The Future Is Here: Precision Automation Demonstrates Its Value as a Tool for Accelerating Drug Discovery

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Background

With more than 70 FDA-approved small molecules, kinase inhibition continues to attract significant investment. Identification and characterization of novel inhibitors is a challenging, yet critical task which sets the tone for future successes and failures. Traditional single shot approaches do not meet current requirements for machine learning and carry significant risks of false negatives. Hit profiling has evolved this concept, generating potency estimates, reducing risks while providing contextual confidence. Accurate hit identification followed by high resolution, kinetic molecular profiling enhances outcomes ensuring better data-driven decision-making earlier in the process, saving time and resources, leading to superior molecular design.

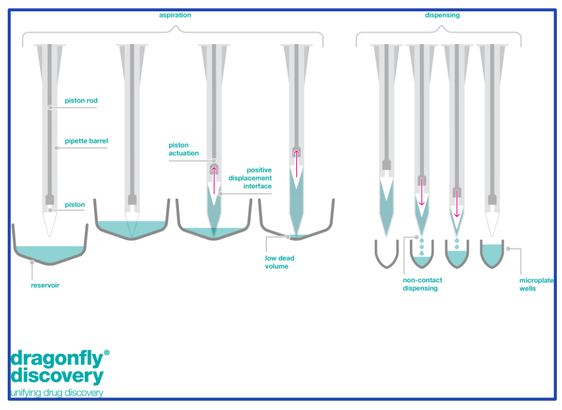


Figure 1. Dragonfly discovery delivers exquisite flexibility and control

Liquid Handling: flexibility and resolution are crucial

- True positive displacement, no valves or air-gaps
- Large aqueous dispense dynamic range (200 nL up to 200 µL, in 1 nL increments)
- Significantly reduced dead volumes, further enhanced by use of auto-feed reservoir
- Can dispense any liquid class (including 70 % glycerol)
- Complemented with digital picoliter dispenser enabling independent, generation of non-serial and asymmetric titrations (virtually impractical using conventional tech)
- Flexible, intuitive, easy-to-use software

Accelerated Assay Onboarding

Reagent characterization, assay development, instrument calibration and optimization were expedited using systematic theory and data-driven experimental design principles. Molecular profiling was executed on Arctoris' Ulysses platform using proprietary experimental and analytical pipelines supported by versatile, non-contact automated liquid handling, providing 9 orders of magnitude range in volume at picolitre resolution, enabling experiments to be digitally dispensed for each molecule.

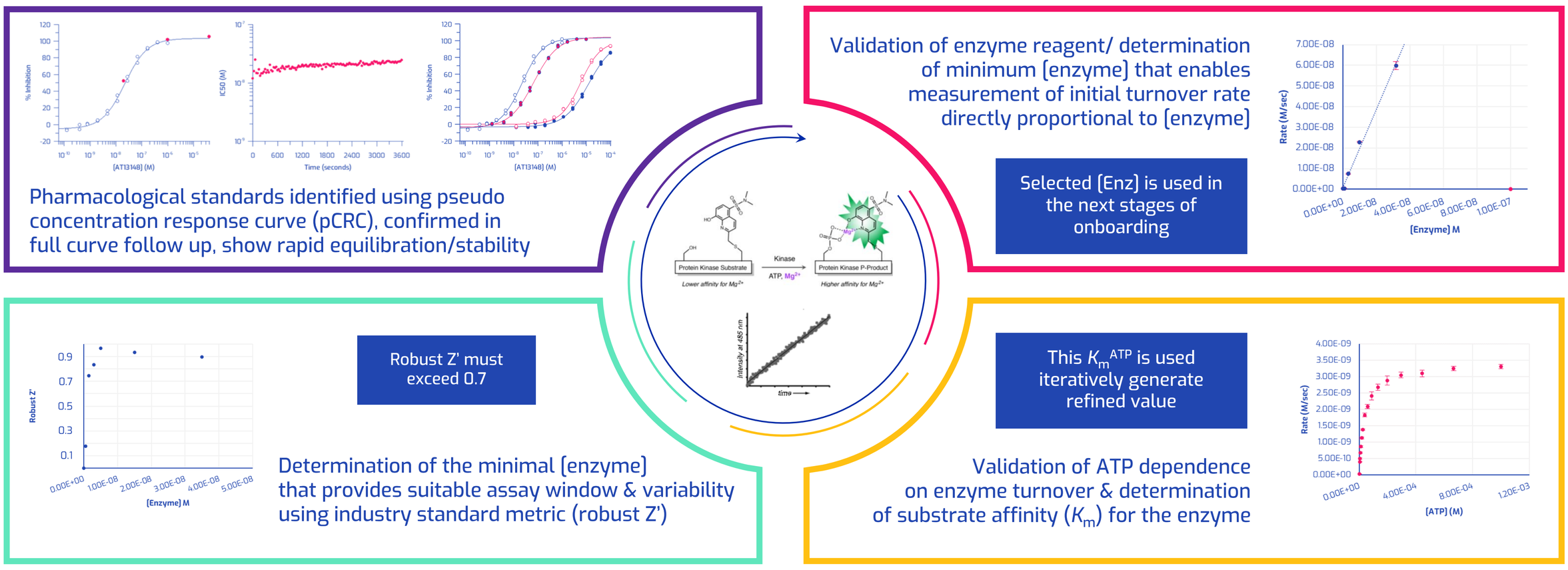
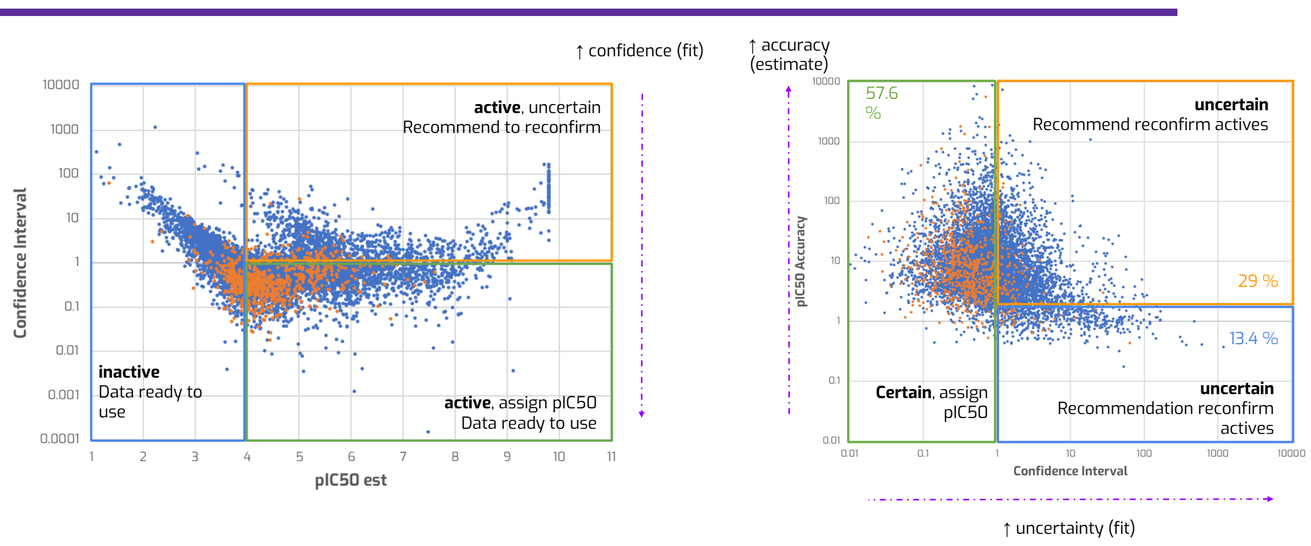


Figure 2. Assay onboarding process map highlighting key stages is routinely completed within a matter of hours from receipt of reagents

Impact and Future Direction



Challenge:

- 100,000s IC50s required for large ML training dataset
- Potential cost of traditional approach: $80-120M
- Extreme precision and consistency required for ML

Innovation:

- Simulation-driven experimental design
- Proprietary automation technologies
- Proprietary analytical pipelines and algorithms
- Automation delivered enabling assay quality: Z' >0.85

Value:

- >80% reduction in full-curve IC50 generation
- Screening 1,000s compounds against 100s targets can be delivered in months not years

Figure 3. Hit profile of 22,500 molecule/target pairs highlighting confidence in the fit of the pIC50 estimate (CI) vs. the estimated pIC50 (qualitative metric; *left*) and accuracy of this prediction relative to a full 11-pt curve value (reproducibility metric; *right*)

- Robotics-enabled inhibitor profiling concept provides unparalleled data capture, going beyond current state-of-the-art of biochemical assay setup
- 9 orders of magnitude concentration range and contact-free dispensing deliver non-serial, independent experiments enabling molecule-specific design
- Differentiated triage strategies enable utilization of data to support machine learning and more traditional hit discovery activities

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