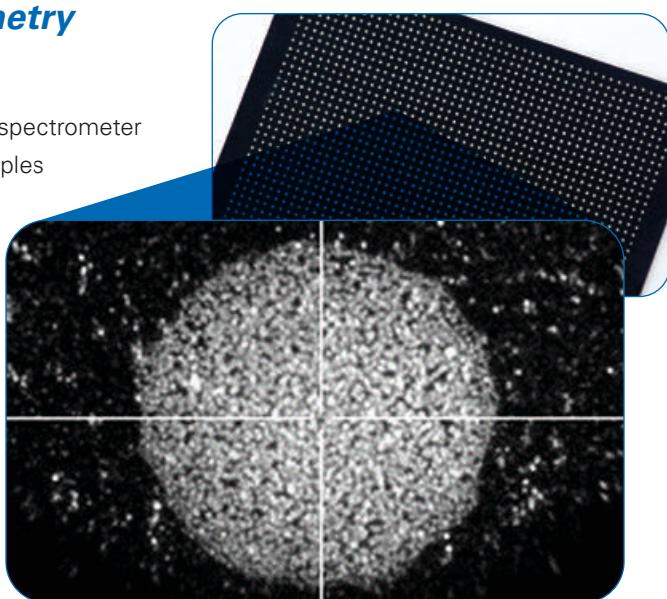
*Label-free detection of native substrates and products*

*Inhibitor-dependent efficiency of biochemical reactions is commonly monitored by measuring the rate of conversion for substrate and product compounds. Mass spectrometry (MS), by design, enables highly specific detection of substrate and product compounds engaged in such biochemical reactions and represents, therefore, a well-suited, ultrafast analysis method allowing for quantitative reaction monitoring. In contrast to other methods, MS does not require the use of fluorescent tags or other labels, but can directly detect target compounds based on their individual  $m/z$  values. State-of-the-art MS instrumentation, because of the enormous resolution and sensitivity it offers, provides a previously unseen level of specificity in compound detection, reducing the need for costly assay development that is often required in label-based analysis methods, which are more prone to interferences. These unique features make mass spectrometry a highly capable screening method enabling time- and cost-efficient assays for novel and challenging drug targets that were difficult to assay in the past.*

## ***Label-free mass spectrometry for drug discovery***

The rapifleX MPP is a MALDI-TOF mass spectrometer with revolutionary speed of up to 10 samples per second. It combines the highest throughput with the specificity of a high-performance mass spectrometer and is driven by a new tailored software suite dedicated to drug discovery workflows.

The rapifleX MPP assists assay development, accelerates HTS and uHTS hit finding, and supports hit confirmation and lead optimization.



# rapifleX MPP – the universal tool for drug discovery



## Full library screens

The rapifleX MPP is the only mass spectrometer for large primary screens of millions of compounds with high diversity. Full automation supports screening of more than one million compounds per week, avoiding time-consuming confirmatory screens.<sup>[1]</sup>

## Focused library screens

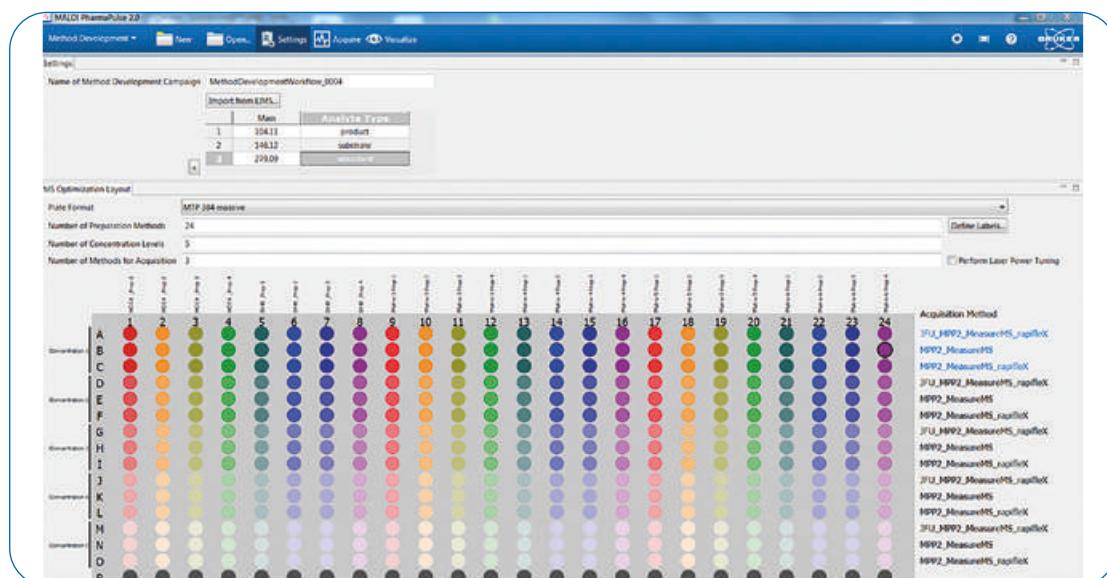
The quality of data obtained with rapifleX MPP meets the requirements of secondary and confir-

matory screens and makes it the ideal detector for focused library screens, such as the identification of kinase inhibitors of a target protein from a smaller subset of the library.<sup>[2]</sup>

## Fragment screening

The mass range and resolution accessible by MALDI-TOF mass spectrometry enables screening of fragments and other low molecular weight compounds.<sup>[3]</sup>

- [1] Winter, M.; Ries, R.; Kleiner, C.; Bischoff, D.; Luippold, A. H.; Bretschneider, T.; Buettner, F. H.; Automated MALDI Target Preparation Concept: Providing Ultra-High-Throughput Mass Spectrometry-Based Screening for Drug Discovery. *SLAS Technology* 2018, <https://doi.org/10.1177/2472630318791981>
- [2] Beeman, K.; Baumgartner, J.; Laubenheimer, M.; Hergesell, K.; Hoffmann, M.; Pehl, U.; Fischer, F.; Pieck, J.C.; Integration of an In Situ MALDI-Based High-Throughput Screening Process: A Case Study with Receptor Tyrosine Kinase c-MET. *SLAS Disc.* 2017, 22, 1203–1210.
- [3] VanderPorten, E.; Scholle, M.; Sherrill, J.; et al. Identification of Small-Molecule Noncovalent Binders Utilizing SAMDI Technology. *SLAS Discov.* 2017, 22(10):1211–1217.

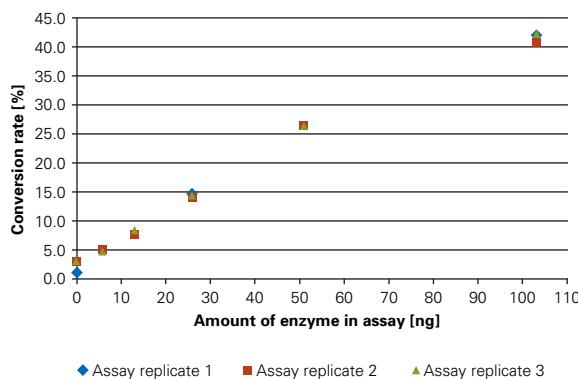


MALDI PharmaPulse assay development module to support assay development for HTS.

# Target evaluation and hit confirmation

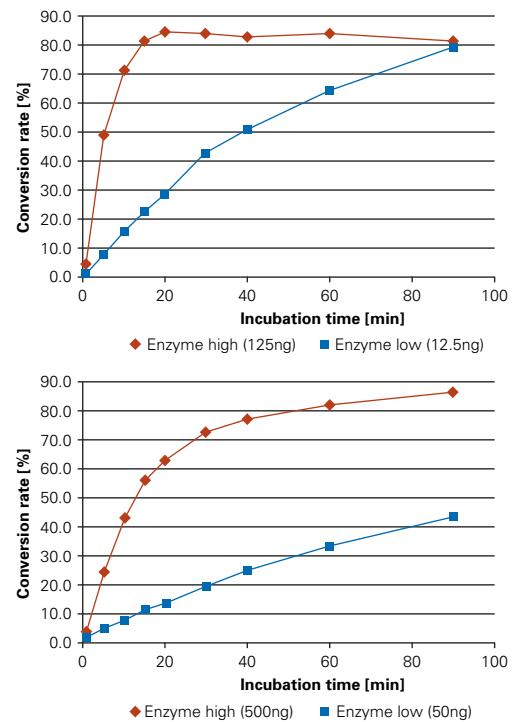
Thorough understanding of enzyme biochemistry and kinetics is essential to develop and validate robust HTS assays. rapiflex MPP assists assay development and hit confirmation with linearity tests, substrate selection, Ki measurements and IC<sub>50</sub> determination.

## Enzyme reaction linearity



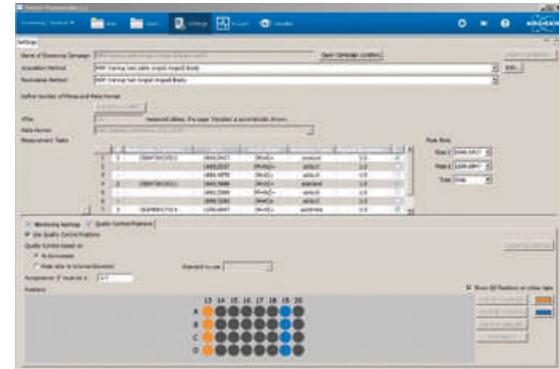
Linearity test: Enzyme titration curve based on 3 technical replicates indicates high level of reproducibility provided by the MALDI-TOF-based assay method.

## Time course study



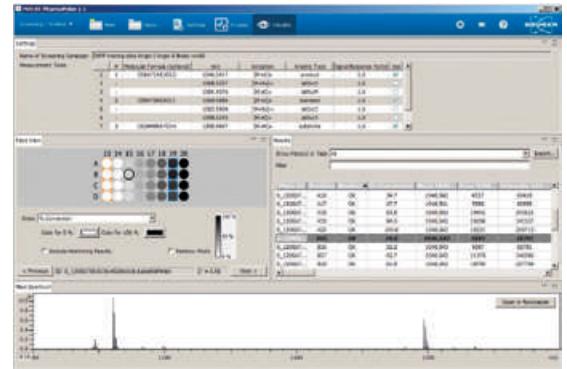
Time course studies performed for two different enzymes (kinases) applied at high and low concentration. Resulting Z' of >0.9 indicates outstanding robustness of the MALDI-TOF-based assay. Validated by radiometric measurements (<sup>33</sup>P).

## MPP software: Settings perspective



MALDI PharmaPulse software supporting easy setup of screening experiments. Color coded spots indicate QC positions for Z' calculation.

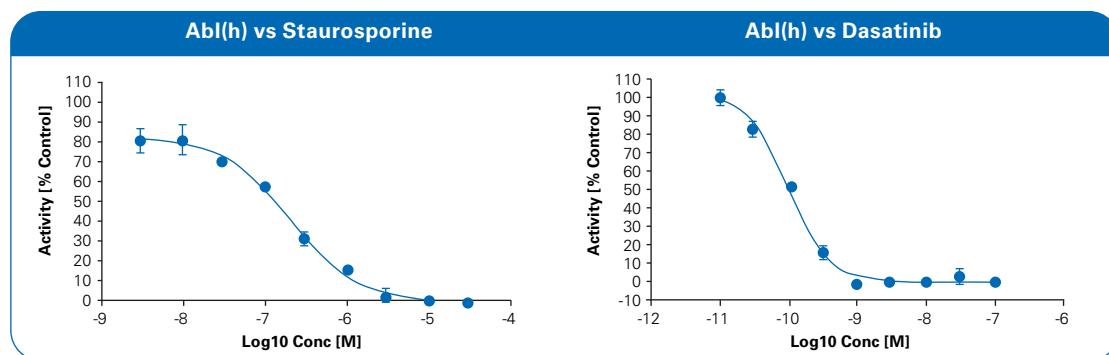
## MPP software: Visualize perspective



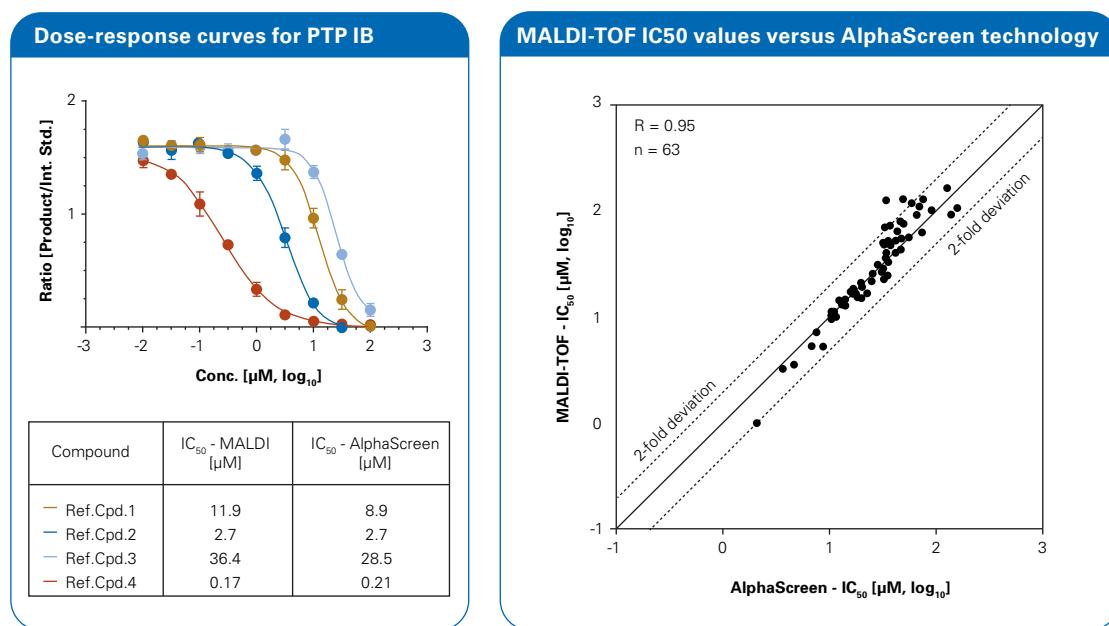
MALDI PharmaPulse software interface enabling instant display of screening results.

# Structure Activity Relationship (SAR) IC50 determination of inhibitors

Half-maximal inhibitor concentration (IC50) is a key parameter in the drug discovery process. MALDI PharmaPulse software supports assay development by featuring a dedicated method development module. Optimal assay conditions obtained using the method development module are applied during MALDI-TOF screening, for example aiming for IC50 determination, which is set up and executed in the software's dedicated screening module.



Dose-response curves obtained from rapifleX MPP measurements. IC50 curves are shown for selected enzymes (kinases): 50  $\mu$ M substrate, 45  $\mu$ M ATP and 3 nM enzyme. Validated by radiometric measurements ( $^{33}$ P).



Comparison of MALDI-TOF-based IC50 data with values obtained from AlphaScreen technology reveals high level of consistency. <sup>[4]</sup>

[4] Winter, M.; Bretschneider, T.; Kleiner, C.; Ries, R.; Hehn, J.P.; Redemann, N.; Luippold, A. H.; Bischoff, D.; Büttner, F. H.; Establishing MALDI-TOF as Versatile Drug Discovery Readout to Dissect the PTP1B Enzymatic Reaction. *SLAS Discov.* 2018, 10, 1-13.

# NEW MALDI PharmaPulse software

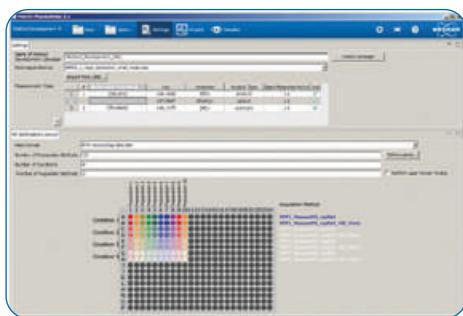
## Full automation including instant self-monitoring

*MALDI PharmaPulse (MPP) is a dedicated software suite to support all rapifleX applications for drug discovery workflows. The open interface design allows for integration with various automation solutions and works in concert with common scheduling software packages from a variety of vendors. Preparation of MALDI sample plates in various formats (384/1536), bar code handling, and seamless LIMS connectivity can be fully automated according to customer needs. The unique MPP assay development module supports assay developers in finding optimal assay conditions for biologically relevant assays.*

*A new intelligent QC module permits monitoring of all relevant parameters during an HTS campaign, including Z' values, enabling instant decision-making with regard to preparation and analysis of replicate sample plates in case of ambiguous first-round results.*

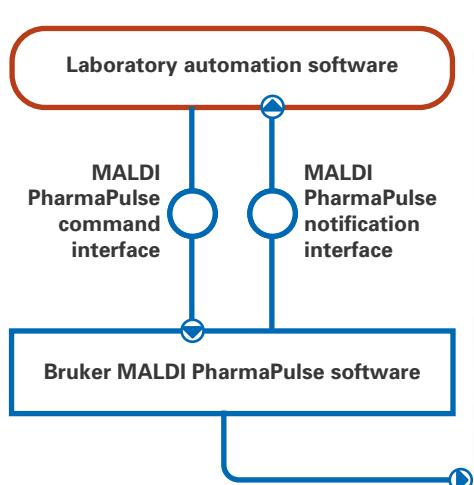
### **Genedata Ready-to-Run Integration**

The new MPP 2.1 software suite allows customers to easily import the results obtained from rapifleX MPP HTS campaigns into Genedata Screener for further data analysis.



### **rapifleX MPP automation interface**

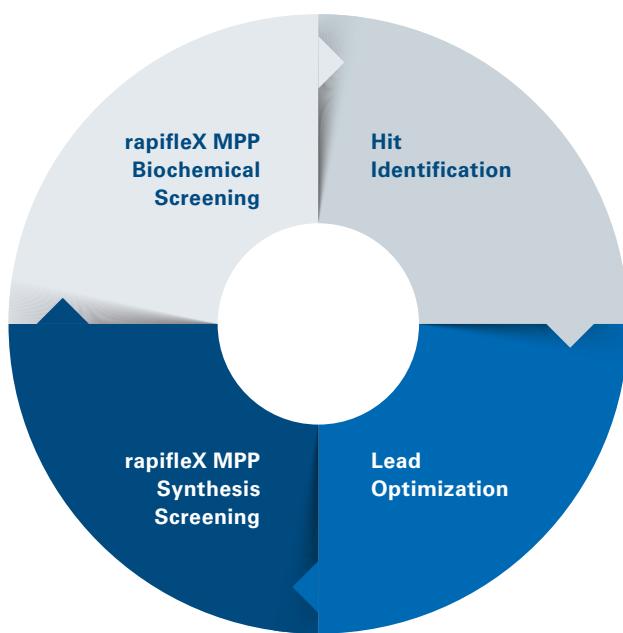
The MPP software suite works seamlessly with various scheduling software solutions.



# rapifleX MPP supports lead optimization

## New software module supports synthesis screening

In biochemical screening experiments, the rapifleX MPP determines the rate of conversion in a biochemical assay when performed in the presence of potential inhibitors. In such a screen, a distinct MS peak ratio comparing product and substrate intensities is monitored throughout large numbers of sample spots, where each spot represents the same biochemical conversion reaction, but measures the effectiveness of a different inhibitor molecule.



*rapifleX MPP in support of lead optimization*

In addition to this screening functionality, a new MPP software module will support "Synthesis Screening", a methodology that requires more flexibility with regard to  $m/z$  values to be targeted by MALDI-TOF MS. Here,  $m/z$  values of interest may vary from spot to spot as each sample may represent a different chemical reaction. Accordingly, the new MPP "Synthesis Screening" software module allows scientists to screen for a large number of compounds per individual sample spot. This new MALDI-TOF-based high-throughput analysis workflow could, therefore, enable highly time-efficient surveying of chemical reactivity landscapes at previously unseen mapping depth.<sup>[5]</sup>

[5] Lin, S.; Dikler, S.; Blincoe, W.D.; Ferguson, R.D.; Sheridan, R.P.; Peng, Z.; Conway, D.V.; Zawatzky, K.; Wang, H.; Cernak, T.; Davies, I.W.; DiRocco, D.A.; Sheng, H.; Welch, C.J.; Dreher, S.D.; Mapping the dark space of chemical reactions with extended nanomole synthesis and MALDI-TOF MS. *Science* 2018, 10.1126/science.aar6236 (2018)

**The high sensitivity and ultimate speed of the rapifleX MPP makes it the ideal detector for miniaturized chemical synthesis screening. The new module allows the determination of different masses per spot and different masses from spot to spot.**

# **Surface plasmon resonance (SPR) for hit-to-lead confirmation and characterization**

## **Introducing Sierra SPR-32**

From fragment screening and epitope binning to kinetics and thermodynamics, Sierra SPR-32 provides industry-leading performance and throughput to support drug discovery workflows.

### **Throughput**

- 32 individually addressable detection spots
- 3000<sup>+</sup> samples per day
- 10,000<sup>+</sup> control-subtracted interactions per day

### **Flexibility**

- Process 1-8 samples per cycle
- Use up to 4 different buffers per assay
- 1 control + 31 active surfaces

### **Performance**

- Continuous flow microfluidics for accurate kinetics
- Fragment sensitivity
- Crude sample robustness



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