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Adapta™ Universal Kinase Assay User Guide

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1. Adapta™ Assay Principle

The Adapta™ Universal Kinase Assay is a homogenous, fluorescent-based immunoassay for measuring kinase activity by correlating ADP formation with substrate phosphorylation. The Adapta™ assay utilizes the Transcreener™ HTS Assay Platform technology (patent pending) under license from Bellbrook Labs, LLC. In contrast to ATP depletion assays, the Adapta™ assay is extremely sensitive to ADP formation, such that a majority of the signal change occurs in the first 10–20% conversion of ATP to ADP. This makes the Adapta™ Universal Kinase Assay ideally suited for use with low-activity kinases. In addition, the Adapta™ assay kit can be optimized for use with a wide range of ATP concentrations (1–500 µM). This eliminates the need to purchase an individual assay kit for each ATP range.

The assay can be divided into two phases: a kinase reaction phase and an ADP detection phase. Figure 1 shows an illustration of an uninhibited and inhibited Adapta™ Universal Kinase Assay.

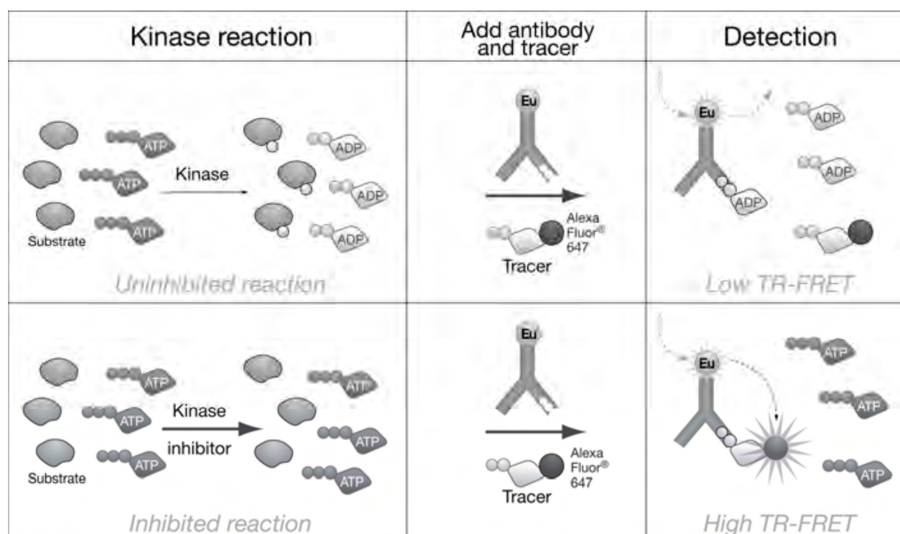

Figure 1. Schematic of the Adapta™ Universal Kinase Assay

In the kinase reaction phase, all components required for the kinase reaction are added to the well, and the reaction is allowed to incubate for a set period of time, typically 60 minutes. After the reaction, a detection solution consisting of a europium-

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labeled anti-ADP antibody, an Alexa Fluor® 647-labeled ADP tracer, and EDTA (to stop the kinase reaction) is added to the assay well. In the absence of an inhibitor, ADP formed by the kinase reaction will displace the Alexa Fluor® 647-labeled ADP tracer from the antibody, resulting in a decrease in the TR-FRET signal. In the presence of an inhibitor, the amount of ADP formed by the kinase reaction is reduced and the resulting intact antibody-tracer interaction results in a high TR-FRET signal.

2. Materials

2.1 Materials Supplied

Description	Composition	Quantity	Storage
Adapta™ Eu-anti-ADP Antibody	Europium-labeled anti-ADP antibody in HEPES buffered saline (see product label for exact concentration)	4 µg	-20°C
10 µM Alexa Fluor® 647 ADP Tracer	10 µM Alexa Fluor® 647 ADP Tracer in HEPES-buffered saline	200 pmol	-20°C
10 mM ATP	10 mM ATP in water	500 µL	-20°C
10 mM ADP	10 mM ADP in water	500 µL	-20°C
5X Kinase Buffer A	250 mM HEPES pH 7.5, 0.05% Brij-35, 50 mM $MgCl_2$, and 5 mM EGTA	4 mL	20-30°C
Kinase Quench Buffer	500 mM EDTA	1 mL	20-30°C
TR-FRET Dilution Buffer	Proprietary buffer, pH 7.5	100 mL	20-30°C

2.2 Materials Required but Not Supplied:

- **Kinase:** Visit www.invitrogen.com/kinases for a complete list of Invitrogen kinases.
- **Kinase substrate:** A wide range of peptide and lipid substrates are available for use with the Adapta™ Universal Kinase Assay kit. Visit www.invitrogen.com/adapta to see if a substrate is available for your specific kinase.
- **A fluorescent plate reader capable of TR-FRET measurements with excitation at 340 nm and emission at 615 nm and 665 nm:** See **Section 7** for typical instrument settings.
- **Pipetting devices for 1–1000 µL volumes, suitable repeater pipettes, or multi-channel pipettes**
- **White, 384-well assay plates:** We recommend white Corning® 384-well, low-volume, round-bottom (non-treated) assay plates (#3674). Other low-volume assay plates, while not tested, may be suitable.
- **Assay Buffer:** The Adapta™ Universal Kinase Assay kit comes with a generic kinase assay buffer (Kinase Buffer A). Depending on the specific kinase, buffer additives or an alternative assay buffer may be required to achieve optimal performance. Visit www.invitrogen.com/adapta to see if there are any buffer considerations for your kinase.

3. Assay Optimization

Note: We suggest that you verify instrument performance with the Adapta™ assay before performing the optimization experiments outlined below. Perform the titration in **Section 5** to verify the performance of your plate reader.

Optimization of an Adapta™ kinase assay takes place in two steps:

Step 1: Optimization of the concentration of Alexa Fluor® 647 ADP Tracer. The optimal concentration of tracer in the detection solution depends on the concentration of ATP used in the assay. Optimal tracer concentrations for a variety of ATP concentrations in assays using Kinase Buffer A are listed on the Certificate of Analysis (COA) supplied with this kit. For different buffers and ATP levels, we recommend performing a titration of the Alexa Fluor® 647 ADP Tracer as described in **Section 3.1**.

Step 2: Optimization of the concentration of kinase to be used in the assay. Once the optimal concentration of tracer has been determined, prepare a kinase titration to identify the optimal kinase concentration to use in determining IC_{50} values of inhibitors.

A growing number of Invitrogen kinases have been validated for use with the Adapta™ Universal Kinase Assay kit. Visit www.invitrogen.com/adapta for a list of kinases that have been validated with Adapta™.

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3.1 Optimization of Alexa Fluor® 647 ADP Tracer Concentration

List of Tracer Concentrations on the Certificate of Analysis

If you are using Kinase Buffer A supplied with the kit as described in this protocol (a 10-µL kinase assay in Kinase Buffer A, followed by a 5-µL addition of detection solution), then the optimal concentration of Alexa Fluor® 647 ADP Tracer for various ATP concentrations is printed on the Certificate of Analysis (COA) supplied with this kit, and you can proceed directly to **Section 3.2**.

Preparing a Tracer Titration

If you modify either the assay buffer or ATP concentration, you will need to optimize the Alexa Fluor® 647 ADP Tracer concentration as outlined in the procedure below. In assay buffer with the desired concentration of ATP to be used in the assay, titrate the Alexa Fluor® 647 ADP Tracer against 2 nM europium-labeled anti-ADP antibody to determine the tracer concentration required to elicit an approximately 50% change between the minimum and maximum TR-FRET emission ratios (the EC_{50} value). This is the tracer concentration that will be used in the detection solution for the following optimization steps and inhibition titrations.

To prepare a tracer titration:

1. Prepare a 5 mL solution of ATP in kinase assay buffer. The concentration of ATP in the assay buffer should be equal to the concentration of ATP that will be used in the kinase assay. (*i.e.,* if [ATP] in assay = 10 µM then prepare a 5 mL solution of 10 µM ATP in kinase assay buffer).
2. In a low-volume 384-well plate, fill each well in columns 1–3, rows 2 through 16 (B through P) with 10 µL of kinase reaction buffer containing ATP.
3. In an appropriate tube or vial, prepare a 100 µL solution of 300 nM Alexa Fluor® 647 ADP Tracer in the kinase reaction buffer with ATP. Since the tracer is supplied at a concentration of 10 µM, adding 3 µL of concentrated tracer to 97 µL of kinase reaction buffer will provide a 300 nM solution of tracer.
4. Add 20 µL of the 300 nM ADP Tracer solution to the top well of columns 1–3.
5. Perform a 2-fold serial dilution of tracer down the plate by removing 10 µL of solution from the top well, adding this to the well below, mixing, and repeating with the next well below. Discard 10 µL of solution from the bottom well such that each well contains 10 µL of solution.
6. In TR-FRET Dilution Buffer, prepare a solution of Kinase Quench Buffer and Adapta™ Eu-anti-ADP antibody at 3 times the desired final concentrations of each reagent.

Reagent	1X Conc.	3X Conc.
Adapta™ Eu-anti-ADP antibody	2 nM	6 nM
Kinase Quench Buffer (500 mM EDTA)	10 mM	30 mM

Note: While the Eu-labeled antibody is stable in 30 mM EDTA, higher concentrations EDTA can remove the europium from the antibody. To prevent this, do not add the antibody directly to the Kinase Quench Buffer. Instead, add Kinase Quench Buffer to the TR-FRET Dilution Buffer first, mix well, and then add antibody.

7. Add 5 µL of the Antibody + Kinase Quench Buffer solution to each well of the assay plate
8. Cover the assay plate and incubate for at least 30 minutes at room temperature before reading on an appropriate plate reader.
9. Plot the resulting TR-FRET emission ratio against the concentration of Alexa Fluor® 647 ADP Tracer, as shown in Figure 2. The final concentration of ADP tracer in the first well was 200 nM and a 2-fold serial dilution was performed. Fit the data to a sigmoidal dose-response curve with a variable slope and calculate the EC_{50} concentration from the curve. This is the concentration of tracer that will be used in the detection solution for the following optimization steps and inhibition titrations.

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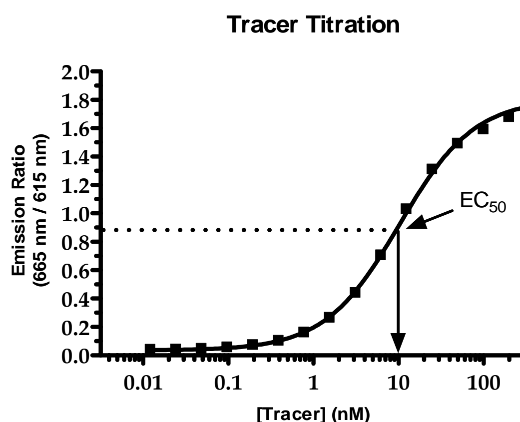

Figure 2. Titration of Alexa Fluor® 647 ADP Tracer against 2 nM Eu-anti-ADP antibody in the presence of 10 µM ATP.

3.2 Optimization of Kinase Concentration

Following the optimization of the tracer concentration, prepare a dilution series of kinase to determine the amount of kinase necessary to displace 70–80% of the ADP tracer from the antibody (*i.e.*, to observe a 70–80% decrease in assay signal, the EC_{80}). This is the concentration of kinase that will be used in the inhibitor titration experiments to determine an IC_{50} value for an inhibitor.

To perform the kinase titration, a 5-µL serial dilution of kinase (at 2X the desired final concentration) is prepared in kinase reaction buffer without ATP in a 384-well plate. To start the kinase reaction, 5 µL of a solution consisting of 2X substrate and 2X ATP is added to each well.

Note: **It is important that the final concentration of substrate present in the reaction is equal to or greater than the concentration of ATP used in the reaction.**

Following a 60-minute reaction, add 5 µL of a 3X detection solution consisting of Adapta™ Eu-anti-ADP antibody (3X concentration = 6 nM), Alexa Fluor® 647 ADP tracer (3X concentration is based upon tracer optimization step above), and EDTA (3X concentration = 30 mM). After an additional 30-minute equilibration period, the plate is read with an appropriate plate reader. A detailed protocol follows below.

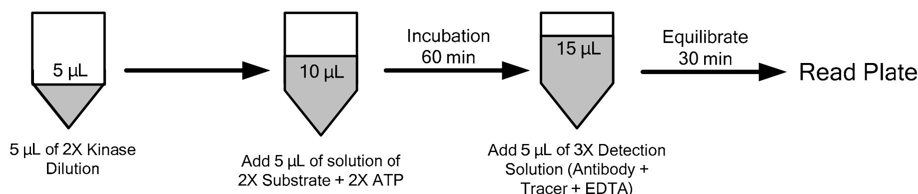

Figure 3. Schematic of the Kinase Titration.

Kinase Titration:

1. In an appropriate tube or vial, prepare a solution of kinase in assay buffer at 2 times the highest concentration of kinase to be tested.
2. In a low-volume 384-well plate, fill each well in columns 1–3, rows 2 through 16 (B through P) with 5 µL of kinase reaction buffer.
3. Place 10 µL of the kinase solution as prepared above in the top well of each column, and then perform a 2-fold serial dilution down the plate by removing 5 µL of kinase from the top well, adding this to the well below, mixing, and repeating with the next well below. Discard 5 µL of solution from the bottom well such that each well contains 5 µL of kinase solution.
4. In an appropriate container, prepare a solution of substrate and ATP in reaction buffer at 2 times the final concentration of each reagent desired in the assay.
5. Initiate the kinase reaction by adding 5 µL of the 2X solution of substrate and ATP prepared above to each well of the assay plate.

6. Cover the assay plate and allow the reaction to proceed for 60 minutes at room temperature.
7. Prepare detection solution (Adapta™ Eu-anti-ADP antibody, Alexa Fluor® 647 ADP tracer, and EDTA) at 3 times the desired final concentrations of each reagent in TR-FRET dilution buffer. The concentration of Alexa Fluor® 647 ADP tracer determined from the ADP tracer optimization above (or from the certificate of analysis) should be used.

Reagent	1X Conc.	3X Conc.
Adapta™ Eu-anti-ADP antibody	2 nM	6 nM
Alexa Fluor® 647 ADP tracer	Varies	Varies
Kinase Quench Buffer (EDTA)	10 mM	30 mM

8. Add 5 µL of the detection solution to each well of the assay plate.
9. Cover the assay plate and allow the plate to equilibrate for at least 30 minutes at room temperature before reading with an appropriate plate reader.
10. Plot the resulting TR-FRET emission ratio against the concentration of kinase (ng/mL), as shown in Figure 4. Fit the data to a sigmoidal dose-response curve with a variable slope and calculate the EC_{80} concentration from the curve. The following equation can be used with GraphPad™ Prism® software:

F=80
logEC80=logECF-(1/HillSlope)*log(F/(100-F))
Y=Bottom+(Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))

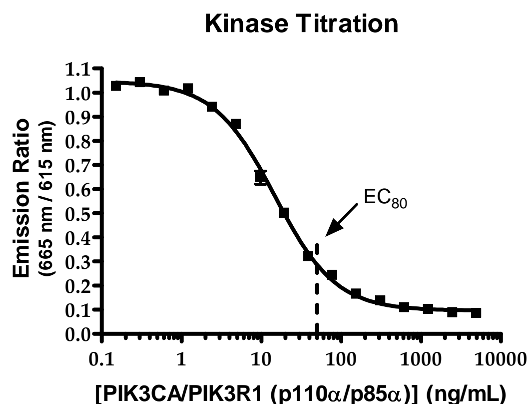

Figure 4. Example of a Kinase Titration Curve. Representative data from a kinase titration of PIK3CA/PIK3R1 (p110α/p85α) (PV4788) with PIP2:PS Lipid Kinase substrate (50 µM; PV5100)) with the Adapta™ Universal Kinase assay. The amount of kinase required to displace ~80% of the ADP tracer from the antibody (the EC_{80}) was determined for use in the inhibitor titrations in Section 4. The EC_{80} typically represents a 10–20% conversion of substrate when compared to an ATP-ADP titration curve (See section 5). In this particular example, approximately 50 ng/mL of kinase was equal to the EC_{80} value.

4. Inhibitor IC_{50} Determinations

After the kinase and tracer concentrations have been optimized, the kinase reaction can be performed in the presence of inhibitors. To perform the inhibitor titration:

1. Add 2.5 µL of a 4X solution of inhibitor, typically in 4% DMSO, to the wells of a 384-well plate.
2. Add 2.5 µL of a 4X solution of kinase to each well.
3. Add 5 µL of a 2X solution of substrate and ATP to initiate the reaction, and incubate for 60 minutes.
4. Following incubation, add 5 µL of a 3X detection solution consisting of Adapta™ Eu-anti-ADP antibody (3X concentration = 6 nM), Alexa Fluor® 647 ADP tracer (3X concentration based on tracer optimization step), and EDTA (3X concentration= 30 mM).
5. Equilibrate for 30 minutes, then read the plate and determine the amount of inhibitor required to elicit a 50% change in the TR-FRET ratio (the IC_{50}).

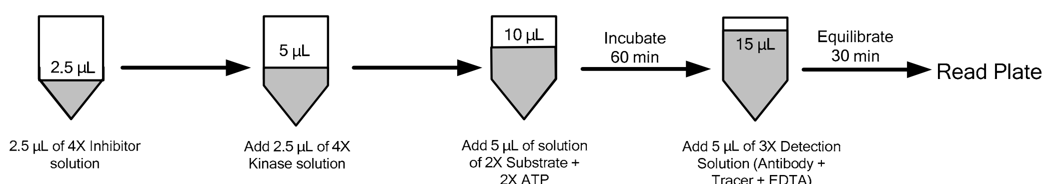

Figure 5. Schematic of the Inhibitor Titration.

For comparing inhibitors across multiple experiments, it may be advantageous to graph the inhibition titrations as % inhibition (instead of TR-FRET ratio) versus inhibition concentration. Use the following equation to convert from TR-FRET ratio to % inhibition:

$$\% \text{ inhibition} = \frac{100 \times (\text{Ratio}_{\text{sample}} - \text{Ratio}_{\text{0\% inhibition}})}{(\text{Ratio}_{\text{100\% inhibiton}} - \text{Ratio}_{\text{0\% inhibition}})}$$

The 0% inhibition value comes from a control well lacking inhibitor. The 100% inhibition value comes from a control well either containing a saturating amount of a known inhibitor, or lacking kinase. Because of the way the Adapta™ assay is formatted, the 100% inhibition control well cannot be a well simply lacking ATP.

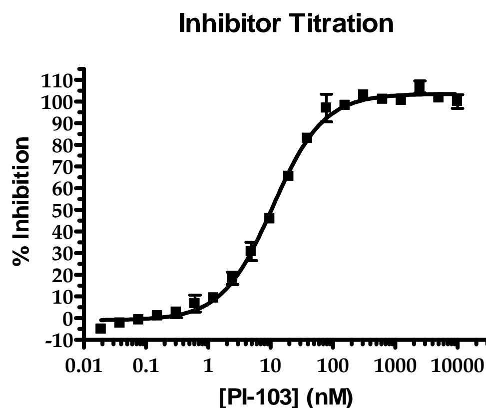

Figure 6. Example of an Inhibitor Titration Curve. Representative data from a titration of PI-103 with PIK3CA/PIK3R1 (p110α/p85α) (PV4788) with the Adapta™ Universal Kinase Assay. The TR-FRET ratios were converted to % inhibition to aid in the comparison of various inhibitors. An IC_{50} value of 10.7 nM was determined for PI-103.

5. ATP-ADP Titration Curve

The Adapta™ assay measures kinase activity by detecting ADP formation. The majority of the signal change occurs in the first 10–20% conversion of ATP to ADP (see Figure 7). This is in contrast to kinase assays that measure ATP depletion, in which a 20% depletion of ATP results in only a 20% change in the assay signal. As a result, the Adapta™ assay produces high Z'-factors

at low conversion percentages, and is ideally suited for use with low-activity kinases, since less ADP has to be formed to achieve an optimal assay window.

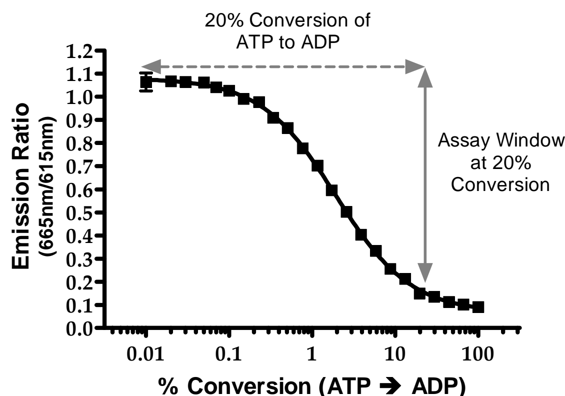

Figure 7. ATP-ADP Titration Curve with the Adapta™ Universal Kinase Assay. Due to the sensitivity of the Adapta™ assay to ADP formation, large assay windows are obtained at only 10–20% conversion of ATP to ADP. The above data is representative of a typical signal change that occurs at ATP concentrations from 1–500 µM.

An ATP-ADP titration curve can be useful for instrument optimization, or to ensure that the assay is being performed under conditions of initial rates (typically < 20% conversion of substrate to product). Since the interaction of the europium-labeled antibody and the ADP tracer is dependant on the total amount of ATP and ADP present, it is important to maintain a constant nucleotide concentration in the ATP-ADP titration curve.

For ease of preparation, an ATP-ADP titration curve can be prepared in a 96-well plate and then transferred to the respective wells of a 384-well plate. The serial dilutions are "staggered" between columns of a 96-well plate and then transferred to the 384-well plate, as shown in Figure 8. To prepare a titration curve:

1. Prepare a 4 mL solution of ATP and a 1 mL solution ADP such that each is at the desired concentration of ATP that will be used in the kinase assay (*i.e.*, if [ATP] in assay = 10 µM, then prepare a 4 mL solution of 10 µM ATP and a 1 mL solution of 10 µM ADP, each in kinase assay buffer).
2. Place 100 µL of the ATP solution to every well of column 1 and 2 of the 96-well plate ***EXCEPT*** well A-1. To well A-1, add 300 µL of the ADP solution.
3. Transfer 200 µL of solution from well A-1 to well A-2 and mix thoroughly. Next, transfer 200 µL of solution from well A-2 to well B-1 and mix thoroughly. Repeat this process for all remaining wells, discarding 200 µL of reagent from the final well (see Figure 8).

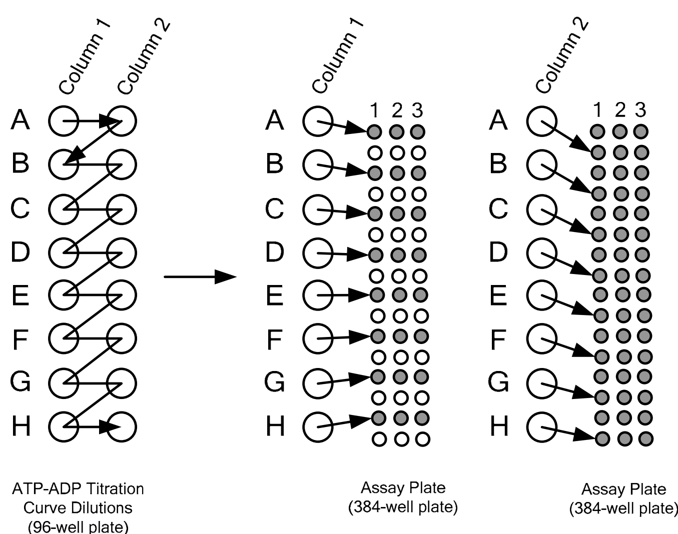

Figure 8. Diagram showing preparation of an ATP-ADP titration curve in a 96-well plate followed by transfer to a 384-well plate.

4. Using a multi-channel pipette, transfer 10 µL of the ATP-ADP titration curve in the 96-well plate to the respective wells of a 384-well plate as shown in Figure 8. Reagent from column 1 of the 96-well plate is placed in rows 1, 3, 5, etc. of the 384-well plate, and reagent from column 2 of the 96-well plate is placed in alternate rows (2, 4, 6, etc.) of the 384-well plate.

5. Add 5 µL of 3X detection solution consisting of Adapta™ Eu-anti-ADP antibody (3X concentration = 6 nM), Alexa Fluor® 647 ADP tracer (3X concentration based on tracer optimization step above), and EDTA (3X concentration= 30 mM) to each well.

6. Cover the assay plate and allow the plate to equilibrate for at least 30 minutes at room temperature before reading on an appropriate plate reader. An example percent conversion table is shown below.

Well in 96-well plate	Corresponding row in 384- well plate	% Conversion of ATP to ADP
A1	A	100.0%
A2	B	66.7%
B1	C	44.4%
B2	D	29.6%
C1	E	19.8%
C2	F	13.2%
D1	G	8.8%
D2	H	5.9%
E1	I	3.9%
E2	J	2.6%
F1	K	1.7%
F2	L	1.2%
G1	M	0.8%
G2	N	0.5%
H1	O	0.3%
H2	P	0.2%

Figure 9. Percent conversion of ATP to ADP based on an ATP-ADP titration curve with a total nucleotide concentration of 10 µM. The calculations are based upon a 1.5-fold serial dilution within the ATP-ADP titration curve.

6. Assays for Kinases Exhibiting a High Degree of Substrate-Independent ATPase Activity

Since the Adapta™ assay monitors kinase activity by correlating ADP formation to substrate phosphorylation, the Adapta™ assay can be used with kinases that exhibit a high degree of substrate-independent ATPase activity. For these particular kinases, the substrate is water, and the Adapta™ assay monitors the formation of ADP resulting from the "phosphorylation" of water (Kashem *et al.*, 2007).

For kinases that exhibit substrate-independent ATPase activity, the Adapta™ Universal kinase assay is optimized and performed as outlined above except the substrate is removed from the reaction. Figure 10 shows example data for such a kinase. While it is possible to monitor substrate-independent ATPase activity with Adapta™, it is important to validate the pharmacology of the kinase with known inhibitors to ensure that you are monitoring activity from the desired kinase and not from a contaminating protein.

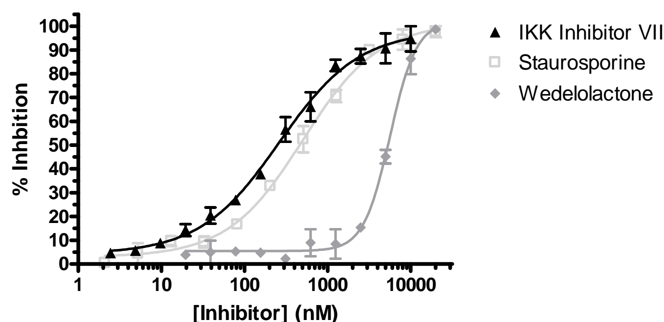

Figure 10. Inhibitor Titrations with CHUK. The intrinsic ATPase activity of CHUK (IKKα; PV4310) allows the kinase to be assayed in a substrate-independent manner with the Adapta™ Universal Kinase assay. The pharmacology of some known inhibitors of CHUK (IKK Inhibitor VII, Staurosporine, and Wedelolactone) showed a high degree of correlation to literature values when assayed without a substrate.

7. Instrument Settings

In general, instruments, instrument settings, and filters that work with other europium-based TR-FRET assay systems will perform well with the Adapta™ Universal Kinase Assay. As with other TR-FRET systems, the europium donor is excited using a 340-nm excitation filter with a 30-nm bandpass. Energy transfer to the Alexa Fluor® 647 tracer is measured using a filter centered at 665 nm with a 10 nm bandpass, and this signal is referenced (or "ratioed") to the emission from europium peak, using a 615 nm, 10-nm bandpass filter. The "emission ratio" is calculated as the 665 nm signal divided by the 615 nm signal.

Guidelines provided by the instrument manufacturer can be used as a starting point for optimization. A delay time of 50–100 µs followed by a 200–400 µs integration time would be typical for an Adapta™ assay. The number of flashes or measurements per well is highly instrument dependant and should be set as advised by your instrument manufacturer. In general, Adapta™ assays can be run on any filter-based instrument capable of time-resolved FRET, such as the Tecan Infinite® F-500, BMG LABTECH PHERAstar, Molecular Device's Analyst™, or PerkinElmer's EnVision™. CCD-based "imaging" readers such as the PerkinElmer ViewLux are also capable of reading Adapta™ assays. Monochromater-based instruments such as the Tecan Safire^2 or MolecularDevices M5 are also capable of reading TR-FRET, but with data quality that is often less than that seen with filter-based instruments.

Ask your Invitrogen representative for instrument-specific setup guidelines, or contact Invitrogen Discovery Sciences technical support at 800-955-6288 (select option 3 and enter 40266), or email tech_support@invitrogen.com for more information on performing Adapta™ assays on your particular instrument.

8. References

1. Kashem, M. A., Nelson, R. M., Yingling, J. D., Pullen, S. S., Prokopowicz, A. S. r., Jones, J. W., Wolak, J. P., Rogers, G. R., Morelock, M. M., Snow, R. J., Homon, C. A., and Jakes, S. (2007) Three mechanistically distinct kinase assays compared: Measurement of intrinsic ATPase activity identified the most comprehensive set of ITK inhibitors. *J. Biomol. Screen.*, *12*, 70-83

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