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CUSTOM KINASE SUBSTRATE PEPTIDE PROFILING

1. INTRODUCTION

The vast majority of the proteins phosphorylated by specific protein kinases in humans and other species are unknown after more than 40 years of intense effort. However, with the emergence of protein kinases as one of the most promising families of drug targets in the pharmaceutical industry today, it is critical to define the proteins that are controlled by these important regulatory enzymes. In response to this challenge, Kinexus has developed a suite of diverse proteomics and bioinformatics services to permit identification of protein kinase substrates. Our Custom Kinase Substrate Peptide Profiling Service uniquely permits experimental definition of key substrate specificity determinants for most known protein kinases. This permits the development of artificial substrates for protein kinases that may be useful for high throughput drug screening and can help identify physiological substrates of protein kinases of interest. Our methodology is superior to other more random peptide arrays that are available from competitors, because the peptide sequences on our microarrays have been pre-selected with our bioinformatics program at Kinexus. With this flexible and convenient protein kinase specificity identification service, clients can send us their own preparations of protein kinases or choose from our vast collection of over 340 diverse and active human kinases. Within three to four weeks of receipt of a client order, Kinexus will provide information about the best peptides from our panel of 445 optimal kinase substrate peptides. Alignment of the amino acid sequences of the best performing peptides for a target kinase permits definition of the key positive determinants for specific kinase substrate recognition. The results from this unique service can be used to define signalling pathways impacted by specific kinases, identify reagents to enable kinase inhibitor discovery in vitro, and ascertain the effectiveness and specificity of kinase inhibitor drugs in living systems.

As a fruit of our bioinformatics efforts, Kinexus recently launched the PhosphoNET KnowledgeBase (www.phosphonet.ca). PhosphoNET is an open access, online resource from Kinexus that features over 93,000 experimentally confirmed human phosphosites as well as an additional 560,000 predicted phosphosites. Each of these phosphosites is profiled for their evolutionary conservation in over 20 other species, and prediction of the top 50 human kinases that target these phosphosites is also provided. These kinase substrate predictions were generated with a novel algorithm developed by Kinexus and its academic partners at the University of British Columbia and Simon Fraser University.

The Kinexus Kinase Predictor algorithm utilized our in-house databases of the carefully aligned sequences of 488 human protein kinase catalytic domains and 10,000 known kinase-substrate phospho-site pairs. From this data and the application of our algorithm, we have been able to generate predicted phospho-site amino acid frequency matrices for any "typical" protein kinase for which the catalytic domain sequence is known and these are available

to clients with our In Silico Kinase Specificity Prediction (IKSP) Service. Our Kinase Predictor algorithm has wider application to other species, including those as diverse as budding yeast. It is also useful for prediction of the possible effects of mutation of human kinases within their catalytic domains on their substrate specificities. These kinase specificity matrices feature the expected probability frequencies of each of the 20 amino acids, 7 amino acids before and after the phospho-acceptor amino acid. The identification of positive and negative determinants in the surrounding amino acids of phosphorylation sites permits the creation of position-specific scoring matrices (PSSM) for each protein kinase. This has allowed Kinexus to produce PSSM's for 488 human protein kinase domains to test any known or putative phosphorylation site as a substrate for all of these protein kinases *in silico*. The results of these analyses for 650,000 confirmed and predicted human phospho-sites are freely available for viewing at PhosphoNET. Our Kinase Predictor algorithm is not perfect and has limitations, but it is the most accurate and versatile bioinformatics method available for this purpose at this time.

While our *in silico* kinase substrate predictions have proven to have high concordance with experimental observations, there remains almost no supporting empirical data for about two thirds of the known human protein kinases. Furthermore, the Kinexus Kinase Predictor Algorithm was developed for the typical protein kinase families, and it will not work with the 38 known atypical human protein kinases. PhosphoNET does provide substrate predictions for 4 of the atypical kinases of the PIKK family (i.e. ATM, ATR, DNAPK and mTOR/FRAP), based on amino acid alignment of phosphosites of some of their known protein substrates.

Most of the known phosphorylation sites have been elucidated through application of tandem MS-MS mass spectrometry. Kinexus offers such a mass spectrometry-based method for kinase substrate identification in cell and tissue lysates with our Mass Spectrometry Kinase Substrate (MSKS) Profiling Service. This powerful and sensitive method can permit identification of hundreds of phosphosites at once, but for most of these phosphorylation sites, commercial phosphosite-specific antibodies are not available. It can take more than 6 months at high expense to develop reliable phosphosite-specific antibodies for their detection by immunoblotting and immunohistochemistry. With the availability of several hundred commercial antibodies from several vendors, Kinexus has reversed the paradigm for kinase substrate discovery by combining our Kinex™ antibody microarray and Kinetworks™ multiimmunoblotting capabilities in our In Vitro Kinase-Substrate ID Custom Kinase Substrate Profiling (CKSP) service. With these methodologies, Kinexus uses panels of phosphosite antibodies to detect known and cross-reactive proteins that display altered phosphorylation in living systems in response to hormonal and pharmacological manipulations or, as with our CKSP service, increased phosphorylation in vitro with purified kinases. Any crossreactive proteins can be easily enriched with the detecting phosphosite antibody and identified with our Protein Identification by Mass Spectrometry (PIMS) Services. Moreover, since the phosphosite epitope of the detection antibody is known, it is often easy to locate the affected phosphorylation site without further sequencing. Thus antibody-driven phosphoprotein discovery is highly cost effective, informative and enabling for immediate follow up analyses with other methodologies that exploit antibodies.

2. SERVICE DESCRIPTION

To expand the range of techniques available from Kinexus to elucidate the protein substrate requirements of kinases, Kinexus has developed its first peptide microarray for characterization of the specificities of these enzymes. Previously, others have used peptide arrays to investigate the substrate specificity of protein kinases. However, such arrays feature peptide sequences that have corresponded to known phosphosites or random peptides and were not optimal for any protein kinase. The 445 peptides spotted in triplicate on the Kinex™ Kinase Substrate Microarray are based on the optimum phosphosite sequences deduced for all of the typical human protein kinase catalytic domains with our Kinase Predictor algorithm. Each Kinex™ Kinase Substrate Microarray permits the testing of 3 different protein kinases and a control incubation that monitors the background binding of the phosphorylation detection stain to unphosphorylated peptides. Incubation of the Kinex™ Kinase Substrate Microarray with purified protein kinases results in the highest phosphorylation for those peptides that conform to the best structures for access to the active sites of these kinases. The phosphorylation of these peptides is detected with a commercial stain for bound phosphate that is measured with our fluorescent scanners and quantification software. Alignment of the sequences of those peptides with the greatest incorporation of phosphate provides for the generation of an optimal consensus sequence for the tested protein kinase.

Clients are able to provide their own preparations of purified protein kinases for use with the KKSM services. Alternatively, for a fee, clients can choose from our growing inventory of over 340 active, human protein kinases as well as more than 60 additional mutant forms of these kinases. A listing of our most recent inventory of these kinases and their prices are provided in Appendix 1 and can be downloaded from our website. Kinexus sources many of these protein kinases from other vendors, and the added fee is based on our cost recovery. Consequently, the sliding price scale for these enzymes reflects the purchase price of these kinases by Kinexus. We are pleased to identify the commercial source of each protein kinase that we use upon request.

3. EXAMPLES OF PROTEIN KINASE SUBSTRATE SPECIFICITY DETERMINATIONS

To illustrate the power of our Kinex™ Kinase Substrate Peptide Microarray Profiling Service, we have provided four examples with well known protein kinases in this section of this customer information package. We have also provided the deduced consensus sequences of these kinases as determined by alignment of known substrate protein phosphosites and by using our Kinase Predictor algorithm.

Table 1 provides the results of Kinex™ Kinase Substrate Peptide Microarray analysis with the MAP kinase Extracellular Regulated Kinase 2 (ERK2), which is a well known proline-directed protein-serine/threonine kinases. In this example, note that the predicted optimum sequence generated with our Kinase Predictor algorithm is not the best sequence for actual recognition by this kinase. This is because while the occurrence of multiple proline residues surrounding the phosphosite amino acid are positive determinants for ERK2 recognition, optimal substrate peptides do not feature a proline residue at each position in the same substrate peptide.

Table 1. Detection of increased phosphorylation of synthetic peptides on the Kinex™ Kinase Substrate Microarray with addition of active recombinant human ERK2. The strength of the detection of phosphate signal from the average value from triplicate measurements is provided.

		Observed Phosphorylation											
-6	-5	-4	-3	-2	-1	0	_1_	2	3	4	5	6	
G	R	G	R	Р	ı	S	Р	G	K	K	G	G	6385
G	G	G	R	Р	L	S	Р	G	K	K	G	G	5431
F	L	S	R	R	ı	S	F	С	N	F	K	Н	2630
G	G	G	R	Р	L	S	Р	V	K	K	G	G	2498
G	R	D	R	R	1	S	F	R	G	G	G	G	2475
G	R	S	R	Р	ı	S	Р	G	G	G	G	Υ	1630
W	R	S	R	Р	L	S	Р	G	K	С	Т	Υ	1482
G	G	G	D	G	М	S	V	Е	Р	G	G	G	1312
ı	G	G	F	Р	ı	S	Р	Υ	V	G	G	G	982
G	R	S	R	Р	L	S	Р	С	K	K	G	G	901
G	R	S	R	Р	L	S	Р	G	K	G	G	Υ	892
G	R	S	R	Т	G	S	P	G	Α	G	G	Н	810
G	R	S	R	L	L	S	Р	G	Р	G	G	G	798
С	D	G	R	Н	G	Т	Р	Υ	K	K	G	G	783
G	R	S	R	R	G	S	F	С	Н	K	Т	G	752
G	G	S	F	Р	ı	S	P	G	K	K	G	G	744
F	R	G	R	R	D	S	P	R	K	K	М	Н	722
X	r	Х	R	Р	il	S	р	Х	k	k	Х	Х	Peptide Consensus
X	р	t	р	Р	ı	St	Р	р	Х	t	р	Х	Protein Consensus
X	р	S	Pr	Р	I	S	Р	t	р	tp	t	у	Kinase Predictor

Table 2 provides an example of the kinase phosphorylation site consensus recognition matrix that have been developed by Kinexus based on the analysis of 250 known substrate phosphorylation sites for ERK2. In this matrix, positive and negative determinants for ERK2 are defined by the expected occurrence of each of the 20 common amino acids in each position surrounding the phosphorylation sites after the calculated random occurrence of each type of amino acid at the protein surface has been compensated for. The "0" position corresponds to the location of the phosphorylated amino acid, and for this position the random occurrence of each of the 20 common amino acids has not been deducted. Over 150 of these type of kinase phosphorylation site consensus recognition matrices were originally used in the training of the Kinexus Kinase Predictor algorithm.

Table 2. Percent amino acid frequency from random surrounding 250 ERK2 known protein substrate phosphorylation sites.

AA	(-7)	(-6)	(-5)	(-4)	(-3)	(-2)	(-1)	0	1	2	3	4	5	6	7
Type	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Α	0	2	-2	-2	1	1	3	0	-6	-1	1	-2	-1	0	1
С	0	0	0	0	0	0	0	0	-1	1	0	-1	1	-1	-1
D	-2	-2	-4	-2	-3	-3	-5	0	-7	-5	-4	-2	-3	-4	0
E	-1	-1	-3	-2	-3	-7	-6	0	-9	-5	-5	-5	-5	-7	-4
F	1	2	2	0	1	-1	1	0	-2	0	3	1	3	3	2
G	0	1	0	0	1	-4	3	0	-7	3	-1	1	-1	0	0
Н	0	0	0	-1	0	-1	0	0	-2	-1	2	1	0	0	-1
1	1	1	2	-1	0	1	1	0	-3	1	-2	1	0	0	0
K	0	-4	-3	-1	-3	-4	-1	0	-6	-2	-2	-2	-4	-2	-4
L	-3	-3	1	1	0	5	6	0	-7	1	1	1	-1	1	-2
M	1	2	1	1	0	-1	4	0	-1	1	0	2	1	2	2
N	4	2	2	2	-1	-2	-1	0	-3	1	-1	0	-1	2	1
Р	5	2	6	4	7	29	1	0	85	5	4	3	7	3	3
Q	2	0	-2	-1	0	-2	0	0	-3	0	3	0	-2	-1	-2
R	-5	-6	-3	-5	-4	-4	-2	0	-8	0	-2	-5	-2	-2	-2
S	-1	1	3	2	1	-5	-3	68	-11	-2	-1	2	4	3	0
Т	3	2	1	5	2	-1	0	31	-5	5	1	5	1	2	3
V	-3	0	-1	1	0	-1	-1	0	-5	0	1	-1	-1	0	1
W	0	-1	-1	-1	-1	-1	-1	0	-1	-1	-1	-1	0	-1	-1
Υ	-1	0	0	0	0	-1	0	0	-2	0	1	0	2	1	2

Table 3. Detection of increased phosphorylation of synthetic peptides on the Kinex™ Kinase Substrate Microarray with addition of active recombinant human cAMP-dependent protein kinase (PKA). The strength of the detection of phosphate signal from the average value from triplicate measurements is provided.

		Observed Phosphorylation											
-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	
G	G	S	R	R	K	S	F	G	V	G	G	Н	19605
G	L	G	R	R	G	S	F	Α	N	L	G	Н	19294
F	L	S	R	R	L	S	F	G	N	G	G	Н	18157
G	R	G	R	R	M	S	F	G	F	G	G	Н	17768
F	L	S	R	R	G	S	F	G	N	G	K	Н	17672
F	L	S	R	R	G	S	F	G	N	G	G	Н	17108
G	L	G	R	R	D	s	F	Α	N	L	G	Н	16395
V	L	S	R	R	L	s	F	G	N	G	G	Н	16013
С	R	G	R	R	L	s	F	G	G	G	G	Н	13330
V	L	S	R	R	L	s	F	С	N	F	G	Н	13238
G	R	s	R	R	L	S	F	С	G	S	G	Н	12720
F	R	S	R	R	L	S	F	С	G	С	М	Н	10729
F	L	S	R	R	G	S	F	R	G	G	G	Н	10654
F	R	S	R	R	L	S	F	G	V	F	G	Н	10589

F	L	S	R	R	L	s	F	С	N	F	K	Н	10566
G	L	G	R	R	G	S	F	С	N	G	G	Н	8275
G	L	G	R	R	D	s	F	V	V	F	G	Н	8166
G	R	S	R	R	G	S	F	С	Н	K	Т	G	7752
G	L	G	R	Е	G	S	V	G	V	G	G	Н	7168
G	R	G	R	R	G	S	F	С	N	G	G	Н	6912
f	lr	S	R	R	1	S	F	Х	n	Х	Х	Н	Peptide Consensus
Х	r	Х	R	R	1	s	f	Х	Х	Х	X	Х	Protein Consensus
Х	R	s	R	R	ı	s	F	Х	Х	Х	Х	h	Kinase Predictor

Table 4. Detection of increased phosphorylation of synthetic peptides on the Kinex™ Kinase Substrate Microarray with addition of active recombinant human Abl protein-tyrosine kinase. The strength of the detection of phosphate signal from the average value from triplicate measurements is provided.

		Observed Phosphorylation											
-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	
G	G	Е	D	D	L	Υ	Υ	С	V	С	G	G	4769
G	L	Е	D	D	L	Υ	V	Υ	F	G	G	G	3472
G	G	Е	D	D	ı	Υ	٧	G	V	G	G	G	3193
G	G	Е	R	D	L	Υ	F	Υ	V	G	G	G	3120
G	G	Е	D	D	V	Υ	V	G	V	G	G	G	3061
G	G	S	M	Т	M	Т	V	Υ	V	G	Т	Υ	2353
G	G	Е	D	D	М	Υ	М	Е	Р	G	W	W	2065
G	R	S	M	Т	M	Т	Р	Υ	V	G	Т	Υ	1981
G	R	S	R	Т	L	Υ	F	Υ	V	R	G	Υ	1722
G	R	G	D	D	Υ	Υ	V	С	V	G	G	G	1668
G	G	G	D	Р	G	Υ	F	С	V	G	G	G	1579
F	L	S	R	R	K	S	F	С	Р	F	G	W	1445
G	R	S	R	Р	L	Υ	F	Υ	٧	R	G	Υ	1364
G	R	G	R	R	L	S	F	G	٧	G	G	G	1269
L	G	Е	D	Е	N	Υ	V	G	٧	G	Р	G	1143
G	L	Е	D	D	D	Υ	V	N	F	G	G	G	1088
G	R	S	R	L	L	S	Р	С	G	G	G	Υ	1036
G	G	N	D	D	N	Υ	V	R	Р	N	G	G	1009
G	L	Е	D	D	L	Υ	G	G	Р	G	Р	G	1002
			1										
X	Х	E	D	D	liv	Υ	vf	X	V	Х	Х	X	Peptide Consensus
X	Х	en	d	Х	vd	Υ	Х	Х	Р	Х	Х	X	Protein Consensus
X	X	ne	De	d	d	Υ	fv	Х	Pv	Х	X	X	Kinase Predictor

Table 5. Detection of increased phosphorylation of synthetic peptides on the Kinex™ Kinase Substrate Microarray with addition of active recombinant human ErbB4 (HER4) protein-tyrosine kinase. The strength of the detection of phosphate signal from the average value from triplicate measurements is provided.

		Observed Phosphorylation											
-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	
G	G	Е	D	D	L	Υ	Υ	С	V	С	G	G	11582
G	L	Е	D	D	L	Υ	V	Υ	F	G	G	G	7282
G	G	Е	D	D	V	Υ	V	G	V	G	G	G	5626
G	G	Е	R	D	L	Υ	F	Υ	V	G	G	G	5508
F	L	S	R	R	L	S	F	С	N	F	K	Н	5009
G	L	G	R	R	G	S	F	С	V	F	G	G	4851
V	L	S	R	R	L	S	F	С	N	F	G	Н	4226
G	G	Е	D	D	ı	Υ	V	G	V	G	G	G	3837
G	R	G	D	D	Υ	Υ	V	С	V	G	G	G	3591
G	L	G	R	D	D	Υ	- 1	K	F	G	D	ı	3132
L	G	Е	D	Е	N	Υ	V	G	V	G	Р	G	2624
G	R	S	R	Т	L	Υ	F	Υ	V	R	G	Y	2598
F	L	S	R	R	K	S	F	С	Р	F	G	W	2503
G	G	G	D	Р	G	Υ	F	С	V	G	G	G	2398
F	R	G	R	R	K	S	F	С	V	S	G	Н	2326
G	R	S	R	R	G	S	F	С	Н	K	Т	G	2274
G	R	F	R	R	K	S	F	R	R	K	G	Н	2187
G	R	G	R	D	L	Υ	V	K	F	G	Т	- 1	2156
L	G	Е	D	G	N	Υ	V	G	V	С	Р	G	2083
G	G	G	R	L	D	Υ	ı	С	F	G	D	Р	1665
_													,
X	1	е	dr	dr	L	Υ	vf	С	V	Х	X	X	Peptide Consensus
h	Is	dp	np	р	ae	Υ	ht	np	ар	s	gn	gn	Protein Consensus
x	-1	en	De	dh	d	Ys	V	n	F	х	X	X	Kinase Predictor

4. PREPARATION FOR STORAGE AND SHIPPING OF KINASES SAMPLES

With our Kinex™ Kinase Substrate Microarray Profiling Services, a wide selection of purified and active protein kinases are available. However, we do provide the option for our clients to submit their own protein kinases for use in this analysis in addition to those offered by Kinexus. In this event, clients should complete the Client Supplied Non-Confidential Kinase Description Form (NSDF-KI) provided in this client information package. If you do not wish to provide the requested information, then a Client Supplied Confidential Kinase Description Form (CSDF-KI) must be completed, and full confidential pricing charges will be applied. We recognize that not all of the requested information about commercial protein kinases may be available to our clients, so please provide as much information as you are able to qualify for non-confidential pricing.

We recommend that the client supplied protein kinases are provided as concentrated as possible, preferably at around 0.1 mg/ml and within *screw cap* vials. We need approximately 10 µg of most protein kinases. As there are large variations in the phosphotransferase activity of protein kinases, and every kinase is unique, and we may be able to perform the KKSM services with less kinase if it still works well at a lower concentration. The vials should be clearly labeled with an indelible marker with a unique identification number (recorded in the NSDF-KI or CSDF-KI forms), <u>parafilmed</u>, and then put into another support structure such as a 50-ml conical or centrifuge tube to provide extra protection during shipping. All kinase samples *must* be shipped on dry ice.

5. SHIPPING INFORMATION

The aforementioned procedure has been designed to reduce the use of shipping materials and courier costs, and to ensure that your precious protein kinase samples arrive in a safe and stable form at our laboratory facilities. Note that clients are responsible for payment of courier costs. The vials should be sent to the address listed below by any express courier. We recommend Federal Express for shipments originating in North America, and World Express is the preferred courier choice outside of North America. Ship the purified protein kinases to the following address:

Kinexus Bioinformatics Corporation Suite 1, 8755 Ash Street Vancouver, B.C. Canada V6P 6T3 Telephone: (604) 323-2547

Facsimile: (604) 323-2548 E-mail: info@kinexus.ca

Please ensure 3 copies of a signed commercial invoice (available near the end of this customer information package) accompany your shipment which specifies your kinase samples are non hazardous and non infectious. Since the protein samples are not for resale, the value of your shipment should be priced at approximately \$1.00 per sample in order to avoid paying additional duties and taxes on entry into Canada. It is highly recommended that customers e-mail their courier airway bill number and the date of departure to info@kinexus.ca so we can track your shipment in transit and ensure it arrives in a timely manner. We will send a confirmation e-mail once your shipment arrives at our facility.

6. PRICING INFORMATION

Kinexus offers the Kinex™ Kinase Substrate Microarray Profiling Services at two different pricing levels depending on the level of confidentiality required. Our regular prices for the KKSM services (excluding the cost of the kinase to be tested) starts at US \$1099 for each for analysis if sample information is to remain fully confidential. At this pricing level, if the client provides their own protein kinase, only partial information about these preparations need to be disclosed in the CSDF-KI forms. To receive a 32% discount off the regular price, or pay US \$749 for the analysis of 3 different protein kinases with a blank control, Kinexus must be allowed after at least a 6 month hold to have the option to include the results in its on-line KiNET DataBank and SigNET KnowledgeBank, which will permit third parties to access the data. If a client supplies their own protein kinases for phosphorylation of the Kinex™ Kinase Substrate Microarray, then they must complete in full a NSDF-KI form to receive Non-confidential pricing.

An up to date listing of all of the protein kinase available through Kinexus is listed on the Kinexus webpage that describes this service at

http://www.kinexus.ca/ourServices/massspectrometry/massspectrometry/kinase_match.html

A listing of over 340 distinct human protein kinases and various mutated forms is provided in Appendix 1 of this customer information package.

For volume discounts or quotations for large orders, please contact the Director of Sales & Marketing at 1-866-KINEXUS (or 1-604-323-2547 (Extension 11 or Option 2 on the telephone directory) or e-mail sales@kinexus.ca.

7. FOLLOW UP SERVICES

As a follow up to this service, with our Custom Peptide Synthesis Services, Kinexus can synthesize soluble versions of any of the kinase substrate peptides on the KinexTM Kinase Substrate Microarray. These soluble peptides can also be tested as substrates in solution in vitro with our In Vitro Kinase and Phosphopeptide Testing (IKPT) Service. This seamless integration of our various services provides a wide range of options for our clients to identify artificial and physiological substrates for important protein kinases. These can define biomarkers for monitoring the catalytic activities of kinases of interest and substrates for high throughput drug discovery. For more information about these services, please contact one of our customer service representatives at info@kinexus.ca.

8. FORMS TO BE COMPLETED

All customers are required to complete the following forms for each order placed:

- A. <u>Kinexus Service Agreement</u>. Customers are required to complete and sign our standard Kinexus Services Agreement before their first order can be processed. Unless otherwise specified, this Agreement is valid for all future orders with a standard term of 15 years.
- B. <u>Service Order Form (KKSM-SOF)</u>. The Service Order Form (SOF) allows us to track all of the various services to be used within an order.
- C. <u>Service Identification Form (KKSM-SIF)</u>. The Service Identification Form (SIF) permits us to determine which client-supplied cell/tissue protein kinases are to be used for the Kinex[™] Kinase Substrate Microarray Profiling Service.

If customers wish to send their own purified and active protein kinases, they must also complete and submit the following forms:

- D. <u>Client Supplied Non-Confidential Kinase Description Form (NSDF-KI)</u>. Completion of this form is necessary for qualification for the Non-Confidential pricing discount.
- E. <u>Client Supplied Confidential Kinase Description Form (CSDF-KI)</u>. Completion of this form is necessary if the customer wishes to use the fully confidential service.
- F. <u>Federal Express Airway Bill</u>. For probing antibodies to be delivered by Federal Express. Clients can pick any courier of their choice, but we recommend Federal Express within North America.
- G. <u>Commercial Invoice</u>. This is required for all customers located outside of Canada that send purified protein kinases.

All orders should have as a minimum: 1 SOF and 1 SIF forms completed. A new Kinexus Services Agreement may not be necessary if the client has previously placed an order with Kinexus and submitted a signed Kinexus Services Agreement at that time.

FOR ALL CUSTOMERS

A. Kinexus Service Agreement

A Kinexus Service Agreement is required to be signed before the first order can be processed.

• This Agreement is required to be signed and dated by an authorized representative, typically a Senior Officer, Senior Scientist, or Principal Investigator, before the first order can be processed, but does not have to be signed again for repeat orders. The Kinexus Service Agreement is typically valid for 15 years. If you require changes or modifications to be made to our standard Service Agreement, please email us at sales@kinexus.ca to request a Microsoft Word version of the document so your requested changes can be made directly into the agreement and emailed to us for our final approval.

B. Service Order Form (KKSM-SOF)

Please ensure:

- Shipping address and contact name and numbers are specified.
- Billing information is completed on the Service Identification Form (CKSP-SIF-01).
- Any promotional vouchers or quotations are listed in the billing sections.
- Include a Purchase Order, Visa or MasterCard number for payment.
- The form is signed and dated.

C. Service Identification Form (KKSM-SIF)

For each KKSM chip to be used, please ensure the following:

- In Section A if the protein kinases are provided by the client the Client Screen ID name found in Box A of
 the NSDF-KI or CSDF-KI forms. Three Client Screen ID names should be provided in the box for the 3
 protein kinases to be tested on the same KKSM chip.
- In Section A if the protein kinases are to be sourced from Kinexus Clients should provide a name that they
 wish to call the KKSM analysis with one KKSM chip with the three protein kinases sourced from Kinexus as
 indicated in Option 2 of Box B of the KKSM-SIF form.
- In Section B, if the client is supplying their own protein kinases, then at least 3 NSDF-KI or 2 CSDF-KI forms should be completed and included with the order.
- In Section B, if the client is sourcing the protein kinases from Kinexus, then the kinase description information from the List of Available Kinases from Kinexus (Appendix 1) should be entered for the 3 kinases to be tested on the same KKSM chip.
- If more than 6 protein kinases are to be tested, please use additional KKSM-SIF forms.
- In Section C, the level of confidentiality is indicated for correct pricing.
- The form is certified correct and signed and dated.

D. Client Supplied Protein Kinase Description Forms (NSDF-KI or CSDF-KI)

For submitted protein kinases, please ensure the following:

- The protein kinases that you are submitting to Kinexus for this study must be identified along with any special instructions on how the kinases should be used for phosphorylating the cell lysate.
- Ensure the form is certified correct and signed and dated.
- Use the NSDF-KI form for Non-confidential pricing and the CSDF-KI form for Confidential pricing.
- Note that the information provided on the NSDF-KI form will eventually become available to thousands of
 other scientists in the future with the non-confidentiality pricing. In the spirit of collegiality, please be as
 accurate as possible in completing the NSDF-KI form in order not to handicap their research efforts should
 they desire to follow up on your Kinex™ Kinase Substrate Microarray Profiling Service results.

E. Airway bill for Federal Express or any other courier

Complete the airway bill and specify:

- Priority overnight delivery.
- Bill transportation charges to your institute.
- It is critical to send your protein kinases in a frozen state. Please provide sufficient dry ice to last several days into a Styrofoam shipping container.
 - Seal the edges of the Styrofoam container with tape to preserve dry ice longer.
 - Dry ice is a "hazardous" item, so ensure proper labels are attached to the outside of the box.
- Do not specify Saturday delivery or hold at courier location.
- For Federal Express shipments telephone 1-800-GO-FEDEX or visit them on-line at www.fedex.com or www.fedex.ca to schedule a pick up or complete your forms.
- For shipments coming from within Canada or the United States, please ship any day from Monday to Wednesday. Do not ship on a Thursday or Friday.
- For international shipments coming from outside of North America, the best day to ship is on a Monday to ensure arrival in Canada for delivery later the same week.
- It is recommended that customers e-mail the date of your shipment and the courier airway bill number with number of samples to Kinexus at info@kinexus.ca to ensure we can track your package should it get held up in Canadian Customs.
- For any customer located outside of Canada, 3 copies of a commercial invoice is required to accompany your shipment (see below).

FOR U.S AND INTERNATIONAL CUSTOMER ONLY

F. Commercial Invoice (not required by Canadian customers)

Please complete the attached commercial invoice with the following information:

Date of exportation.

- Shipper/Exporter name, address, phone number.
- Country of export/Country of origin.
- · Name of courier and the airway bill number.
- Number, type and total weight of package(s).
- Total declared value of shipment (number of samples x \$1.00 per sample) and please specify currency.
- Date, name, signature, and title of authorized person.

Include three (3) copies of the commercial invoice with the airway bill

NOTE: Do not change the value of your shipment to more than \$1.00 per sample as this will prompt the custom brokers to charge Kinexus with a duty and GST fee on your package. Since the protein kinase samples are processed internally and not returned to the customer or resold, there is no real commercial value.

The international air waybill is required for all international shipments between Canada and the rest of the world. It is also your customs declaration, which can possibly be used to clear your shipment through customs at the destination. The customs clearance process begins with the description of the air waybill. If the description is too vague or missing, customs authorities may select the shipment for further inspection. All customs paperwork, such as the commercial invoice, must have detailed commodity descriptions. A detailed description on the air waybill and other customs documentation will help speed up the clearance time and reduce your delivery time. In the event that Kinexus must go to a Canada Customs facility to claim the package of samples for client order due to inadequate completion of the commercial invoice, additional charges will apply.

Appendix 1 - List of Active Protein Kinases

This list may change with respect to availability and pricing.

Protein Kinase Name	Code	U.S. Price	Protein Kinase Name	Code	U.S. Price
Abl1	AB01	\$200.00	BUBR1(BUB1B)	BU01	\$600.00
Abl1 [E255K]	AB02	\$400.00	CaMK1δ (CAMK1D)	CA03	\$200.00
Abl1 [G250E]	AB03	\$400.00	CAMK1 _Y	CA04	\$200.00
Abl1 [H369P]	AB04	\$600.00	CAMK2α (CAMK2B)	CA05	\$200.00
Abl1 [T315I]	AB05	\$400.00	CaMK2β (CAMK2B)	CA06	\$200.00
Abl1 [Y253F]	AB06	\$400.00	CaMK2δ (CAMK2D)	CA07	\$400.00
<u> </u>			CaMK2 _Y (CAMK2G)		
Abl1 [M351T]	AB07	\$600.00	CAMK3y	CA08	\$600.00
Abl3 (Ass)	AB08	\$600.00	·	CA09	\$200.00
Abl2 (Arg) ACK	AB09 AC01	\$200.00 \$200.00	CAMK4 CAMK4 (CaMKIV)	CA10 CA11	\$200.00 \$400.00
ACVR1 (ALK2)	AC02	\$400.00	CAMKK1 (CAMKKA)	CA11	\$200.00
ACVRL1	AC03	\$400.00	CAMKK2	CA13	\$200.00
ADRBK1 (GRK2)	AD01	\$200.00	CAMKK2 (CaMKK beta)	CA14	\$400.00
ADRBK2 (GRK3)	AD02	\$400.00	CDC42 BPA (MRCKA)	CD01	\$400.00
Akt1/PKBα	AK01	\$200.00	CDC42 BPB (MRCKB)	CD02	\$400.00
Akt1/PKBα [δPH, S473D]	AK02	\$600.00	CDC7/ASK	CD03	\$600.00
Akt1/PKBα [δPH]	AK03	\$600.00	CDK1/cyclin B1	CD04	\$400.00
Akt2/PKBβ	AK04	\$200.00	CDK1/CyclinA2	CD05	\$200.00
Akt2/PKBβ [δPH, S474D]	AK05	\$600.00	CDK2/cyclin A	CD06	\$400.00
Akt3/PKBγ	AK06	\$200.00	CDK2/Cyclin E1	CD07	\$600.00
Akt3/PKB _γ [S472D]	AK07	\$600.00	CDK2/CyclinA2	CD08	\$200.00
ALK1	AL01	\$200.00	CDK3/Cyclin E1	CD09	\$600.00
ALK4 (ACVR1B)	AL02	\$200.00	CDK4//Cyclin D3	CD10	\$600.00
AMPK α 1/ β 1/ γ 1 (PRKAA1/B1/G1)	AM01	\$200.00	CDK4/Cyclin D1	CD11	\$200.00
AMPKα1/β1/γ2 (PRKAA1/B1/G2)	AM02	\$200.00	CDK5	CD12	\$600.00
AMPKα1/β1/γ3 (PRKAA1/B1/G3)	AM03	\$200.00	CDK5/p25	CD13	\$200.00
AMPKα1/β2/γ1 (PRKAA1/B2/G1)	AM04	\$200.00	CDK5/p35	CD14	\$400.00
AMPK α 2/β1/γ1 (PRKAA2/B1/G1)	AM05	\$200.00	CDK6//Cyclin D3	CD15	\$600.00
Ark5	AR01	\$600.00	CDK6/cyclin D1	CD16	\$400.00
Ask1 (MAP3K5)	AS01	\$200.00	CDK7/Cyclin H1/MAT1	CD17	\$200.00
Aurora A (Aura, AURKA)	AU01	\$200.00	CDK8/Cyclin C	CD18 CD19	\$400.00
Aurora B (AurB, AURKB, INCENP) Aurora C (AurC, AURKC)	AU02 AU03	\$200.00 \$200.00	CDK9/Cyclin K CDK9/Cyclin T1	CD19	\$200.00 \$400.00
AxI	AX01	\$200.00	CGK2 (PRKG2)	CG01	\$600.00
BARK1 (ADRBK1)	BA01	\$600.00	CHK1 (CHEK1)	CH01	\$200.00
BARK2 (ADRBK2)	BA02	\$600.00	CHK2 (CHEK2)	CH02	\$200.00
Blk	BL01	\$200.00	CK1α (CSNK1A1)	CK01	\$400.00
BMPR1A (ALK3)	BM01	\$600.00	CK18 (CSNK1D)	CK02	\$400.00
BMPR1B (ALK6)	BM02	\$600.00	CK1δ (CSNK1D) [1-294]	CK03	\$600.00
Bmx	BM03	\$200.00	CK1ε (CSNK1E)	CK04	\$400.00
B-Raf	BR01	\$200.00	CK1γ1 (CSNK1G1)	CK05	\$400.00
B-Raf [81-415]	BR02	\$600.00	CK1γ2 (CSNK1G2)	CK06	\$400.00
B-Raf [V599E]	BR03	\$200.00	CK1γ3 (CSNK1G3)	CK07	\$400.00
Brk (PTK6)	BR04	\$200.00	CK1γ3 (CSNK1G3)	CK08	\$400.00
BrSK1 (SAD1)	BR05	\$400.00	CK2α1 (CSNK2A1)	CK09	\$200.00
BrSK2	BR06	\$600.00	CK2α2 (CSNK2A2)	CK10	\$400.00
Btk	BT01	\$200.00	CLK1	CL01	\$200.00
Btk [E41K]	BT01	\$600.00	CLK2	CL02	\$200.00
Btk [R28H]	BT02	\$600.00	CLK3	CL03	\$400.00

Appendix 1 - List of Active Protein Kinases (Cont'd) - 2

Protein Kinase Name	Code	U.S. Price	Protein Kinase Name	Code	U.S. Price
CLK4	CL04	\$400.00	FGFR4	FG08	\$200.00
COT (MAP3K8)	CO01	\$200.00	Fgr	FG09	\$600.00
CRIK	CR01	\$600.00	Flt1 (VEGFR1)	FL01	\$400.00
Csk	CS02	\$200.00	Flt3	FL02	\$200.00
C-TAK1	CT01	\$600.00	Flt3 [D835Y]	FL03	\$400.00
СТК	CT02	\$600.00	Flt4 (VEGFR3)	FL04	\$200.00
DAPK1	DA01	\$200.00	Fms (CSF1R)	FM01	\$400.00
DAPK2	DA02	\$400.00	FRAP1 (mTOR)	FR01	\$600.00
DAPK3 (ZIPK)	DA03	\$200.00	FRK (PTK5)	FR02	\$400.00
DCAMKL1	DC01	\$600.00	Fyn	FY01	\$200.00
DCAMKL2 (DCK2)	DC02	\$400.00	GRK4	GR01	\$400.00
DDR1	DD01	\$600.00	GRK5	GR02	\$200.00
DDR2	DD02	\$200.00	GRK6	GR03	\$400.00
DLK (MAP3K12)	DL01	\$600.00	GRK7	GR04	\$600.00
DMPK1 (DMPK)	DM01	\$400.00	GSK3α	GS01	\$200.00
DRAK1 (STK17A)	DR01	\$600.00	GSK3β	GS02	\$400.00
DYRK1A	DY01	\$400.00	Haspin (GSG2)	HA01	\$200.00
DYRK1B	DY02	\$400.00	Hck	HC01	\$200.00
DYRK2	DY03	\$600.00	Hgk (MAP4K4)	HG01	\$400.00
DYRK3	DY04	\$400.00	HIPK1 (Myak)	HI01	\$200.00
DYRK4	DY05	\$400.00	HIPK2	HI02	\$200.00
eEF2K	EE01	\$400.00	HIPK3	HI03	\$200.00
EGFR (ErbB1)	EG01	\$400.00	HIPK3 (YAK1)	HI04	\$200.00
EGFR (ErbB1) [L858R]	EG02	\$400.00	HIPK4	HI05	\$600.00
EGFR (ErbB1) [L861Q]	EG03	\$400.00	IGF1R	IG01	\$400.00
EGFR (ErbB1) [T790M, L858R]	EG04	\$400.00	IGF1R [δ1-958]	IG02	\$600.00
EGFR (ErbB1) [T790M]	EG05	\$400.00	IKKα (CHUK)	IK01	\$200.00
EIF2AK3 (PERK)	EI06	\$400.00	ΙΚΚβ (ΙΚΒΚΒ)	IK02	\$200.00
EphA1	EP01	\$200.00	IKKε (IKBKE)	IK03	\$400.00
EphA2	EP02	\$400.00	INSRR (IRR)	IN01	\$200.00
EphA3	EP03	\$400.00	Insulin Rec. (INSR)	IN02	\$400.00
EphA4	EP04	\$400.00	IRAK1	IR01	\$600.00
EphA5	EP05	\$400.00	IRAK2	IR02	\$200.00
EphA6	EP06	\$600.00	IRAK4	IR03	\$400.00
EphA7	EP07	\$600.00	Itk	IT01	\$200.00
EphA8	EP08	\$600.00	JAK1	JA01	\$600.00
EphA8	EP09	\$400.00	JAK2	JA02	\$200.00
EphB1	EP10	\$600.00	JAK2 [JH1, JH2, V617F]	JA03	\$600.00
EphB2	EP11	\$400.00	JAK2 [JH1, JH2]	JA04	\$400.00
EphB3	EP12	\$200.00	JAK3	JA05	\$400.00
EphB4	EP13	\$200.00	JNK1a1 (MAPK8)	JN01	\$400.00
ErbB2 (HER2, Neu)	ER01	\$200.00	JNK2α2 (MAPK9)	JN02	\$600.00
ErbB4 (HER4)	ER02	\$400.00	JNK3 (MAPK10)	JN03	\$600.00
Erk1 (MAPK3)	ER03	\$600.00	KDR (VEGFR2)	KD01	\$400.00
Erk2 (MAPK1)	ER04	\$600.00	KHS1(MAP4K5)	KH01	\$400.00
Erk5 (MAPK7)	ER05	\$200.00	Kit	KI01	\$200.00
FAK (PTK2)	FA01	\$400.00	Kit [D816H]	KI02	\$600.00
Fer	FE01	\$200.00	Kit [D816V]	KI03	\$600.00
Fes (Fps)	FE02	\$200.00	Kit [T670I]	KI04	\$400.00
FGFR1 (FLT2)	FG01	\$200.00	Kit [V560G]	KI05	\$200.00
FGFR1 (FLT2) [V561M]	FG02	\$200.00	Kit [V654A]	KI06	\$200.00
FGFR2	FG03	\$400.00	Lck	LC01	\$200.00
FGFR2 [N549H]	FG04	\$600.00	LIMK1	LI01	\$200.00
FGFR3	FG05	\$200.00	LIMK2	LI02	\$400.00
FGFR3 [K650E]	FG06	\$400.00	LKB1 (MO25α, STRADα, STK11)	LK01	\$600.00
FGFR3 [K650M]	FG07	\$600.00	LOK (STK10)	LO01	\$600.00
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Appendix 1 - List of Active Protein Kinases (Cont'd) - 3

Protein Kinase Name	Code	U.S. Price	Protein Kinase Name	Code	U.S. Price
LRRK2	LR01	\$600.00	MST4	MS07	\$200.00
LRRK2 [G2019S]	LR02	\$400.00	MUSK	MU01	\$200.00
LTK (TYK1)	LT01	\$400.00	MYLK2 (skMLCK)	MY01	\$400.00
Lyn A	LY01	\$200.00	МΥО3β	MY02	\$400.00
Lyn B	LY02	\$200.00	MYT1 (PKMYT1)	MY03	\$200.00
MKK5 (MEK5, MAP2K5)	MK01	\$600.00	NDR1 (STK38)	ND01	\$200.00
MAP3K14 (NIK)	MA01	\$600.00	NEK1	NE01	\$200.00
MEKK3 (MAP3K3)	ME01	\$200.00	NEK11 (FLJ23495)	NE02	\$200.00
MAP3K4	MA02	\$600.00	NEK2	NE03	\$200.00
MAP3K7-MAP3K7IP1 (TAK1-TAB1)	MA03	\$400.00	NEK3	NE04	\$200.00
GCK (MAP4K2)	GC01	\$400.00	NEK4	NE05	\$400.00
MAPKA PKA	MA04	\$600.00	NEK6	NE06	\$200.00
MAPKAPK2	MA05 MA06	\$400.00	NEK7 NEK9	NE07	\$600.00
MAPKAPK3 MAPKAPK5 (PRAK)	MA07	\$400.00 \$400.00	NLK	NE08 NL01	\$600.00 \$400.00
MARK1 (MARK)	MA08	\$400.00	NUAK1 (ARK5)	NU01	\$400.00
MARK2	MA09	\$400.00	p38α (MAPK14)		\$200.00
MARK3	MA10	\$400.00	p38α (MAPK14) [T106M]	MA13 MA14	\$400.00
MARK4	MA11	\$400.00	p38β (MAPK11)	MA15	\$400.00
MATK (HYL)	MA12	\$400.00	p38δ (MAPK13)	MA16	\$200.00
MEK1 (MKK1, MAP2K1)	ME01	\$200.00	p38γ (MAPK12)	MA17	\$200.00
MEK1 (MKK1, MAP2K1) [S218E, S222E]	ME02	\$200.00	p70S6K (RPS6KB1)	RS01	\$400.00
MEK2 (MKK2,MAP2K2)	ME03	\$200.00	p70S6K (RPS6KB1) [T412E]	RS02	\$400.00
MEKK2 (MAP3K2)	ME04	\$200.00	p70S6Kβ (RPS6KB2)	RS03	\$400.00
MEKK3 (MAP3K2)	ME05	\$200.00	PAK1/CDC42	PA01	\$200.00
MELK	ME06	\$400.00	PAK2 (PAK65)	PA02	\$600.00
MERTK (Mer)	ME07	\$200.00	PAK3	PA03	\$200.00
Met	ME08	\$400.00	PAK4	PA04	\$200.00
Met [M1250T]	ME09	\$200.00	PAK6	PA05	\$200.00
Met [Y1235D]	ME10	\$400.00	PAK7 (KIAA1264, PAK5)	PA06	\$600.00
MGC42105	MG01	\$200.00	PAR-1Ba/MARK2	PA07	\$200.00
MINK1 (MINK)	MI01	\$200.00	PASK	PA08	\$400.00
MKK3 (MEK3, MAP2K3)	MK01	\$200.00	PBK (TOPK)	PB01	\$200.00
MKK4 (MEK4, MAP2K4)	MK02	\$400.00	PCTAIRE1 (PCTK1)	PC01	\$400.00
MKK6 (MEK6, MAP2K6)	MK03	\$200.00	PDGFRα	PD01	\$200.00
MKK6 (MEK6, MAP2K6) [S599D, T603D]	MK04	\$600.00	PDGFRα [550-end, D842V]	PD02	\$200.00
MKK7α1 (MEK7α1, MAP2K7A1)	MK05	\$400.00	PDGFRα [550-end, V561D]	PD03	\$400.00
MKK7β1 (MKK7β1, MAP2K7B1)	MK06	\$600.00	PDGFRα [D842V]	PD04	\$200.00
MLCK (MLCK2, MYLK)	ML01	\$200.00	PDGFRα [T674I]	PD05	\$600.00
MLK1 (MAP3K9)	ML02	\$200.00	PDGFRα [V561D]	PD06	\$400.00
MLK2 (MAP3K10)	ML03	\$200.00	PDGFRβ	PD07	\$400.00
MLK3 (MAP3K11)	ML04	\$200.00	PDHK2 (PDK2)	PD08	\$600.00
MNK1 (MKNK1)	MN01	\$600.00	PDHK3 (PDK3)	PD09	\$200.00
MNK2 (MKNK2)	MN02	\$600.00	PDHK4 (PDK4)	PD10	\$600.00
MOS	MO01	\$600.00	PDK1	PD11	\$600.00
MRCKα (CDC42BPA)	MR01	\$600.00	PEK (EIF2AK3)	PE01	\$400.00
MRCKβ (CDC42BPB)	MR02	\$200.00	PhKγ1 (PHKG1)	PH01	\$400.00
MSK1 (RPS6KA5)	MS01	\$600.00	PhKγ2 (PHKG2)	PH02	\$400.00
MSK2 (RPS6KA4)	MS02	\$600.00	Pim1	PI01	\$200.00
MSSK1 (STK23)	MS03	\$200.00	Pim2	PI02	\$600.00
MST1 (STK4)	MS04	\$600.00	Pim3	PI03	\$600.00
MST2 (STK3)	MS05	\$200.00	PKAcα (PRKACA)	PK01	\$600.00
MST3 (STK24)	MS06	\$600.00	PKAcβ (PRKACB)	PK02	\$200.00

Appendix 1 - List of Active Protein Kinases (Cont'd) - 4

Protein Kinase Name	Code	U.S. Price	Protein Kinase Name	Code	U.S. Price
PKAcy (PRKACG)	PK03	\$600.00	SGK2	SG03	\$400.00
PKCµ (PRKD1)	PK04	\$400.00	SGK3 (SGKL)	SG04	\$600.00
PKCα (PRKCA)	PK05	\$400.00	SGT220	SG05	\$200.00
PKCβ1 (PRKCB1)	PK06	\$200.00	SGT222-25UG	SG06	\$200.00
PKCβ2 (PRKCB2)	PK07	\$200.00	SIK	SI01	\$200.00
PKCδ (PRKCD)	PK08	\$600.00	skMLCK (MYLK2)	SK01	\$400.00
PKCε (PRKCE)					
,	PK09	\$200.00	SLK (STK2)	SL01	\$200.00
PKC _γ (PRKCG)	PK10	\$200.00	smMLCK (MYLK)	SM01	\$600.00
PKCη (PRKCH)	PK11	\$200.00	SNF1LK2 (QIK)	SN01	\$200.00
PKCι (PRKCI)	PK12	\$200.00	SOK	SO01	\$200.00
PKCλ (PRKCL)	PK13	\$200.00	Src	SR01	\$200.00
PKCθ (PRKCQ)	PK14	\$200.00	Src [T341M]	SR02	\$600.00
PKCζ (PRKCZ)	PK15	\$200.00	SRMS (Srm)	SR03	\$600.00
PKD1 (PRKD1)	PK16	\$200.00	SRPK1	SR04	\$600.00
PKD2 (PRKD2)	PK17	\$200.00	SRPK2	SR05	\$600.00
PKD3 (PRKD3, PRKCN)	PK18	\$200.00	STK16 (PKL12)	ST01	\$400.00
PKG1α (PRKG1A)	PK19	\$200.00	STK25 (YSK1)	ST02	\$400.00
PKG1β (PRKG1B)	PK20	\$200.00	STK33	ST03	\$200.00
PKG2 (PRKG2)	PK21	\$600.00	Syk	SY01	\$600.00
PKN1 (PRK1)	PK22	\$600.00	TAO2	TA01	\$400.00
PKN2 (PRK2)	PK23	\$200.00	TAO3	TA02	\$200.00
PKR (EIF2AK2)	PK24	\$200.00	TAOK1	TA03	\$400.00
PLK1	PL01	\$200.00	TAOK2 (TAO1)	TA04	\$400.00
PLK2	PL02	\$600.00	TAOK3 (JIK)	TA05	\$200.00
PLK3 PLK4	PL03 PL04	\$200.00 \$400.00	TBK1 TEC	TB01 TE01	\$200.00
PRKX	PR01	\$600.00	TESK1	TE02	\$400.00 \$200.00
PTK2B (FAK2)	PT01	\$600.00	TGFβR1 (TGFBR1, ALK5)	TG01	\$600.00
PTK5	PT02	\$400.00	TGFβR2	TG02	\$600.00
Pyk2	PY01	\$400.00	Tie2 (Tek)	TI01	\$200.00
Raf1 [Y340E, Y341E]	RA01	\$400.00	Tie2 (Tek) Tie2 (Tek) [R849W]	TI01	\$200.00
Raf1 (truncated)	RA01	\$600.00	Tie2 (Tek) [K049W] Tie2 (Tek) [Y1108F]	TI02	\$400.00
Raf1 [Y340D, Y341D]	RA03	\$200.00	Tie2 (Tek) [Y897S]	TI04	\$400.00
Ret	RE01	\$600.00	TLK2	TL01	\$400.00
Ret [V804L]	RE02	\$400.00	TNK1	TN01	\$600.00
Ret [V804M]	RE03	\$400.00	TNK2 (ACK)	TN02	\$600.00
Ret [Y791F]	RE04	\$600.00	TrkA (NTRK1)	TR01	\$200.00
RIPK2	RI01	\$200.00	TrkB (NTRK2)	TR02	\$200.00
RIPK5	RI02	\$400.00	TrkC (NTRK3)	TR03	\$600.00
ROCK1 (ROKβ)	RO01	\$600.00	TSSK1 (STK22D)	TS01	\$200.00
ROCK2 (ROKα)	RO02	\$200.00	TSSK2 (STK22B)	TS02	\$200.00
RON (MST1R)	RO03	\$200.00	TTBK1	TT01	\$600.00
ROR1	RO04	\$600.00	TTK	TT02	\$600.00
ROR2	RO05	\$400.00	TXK	TX01	\$400.00
Ros	RO06	\$400.00	TYK2	TY01	\$200.00
Rse	RO07	\$200.00	TYRO3 (RSE)	TY02	\$200.00
RSK1 (RPS6KA1)	RS04	\$400.00	VRK1	VR01	\$600.00
RSK2 (PRS6KA3) RSK3 (RPS6KA2)	RS05 RS06	\$200.00 \$200.00	Wee1 WNK1	WE01 WN01	\$600.00 \$200.00
RSK4 (RPS6KA6)	RS07	\$200.00	WNK2	WN02	\$600.00
SGK1	SG01	\$600.00	WNK3	WN03	\$600.00
SGK1 [δ1-59, S422D]	SG02	\$200.00	WNK4	WN04	\$200.00
r , = 1	2 2 3 2	Ţ_30.00		or	+_00.00

Appendix 1 - List of Active Protein Kinases (Cont'd) - 5

Protein Kinase Name	Code	U.S. Price
YES1	YE01	\$600.00
ZAK	ZA01	\$200.00
ZAP70	ZA02	\$600.00
ZIPK	ZI01	\$600.00



KINEX™ KINASE SUBSTRATE MICROARRA

SERVICE ORDER FORM

Form: KKSM-SOF

KINEXUS ORDER NUMBER

	Subject to terms Proteomics Serv	of the Kinexus ices Agreement	To Rinexus internal use only.
CUSTOMER INFORMATION REPEAT CUSTOMER	OR NEV	v Customer	
Dr. Mr. Ms.			
Name of Authorized Representative or Principal Investigator	Title/Position		
Company Name or Institute	Department		
Street Address			
City	State or Province	Country	Zip or Postal Code
Email Address	(Area Code) Te	lephone Number (Area Co	de) Facsimile Number
Contact Person (if different from Authorized Representative)	Email Address	(Area Co	de) Telephone Number
STUDY REPORTS			
RESULTS SENT BY EMAIL TO: AUTHORIZED REPRESENTA	TIVE/INVESTIGATO	OR AND/OR CONTACT PERSON	
PRICING INFORMATION			
The Kinex™ Kinase Substrate Microarray Profiling Services per chip.	use a peptide m	icroarray to identify potential substra	tes for up to 3 protein kinases
The base study design consists of one blank contro expected (but not guaranteed) to identify over 10 pecost of protein kinases sourced from Kinexus.			
,		A Number	II prices in U.S. Funds
Non-confidential base study – 1 control and 3 kinases test	ted in triplicate	@ US \$749 per base study	y \$
Confidential base study – 1 control and 3 kinases tested in	n triplicate	@ US \$1099 per base stud	dy \$
Possible additional cost for recombinant kinases		@ US \$ 200 per kinase	\$
Possible additional cost for recombinant kinases		@ US \$ 400 per kinase	\$
Possible additional cost for recombinant kinases		@ US \$ 600 per kinase	\$
			Subtotal = \$
Quotation or Reference Number for any promotional of	discount:		- \$
	ESTIMATE	ED TOTAL COST FOR THIS ORDER	R = \$
FOR CANADIAN CUSTOMERS ONLY:			
Add an additional 12% to the above total for HST (No.	893907329 RT0	,	=\$
		rotal amou	INT PAYABLE IN U.S FUNDS

PAYMENT METHOD					
PURCHASE ORDER ACCEP VISA OR MASTERO		IIES AND INSTITUTES WITH APPROVI	ED CREDIT.	P.O. NUMBER:	
Print Cardholder Name		Visa Number		Expires (M/Y)	Cardholder Signature
BILLING INFORMATION Dr Mr Ms	SEND INVOIC	E TO CUSTOMER AT ABOVE ADDRES	SS OR	SEND INVOICE TO) ACCOUNTS PAYABLE CONTACT:
Accounts Payable Contact Name			Company Na	ame or Institute	
Street Address			City		
State or Province	Country	Zip or Postal Code	(Area Code)	Telephone Number	
AUTHODIZATION					

AUTHORIZATION

CUSTOMER HAS READ THE KINEXUS PROTEOMICS SERVICES AGREEMENT AND AGREES TO BE BOUND BY THE TERMS AND CONDITIONS:

Print Name of Authorized Representative of Principal Investigator	Authorized Signature	Date ymra)
How did you originally hear about the KKSM Services? Direct Mail	Email Web Site Advertisement Referra	Conference or Trade Show Other



KINEX™ KINASE SUBSTRATE MICROARRAY

SERVICE REQUESTED:

(Authorized Representative or Principal Investigator)

NAME: ___

SERVICE IDENTIFICATION FORM

Subject to terms of the Kinexus Proteomics Services Agreement

COMPANY/INSTITUTE:

KINEXUS ORDER NUMBER

Form: KKSM-SIF

	chip. A blank control incubation is performed in	protein kinases to phosphorylate potential substrate the absence of added kinase on a fourth grid of
		calling toll free in North America 1-866-KINEXUS in can be downloaded from the Kinexus website at
KKSM CUSTOM SERVICE REQUESTED:	VINEVIIO ID NUMBER	A. CLIENT SCREEN ID NAME:
The base study consists of one control and in vitro treatments with 3 protein kinases carried out in triplicate.	(Bar Code Identification Number) For Kinexus Internal Use Only.	Study ID:
B. PROTEIN KINASE:		C. PRICING:
Option 1 Please attach a completed NSDF-KI (non-confider description of the protein kinases to be used in the Option 2 For protein kinases sourced from Kinexus, please code and price shown for the protein kinase to be	study if it is to be supplied by the client. provide from the list in Appendix 1, the name,	Please refer to pricing section of the KKSM- SOF Service Order Form and Appendix 1 with a list of available protein kinases. An updated list of available protein kinases may also be downloaded from the Kinexus website at www.kinexus.ca.
Protein Kinase Name Code U.S	S. Price	Please indicate the confidentiality level requested:
1		Non-confidential analysis
2.		Confidential analysis
KKSM CUSTOM SERVICE REQUESTED:		A. CLIENT SCREEN ID NAME:
The base study consists of one control and in vitro treatments with 3 protein kinases carried out in triplicate.	(Bar Code Identification Number) For Kinexus Internal Use Only.	Study ID:
B. PROTEIN KINASE:		C. PRICING:
Option 1 Please attach a completed NSDF-KI (non-confidential) or CSDF-KI (confidential) form with a description of the protein kinases to be used in the study if it is to be supplied by the client. Option 2 For protein kinases sourced from Kinexus, please provide from the list in Appendix 1, the name, code and price shown for the protein kinase to be tested. Please refer to pricing section of the KKSM-SOF Service Order Form and Appendix 1 with a list of available protein kinases. An updated list of available protein kinases may also be downloaded from the Kinexus website at www.kinexus.ca.		
Protein Kinase Name Code U.S	S. Price	Please indicate the confidentiality level requested:
1		☐ Non-confidential analysis
2		Confidential analysis
Name of person completing this form	Signature	Date (Y/M/D)



CLIENT-SUPPLIED NON-CONFIDENTIAL KINASE DESCRIPTION FORM

Subject to terms of the Kinexus Service Agreement

Form: NSDF-KI

KINEXUS ORDER NUMBER

NAME: COMPAN	ny/Institute:
(Authorized Representative or Principal Investigator)	
CUSTOM KINASE SUBSTRATE PROFILING SERVICE R	REQUESTED: (WITH CLIENT SUPPLIED KINASE)
Clients have the option of using their own purified protein kinases for our custom Kina name, purity and source of the kinase (including full name, UniProt ID number, the an that the kinase was expressed in if it is recombinant, and the vender's name and catal do not wish to disclose the source or nature of the antibodies that they are providing instead. Please check the appropriate tick boxes.	imal species for which the amino acid sequence of the kinases is from, the species ogue number if it is commercially sourced). Please note that in the event that clients
A. CLIENT SCREEN ID NAME:	B. KINASE IDENTIFICATION:
Client ID:	Client Name for Kinase:
Use the Client Screen ID Name that you entered on the Service Identification Form	Concentration: Volume:
(SIF) Clients should provide at least enough active kinase for making at least 1 ml of assay solution at the desired final concentration	Recommended dilution for enzyme assay:
C. KINASE DESCRIPTION:	KINEXUS ID NUMBER (FOR INTERNAL USE ONLY)
Kinase name:	(Bar Code Identification Number)
UniProt ID number:	D. COMMERCIAL SOURCE OF KINASE: (if applicable)
Species of origin: (based on amino acid sequence):	Supplier Name:
Human Cow Rat	
☐ Mouse ☐ Rabbit ☐ Other – Provide name:	Supplier Catalog Number:
Purity Description:	Supplier Lot Number:
E. RECOMBINANT KINASE INFORMATION: (if applicable)	F. SPECIAL INSTRUCTIONS – Handling and assay of kinase:
Species for expression:	
Mutation or tagging:	
I hereby certify that all of the information about the protein kinases that I prov	vided in this order is correct and accurate to the best of my knowledge.
Name of person completing this form	Signature Date (m/d/v)



CLIENT-SUPPLIED CONFIDENTIAL KINASE DESCRIPTION FORM

Subject to terms of the Kinexus Service Agreement

Form: CSDF-K

KINEXUS ORDER NUMBER

Date (m/d/y)

NAME:CC	DMPANY/INSTITUTE:
(Authorized Representative or Principal Investigator)	
CUSTOM KINASE SUBSTRATE PROFILING SERVI	
purity and source of the kinase (including full name, Swiss-Prot ID number, the is recombinant, and the vender's name and catalogue number if it is commercial	Im Kinase Substrate Profiling analysis at a substantial discount if they fully describe the namerial animal species for which the kinase is from, the species that the kinase was expressed in if ally sourced). In this event, clients should instead complete a NSDF-KI form. This form applies ses that they are providing, and Confidential Pricing must apply. Please check the appropriate application.
A. CLIENT SCREEN ID NAME:	B. KINASE IDENTIFICATION:
CLIENT ID:	Client Name for Kinase:
	Concentration: Volume:
Use the Client Screen ID Name that you entered on the Service Identification Form (SIF)	Recommended dilution for enzyme assay:
	Clients should provide at least enough active kinase for making at least 1 ml of assay solution at the desired final concentration.
C. SPECIES OF KINASE ORIGIN: (based on amino acid sequence	KINEXUS ID NUMBER (FOR INTERNAL USE ONLY)
☐ Human ☐ Cow	(Bar Code Identification Number)
☐ Mouse ☐ Rabbit	D. SPECIAL INSTRUCTIONS FOR HANDLING AND ASSAY OF
Rat	KINASE:
Other – Provide common name:	-
Purity Description:	
A. CLIENT SCREEN ID NAME:	B. KINASE IDENTIFICATION:
CLIENT ID:	Client Name for Kinase:
CLIENTID.	Concentration: Volume:
Use the Client Screen ID Name that you entered on the Service Identification Form (SIF)	
Fulli (SIF)	Clients should provide at least enough active kinase for making at least 1 ml of assay solution at the desired final concentration.
C. SPECIES OF KINASE ORIGIN: (based on amino acid sequence	KINEXUS ID NUMBER (FOR INTERNAL USE ONLY)
☐ Human ☐ Cow	(Bar Code Identification Number)
☐ Mouse ☐ Rabbit	D. SPECIAL INSTRUCTIONS FOR HANDLING AND ASSAY OF
Rat	KINASE:
Other – Provide common name:	
Purity Description:	
,	
I hereby certify that all of the information on protein kinases that I prov	ided in this order is correct and accurate to the best of my knowledge.

Signature

Name of person completing this form

COMMERCIAL INVOICE

	1	
DATE OF EXPORTATION	EXPORT REFERENCES	
SHIPPER/EXPORTER	CONSIGNEE	
SHIFFERENCENORIER	CONSIGNEE	
	Kinexus Bioinformatics Corporation	
	Suite 1	
	8755 Ash Street	
	Vancouver, B.C.	
	Canada V6P 6T3	
	Telephone: (604) 323-2547	
	Facsimile: (604) 232-2548	
	Email: info@kinexus.ca	
COUNTRY OF EXPORT	TERMS OF SALE	
	Not for resale, sample for analysis	
COUNTRY OF ORIGIN	PURPOSE	
	Research and development	
COUNTRY OF ULTIMATE DESTINATION	EXPORTING CARRIER	
Canada		
INTERNATIONAL AIR WAYBILL NUMBER		
Courier Name:	Number:	
NO TYPE QUANTITY		

NO. OF PKGS	TYPE OF PACKAGING	QUANTITY OF SAMPLES	COMPLETE AND ACCURATE COMMODI	TY DESCRIPTION	UNIT VALUE
	FedEx Letter FedEx Pak Box Other	Total number of 1.5 ml Eppendorf tubes:	Non hazardous, non infectious prand development diagnostic purpont for resale and there is no common Samples are packaged on Dry 1845, Group 3 (X kgs).	oses. Samples are mercial value. Ice, Class 9, UN	\$1.00 per sample
тот	TAL NO. OF PAC	KAGES	TOTAL WEIGHT OF PACKAGES	TOTAL DECLARE	D VALUE
				\$	

These commodities were exported from the Country indicated above in accordance with the Export Administration Regulations and are licensed for the ultimate designation shown. It is hereby certified that this commercial invoice shows the actual price of the goods described, that no other invoice has been or will be issued for these goods, and that all particulars are true and correct.

SIGNATURE AND STATUS OF AUTHORIZED PERSON			
Print Name	Title		
Authorized Signature	Date (month/day/year)		



PROTEOMICS SERVICES AGREEMENT

SERVICE AGREEMENT NO.

This Agreement is entered into effective as of the Effective Date by and between Kinexus Bioinformatics
Corporation ("Kinexus"), a Canadian corporation with a principal place of business at Suite 1, 8755 Ash Street,
Vancouver, British Columbia, Canada, V6P 6T3 AND the corporation or other entity ("Customer") having the
following name and business or institution address:

RECITALS

WHEREAS Kinexus is a bioinformatics company employing proprietary proteomics and bioinformatics services to create and interpret data to map protein signalling networks and compile databases with this knowledge to enable disease biomarker and therapeutics discovery.

WHEREAS the Customer desires to have Kinexus perform standard and/or customized proteomics services with materials and/or information provided by the Customer.

WHEREAS Kinexus is willing to provide these proteomics services under the terms and conditions set forth herein.

THEREFORE, in consideration of the premises and covenants and agreements contained herein, and other good and valuable consideration the receipt and sufficiency of which is hereby acknowledged, Kinexus and the Customer agree as follows:

1. **DEFINITIONS**

- 1.1 "Academic Collaborator" means a principal investigator, employed at a university or other not-for-profit academic research institution.
- 1.2 "Affiliate" means any corporation or other entity that directly or indirectly controls, is controlled by or is under common control with a party to this Agreement. A corporation or other entity shall be regarded as in control of another corporation or entity if it owns or directly or indirectly controls more than fifty percent (50%) of the outstanding voting stock or other ownership interest of the other corporation or entity.
- 1.3 "Corporate Partner" means any Third Party which enters into an agreement with the Customer or its Affiliates involving the grant to such Third Party of rights for the development or commercialization of a product that was discovered, identified, selected, characterized or determined to have therapeutic or diagnostic use through use of the Proteomics Analyses provided to the Customer pursuant to this Agreement.
- 1.4 <u>"Confidential Information"</u> means any information or data received by a party (the "Receiving Party") from the other party (the "Disclosing Party") in connection with the performance of this Agreement that, if

disclosed in writing, is marked or otherwise identified by the Disclosing Party as confidential or, if disclosed orally is identified in writing by the Disclosing Party as confidential within ten (10) days following the disclosure. Confidential Information shall not include any information or data that the Receiving Party can demonstrate:

- (a) was generally available to the public before its disclosure to the Receiving Party or became generally available to the public after its disclosure to the Receiving Party, provided that such information or data did not become generally available to the public by means of an unauthorized act or omission of the Receiving Party;
- (b) was already in the possession of the Receiving Party before its disclosure under this Agreement, as demonstrated by Receiving Party's written records, provided that such information or data was not obtained directly or indirectly from the Disclosing Party under an obligation of confidentiality;
- (c) was disclosed to the Receiving Party, whether before or after its disclosure under this Agreement, by a Third Party, provided that such information or data was not obtained directly or indirectly from the Disclosing Party under an obligation of confidentiality; or
- (d) was independently developed or discovered by employees or agents of the Receiving Party without any use of Confidential Information of the Disclosing Party as demonstrated by Receiving Party's written records.

All of the Proteomics Services technologies provided by Kinexus will be deemed to have been identified as proprietary and considered the Confidential Information of Kinexus.

- 1.5 <u>"Contact"</u> means the contact person of the Customer that is designated on the Service Order Forms, who is deemed to have the authority to deliver Samples, Service Order Forms, Service Information Forms, and Sample Description Forms to Kinexus, on behalf of the Customer, under this Agreement.
- 1.6 <u>"Proteomics Analyses"</u> means one or more of the Custom and Standard Proteomics Services offered by Kinexus that may permit the identification and/or quantification of proteins, their phosphorylation states, their interactions with proteins, peptides, and other compounds, and the regulation of their functional activities by these agents.
- 1.7 <u>"Proteomics Products"</u> means the products of the Custom Proteomics Services offered by Kinexus to manufacture one or more proteins using recombinant DNA technology, and designer peptides by chemical synthesis.
- 1.8 <u>"Sample"</u> means a lysate or semi-purified fraction from cells and tissues, a protein, and/or a compound provided to Kinexus by the Customer, which the Customer has prepared and shipped in a manner that it can be properly used by Kinexus for the Proteomics Analyses. Samples for Proteomics Analyses may also be provided by Kinexus at the request of the Customer.
- 1.9 <u>"Sample Description Form"</u> means the Kinexus form to be completed by the Customer to provide information on the nature of each Sample submitted for the Proteomics Analyses. It is included in the Proteomics Services Customer Information Package with this Agreement, and may be amended from time to time as updated on the Kinexus website
- 1.10 <u>Antibody</u>" means the immunoglobulin reagent that permits detection of a target protein or phosphorylation site.
- 1.11 "Antibody Description Form" means the Kinexus form to be completed by the Customer to provide information on the nature of each Antibody submitted by the Customer for the Proteomics Analyses. It is included

in the Proteomics Services Customer Information Package with this Agreement, and may be amended from time to time as updated on the Kinexus website.

- 1.12 "Service Order Form" means the Kinexus form to be completed by the Customer to provide Kinexus with the Customer's contact and billing information for the Proteomics Analyses or Proteomics Products. This form indicates the level of confidentiality requested by the Customer. It is included in the Proteomics Services Customer Information Package with this Agreement, and may be amended from time to time as updated on the Kinexus website.
- 1.13 "Service Information Form" means the Kinexus form to be completed by the Customer to provide Kinexus with a specific listing of the Samples to be tested for the Proteomics Analysis or a specific description of the Proteomics Products that are requested. It is included in the Proteomics Services Customer Information Package with this Agreement, and may be amended from time to time as updated on the Kinexus website.
- 1.14 "Report" means the underlying raw data and the report provided to The Customer hereunder consisting of the Proteomic Analyses of Samples, including, but not limited to tables of the experimental results. For Proteomics Products, the Report may include raw data confirming the composition and purity of the Proteomics Products.
- 1.15 <u>"Field of Use"</u> means use by Kinexus and its Affiliates and Academic Collaborators of data from the Report for research and commercial purposes relating to the creation and interpretation of knowledge about the composition, architecture and operation of cell signalling networks, improving its Proteomics Services, and the compilation of databases that may become accessible to Third Parties on-line over the Internet.
- 1.16 <u>"Third Party"</u> means any entity other than Kinexus', Kinexus' Affiliates, the Customer and the Customer's Affiliates.
 - 1.17 "Effective Date" means the date of the last signature on this Agreement.

2. REQUEST FOR AND DELIVERY OF PROTEOMICS SERVICES

- Request for Proteomics Services. From time to time, over the Term of this Agreement (as defined in Section 6.1 herein), the Customer can engage Kinexus to provide its Proteomics Analyses or Proteomics Products. After submission of a quotation from Kinexus to the Customer, by delivery to Kinexus of a Service Order Form, a Service Information Form and a Sample Description Form with Samples as appropriate, the Customer hereby requests and authorizes Kinexus to perform Proteomics Services and deliver the results of these services to the Customer, pursuant to the terms and conditions in this Agreement. In the case of Customer requested Proteomics Analyses, this would include the delivery of a Report. In the case of Customer requested Proteomics Products, this would include the delivery of the Proteomics Products and a Report.
- 2.2 <u>Representation and Warranty</u>. The Customer represents and warrants that: (a) it has all right and authority to provide the Sample to Kinexus for analysis under the terms and conditions of this Agreement, (b) it collected the Sample lawfully and with all necessary consents and approvals, and (c) that the collection, use and disclosure of the Sample by Kinexus pursuant to this Agreement will not violate the rights of any Third Party.
- 2.3 <u>Delivery Conditions for Customer Sample.</u> The Customer shall be responsible for making shipping arrangements to deliver Samples to Kinexus. The Customer shall also be responsible for complying with all applicable laws and regulations (including but not limited to customs requirements and relevant handling procedures and protocols) and obtaining any and all permits, forms or permissions that may be required by all regulatory authorities to ship and deliver the Sample, to Kinexus and for Kinexus to accept delivery of the Sample.

- 2.4 <u>Processing and Delivery of Report and Proteomics Products.</u> Subject to the terms of this Agreement, Kinexus shall analyze Samples with the Customer-specified Proteomics Services or produce Customer-specified Proteomics Products, and deliver a Report to the Customer as requested on the Service Order Form and Service Information Form.
- 2.5 Quality of Samples for Proteomics Analyses. Kinexus shall not deliver a Report on any Sample that Kinexus, in its sole discretion, believes has not been prepared and delivered in a manner that would compromise its ability to provide a reliable result. Under such a circumstance, the Sample will be destroyed by Kinexus after ten (10) days notification by e-mail to the Customer or at the request of the Customer prior to the scheduled destruction of the Sample, it will be returned to the Customer provided that the Customer agrees to reimburse Kinexus for the courier costs for its delivery.

3. PAYMENTS

- 3.1 <u>Payments for Proteomics Services</u>. For each Proteomics Analyses and Proteomics Product requested under this Agreement, the Customer shall pay to Kinexus a fee in accordance with the amount specified on the Service Order Form and the Service Identification Form for the requested service, which may be amended from time to time as updated on Kinexus' website. This amount will be based on a formal quotation issued by Kinexus to the Customer. In the absence of a formal quotation, the pricing will be based on the pricing specified in the latest versions of the Customer Information Packages for Proteomics Services that are downloadable from the Kinexus website (www.kinexus.ca). The category of pricing depends on the level of requested confidentiality for analysis:
 - (a) Non-Confidential Analyses. If the Samples are provided by the Customer, then all of the Sample information on the Client Supplied Non-Confidential Sample Description Form is completed and is not designated as Confidential Information on the Service Identification Form. If Antibodies are supplied by the Customer, then all of the Antibody information on the Client Supplied Antibody Description Form (see example in Appendix) must be completed and is not designated as Confidential Information on the Service Identification Form
 - (b) <u>Confidential Analyses</u>. If the Samples are provided by the Customer, then all of the Sample information on the Client Supplied **Confidential** Sample Description Form must be completed and **is** designated as Confidential Information on the Service Identification Form.
- 3.2 The Customer shall issue a purchase order or provide a charge account at the time the Customer sample arrives at Kinexus' offices at Suite 1, 8755 Ash Street, Vancouver, British Columbia, Canada, V6P 6T3. Kinexus will invoice Customer when the Proteomics Analyses or Proteomics Products are complete and delivered to Customer. Payment terms are net 30 days from date of invoice.
- 3.3 <u>Interest on Late Payments.</u> Any overdue payments by the Customer to Kinexus under this Agreement shall bear interest, to the extent permitted by applicable law at 18% per annum, calculated on the total number of days payment is delinquent; provided, however, that interest shall not accrue pursuant to this Section 3.3 on any amounts payable under this Agreement with respect to which payment is disputed in good faith; provided, further that interest shall accrue pursuant to this Section 3.3 once such dispute has been resolved if payment is not made promptly thereafter.

4. INTELLECTUAL PROPERTY RIGHTS

- 4.1 <u>Ownership of Sample Information</u>. The Customer owns all rights to the Sample information provided to Kinexus. For Non-Confidential Proteomics Analyses, the Customer grants Kinexus a non-exclusive, royalty-free fully paid up worldwide perpetual license to use, copy, publish, compile, display, communicate, modify, translate and otherwise exploit (and authorize Third Parties to do any of the foregoing) to use the information on the Client Supplied **Non-Confidential** Sample Description Form in the Field of Use, provided that the Customer's identity is not linked to, or otherwise disclosed with respect to, such data.
- 4.2 <u>Ownership of Report</u>. The Customer shall own the data in the Report. For Non-Confidential Proteomics Analyses, the Customer grants Kinexus a non-exclusive, royalty-free fully paid up worldwide perpetual license to use, copy, publish, compile, display, communicate, modify, translate and otherwise exploit (and authorize Third Parties to do any of the foregoing) data from the Report in the Field of Use.
- 4.3 <u>Confidentiality of Sample Information</u>. Kinexus will have no rights with respect to the Confidential Sample information until the Sample information is published or otherwise enters the public domain. Thereafter, Kinexus can use the results of the Proteomics Analyses of the Customer Samples for its internal research and development programs.
- 4.4 <u>Ownership of Proteomics Products.</u> The Customer owns the Proteomics Products that have been delivered to the Customer in the amounts specified in the Service Order Form and the Service Information Form. Kinexus owns any excess Proteomics Products and may dispose of these in its best interests.
 - 4.5 Ownership of New Intellectual Property.
 - (a) The Customer shall own and have rights to all inventions, discoveries, improvements, know-how, technical information, data or other technology discovered, conceived, made, developed and/or reduced to practice through the use of the data in the Report and Proteomics Products solely by employees of the Customer or jointly with its Affiliates;
 - (b) Kinexus shall own and have rights to all inventions, discoveries, improvements, know-how, technical information, data or other technology discovered, conceived, made, developed and/or reduced to practice through the use of the data in the Report and Proteomics Products solely by employees of Kinexus or jointly with its Affiliates.
- 4.6 <u>Non-Exclusive License to Preserve Kinexus Proteomics Services Freedom of Operation.</u> In the event one or more claims of an issued patent arising from the use of a Report by the Customer, its Affiliates, Academic Collaborators or Corporate Partners would, absent a license from the Customer or its Affiliates, prevent Kinexus from using or permitting others to use the Kinexus Proteomics Services or any data therein, then the Customer and/or its Affiliates (as applicable) shall grant to Kinexus a non-exclusive, royalty-free fully-paid up perpetual license, including the right to grant sublicenses, under any such patent claim to use and permit others to use the Proteomics Services.

5. CONFIDENTIALITY

5.1 <u>Confidentiality.</u> Each Receiving Party shall treat the Confidential Information of the Disclosing Party as strictly confidential and (a) take reasonable precautions to protect such Confidential Information (including, without limitation, all precautions such as the Receiving Party employs with respect to its own confidential information), (b) not disclose or make available to any Third Party such Confidential Information without the express prior written consent of the Disclosing Party and (c) use such Confidential Information only for purposes specifically authorized under this Agreement. Each Receiving Party may disclose Confidential

Information to its employees, consultants, Affiliates and agents, and to licensees or prospective licensees of its rights to any invention, on a need-to-know basis and on the condition that such employees, Affiliates, agents, licensees and prospective licensees are obligated to maintain the confidentiality of the Confidential Information under written agreements that contain terms and conditions no less restrictive than the terms and conditions of this Section 5. Each Receiving Party may disclose Confidential Information of the Disclosing Party pursuant to a demand issued by a court or governmental agency or as otherwise required by law, provided, however, that the Receiving Party notifies the Disclosing Party promptly upon receipt thereof, giving the Disclosing Party sufficient advance notice to permit it to seek a protective order or other similar order with respect to such Confidential Information, and provided, further, that the Receiving Party furnishes only that portion of the Confidential Information which it is advised by counsel is legally required whether or not a protective order or other similar order is obtained by the Disclosing Party.

- 5.2 <u>Publication</u>. The Customer may publish and/or present the Report, abstracts or manuscripts generated utilizing the Report, and any data and/or results generated by the Customer utilizing the Report. The Customer is encouraged to disclose in scientific publications any Proteomics Analyses that were performed by Kinexus and any Proteomics Products were produced by Kinexus that meaningfully contributed to the described work. Please refer to "Kinexus Bioinformatics Corporation (Vancouver, Canada)." For all Samples submitted for analysis and identified as Non-Confidential by the Customer, Kinexus will not use, copy, publish, compile, display, communicate, modify, or translate the Sample Information or the data from the Report for a period of 180 days (6 months) following the return of the Report to the Customer. At any time, the Customer may opt to pay the difference in price between the Non-Confidential pricing level to the Confidential pricing level for each applicable Sample, to ensure the confidentiality status of such sample is changed.
- 5.3 <u>Confidential Sample Information.</u> All parties agree that the term of confidentiality pertaining to that Sample information will expire when the Sample information is published or otherwise enters public domain through no fault of Kinexus.
- 5.4 <u>Use of Customer Name</u>. Except as expressly provided in Section 9.5, no right or license is granted hereunder by Customer for Kinexus to use the Customer's name in relation to data from a Report to a third party.

6. TERM AND TERMINATION

- 6.1 <u>Term.</u> The term of this Agreement ("**Term**") shall commence on the Effective Date and shall remain in effect for fifteen (15) years or until the termination of this Agreement pursuant to the terms hereof.
- 6.2 <u>Early Termination.</u> Each party shall have the right to terminate this Agreement at any time prior to Kinexus' delivery of a Report or Proteomics Product to the Customer hereunder, upon ten (10) days written notice to the other party, if such party reasonably determines that the production, or use of such Sample infringes intellectual property rights of any Third Party, and the Customer elects not to obtain a license under the necessary Third Party intellectual property rights at its sole expense. If this Agreement is terminated by either party pursuant to this Section 6.2, neither party shall have any obligation to the other with respect to payments under this Agreement regarding the Sample or Proteomics Product at issue.

Kinexus shall have the right to terminate any work order for any Proteomics Services upon ten (10) days written notice to the Customer, upon the identification of a technical difficulty related to the Sample or Proteomics Product which would prevent it from delivering the Report or Proteomics Product using reasonable efforts. If Kinexus terminates a work order as a result of a technical difficulty related to a Customer Sample that is the fault of Kinexus, Kinexus shall provide for the reanalysis of the same number of problematic Customer Samples for the Proteomics Analyses at the original agreed upon price without any additional expenses incurred by the Customer, or Kinexus shall repay any prepayment fee paid by the Customer for such a Customer Sample and neither party shall have any further obligation to the other with respect to that Customer Sample.

If Kinexus terminates a work order for Proteomics Analyses as a result of a technical difficulty related to the Customer Sample (including insufficient material or other problems associated with the quality of the Sample) that is the fault of the Customer, then Kinexus shall provide for the reanalysis of the problematic Customer Samples at the original agreed upon price without any additional expenses incurred by the Customer, provided Kinexus completes the full Proteomics Analyses for all Samples. For any subsequent resubmission of Customer Samples for Proteomics Analyses due to technical difficulty that is again the fault of the Customer, Kinexus shall provide for the reanalysis of the problematic Customer Samples at an additional charge per sample at a price mutually agreed by the Customer and Kinexus. If the Customer elects not to resubmit Samples for Proteomics Analyses, then the Customer will pay Kinexus an amount equivalent to 50% of the quoted price for the work performed by Kinexus to this point.

6.3 Events of Default. An event of default (an "Event of Default") shall be deemed to occur upon a material breach of this Agreement by a party (including, without limitation, any breach of the provisions of Section 5) if the breaching party fails to remedy such breach within thirty (30) days after written notice thereof by the non-breaching party.

6.4 <u>Effect of an Event of Default.</u>

- (a) Remedies Available to Kinexus. If an Event of Default occurs relating to a material breach by the Customer, then Kinexus shall have the right, at its option exercisable in its sole discretion, in addition to any other rights or remedies available to it at law or in equity, to immediately terminate this Agreement upon notice thereof to the Customer, in which case the Customer shall return to Kinexus, or, upon Kinexus' written instruction, destroy any Report, Proteomics Products, and all information, other materials or documentation provided or made available by Kinexus pursuant to this Agreement, and any copies thereof (including electronic copies).
- (b) Remedies Available to the Customer. If an Event of Default occurs relating to a material breach by Kinexus, then the Customer shall have the right, at its option exercisable in its sole discretion, in addition to any other rights or remedies available to it at law or in equity and subject to the limitations set forth in Section 7, to terminate this Agreement upon notice thereof to Kinexus.
- 6.5 <u>Effect of Expiration or Termination of Agreement.</u> The expiration or termination of this Agreement shall not relieve the parties of any obligation accruing prior to such expiration or termination. Kinexus will not be required to continue Custom Immunohistochemistry Analyses on a Sample after termination, and the Customer will be required to pay for work done prior to termination. The provisions of Sections 4, 5, 6, 7, 8, and 9 hereof shall survive any expiration or termination of this Agreement.

7. DISCLAIMER OF WARRANTIES AND LIMITATION OF LIABILITY

- 7.1 <u>Disclaimer of Warranties</u>. THE PROTEOMICS SERVICES ARE BEING SUPPLIED TO CUSTOMER WITH NO EXPRESS, IMPLIED, STATUTORY OR OTHER WARRANTIES, REPRESENTATIONS, CONDITIONS OR GUARANTEES, INCLUDING THOSE OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, TITLE AND DURABILITY. WITHOUT LIMITING THE FOREGOING, KINEXUS MAKES NO REPRESENTATION OR WARRANTY THAT THE USE OF THE REPORT, ANY PROTEOMICS PRODUCTS OR THE DATA THEREIN OR THE PERFORMANCE OF THIS AGREEMENT WILL NOT INFRINGE ANY INTELLECTUAL PROPERTY OR OTHER RIGHTS OF ANY THIRD PARTY.
- 7.2 <u>Limitation of Liability</u>. Kinexus shall not be liable for any use by the Customer, its Affiliates, Corporate Partners, or Academic Collaborators of the Report and any Proteomics Products or any loss, claim,

damage or liability, of whatever kind or nature, which may arise from or in connection with the use of the Report or the data therein, and any Proteomics Products. NOTWITHSTANDING ANYTHING ELSE IN THIS AGREEMENT OR OTHERWISE TO THE CONTRARY, NEITHER KINEXUS NOR CUSTOMER WILL BE LIABLE TO EACH OTHER WITH RESPECT TO ANY MATTER ARISING UNDER THIS AGREEMENT UNDER ANY CONTRACT, NEGLIGENCE, STRICT LIABILITY OR OTHER LEGAL OR EQUITABLE THEORY FOR (I) ANY PUNITIVE, EXEMPLARY, INCIDENTAL OR CONSEQUENTIAL DAMAGES OR LOST PROFITS OR (II) COST OF PROCUREMENT OF SUBSTITUTE GOODS, TECHNOLOGY OR SERVICES. WITHOUT IN ANY WAY LIMITING THE FOREGOING, KINEXUS SHALL NOT, IN ANY EVENT, HAVE ANY LIABILITY WHATSOEVER IN CONNECTION WITH THIS AGREEMENT IN EXCESS OF AN AMOUNT EQUAL TO THE FEES PAID TO KINEXUS BY CUSTOMER HEREUNDER IN RESPECT OF THE PROTEOMICS SERVICES AT ISSUE.

8. INDEMNIFICATION

Except to the extent prohibited by law, the Customer shall assume all liability for, and shall defend, indemnify and hold Kinexus, its Affiliates and their respective directors, officers, employees and agents harmless from, all claims, losses, damages or expenses (including reasonable attorneys' fees) arising directly or indirectly as a result of: (a) the use of the Report or the data therein and any Proteomics Products by the Customer or its Affiliates, Corporate Partners or Academic Collaborators, or (b) the breach, untruthfulness or inaccuracy of any of the Customer's representations and warranties in this Agreement.

9. MISCELLANEOUS

- 9.1 <u>Entire Agreement.</u> The Appendices to this Agreement, together with all terms and conditions contained within this Agreement constitute the entire understanding between the parties with respect to the subject matter hereof and, with respect to any conflicting terms from prior agreements between the parties, supersedes and cancels such conflicting sections from all previous registrations, agreements, commitments and writings in respect thereof. This Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by both parties hereto.
- Assignment and Waiver. This Agreement may not be assigned or otherwise transferred by either party without the written consent of the other party, such consent will not be unreasonably withheld. Notwithstanding the foregoing, Kinexus may, without such consent, assign its rights and obligations under this Agreement (a) to any Affiliate or (b) to a Third Party in connection with a merger, consolidation or sale of such portion of its assets that includes rights under this Agreement provided, however, that Kinexus' rights and obligations under this Agreement shall be assumed by its successor in interest in any such transaction. In the event of such a transaction with Third Party, notwithstanding the other provisions of this Agreement, the intellectual property rights of such Third Party shall not be subject to the licenses granted by Kinexus under this Agreement. Any purported assignment in violation of the provisions of this Section 9.2 shall be void. Any permitted assignee shall assume all obligations of its assignor under this Agreement. The waiver by either party hereto of any right hereunder or the failure to perform or of a breach by the other party shall not be deemed a waiver of any other right hereunder or of any other breach or failure by said other party whether of a similar nature or otherwise.
- 9.3 Force Majeure. Neither party shall be held liable or responsible to the other party nor be deemed to have defaulted under or breached this Agreement for failure or delay in fulfilling or performing any obligation under this Agreement when such failure or delay is caused by or results from causes beyond the reasonable control of the affected party, including but not limited to fire, floods, embargoes, war, acts of war (whether war is declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor or supply disturbances, acts of God or acts, omissions or delays in acting by any governmental authority or the other party; provided, however, that the party so affected shall use reasonable commercial efforts to avoid or remove such causes of nonperformance, and

shall continue performance hereunder with reasonable dispatch whenever such causes are removed. Either party shall provide the other party with prompt written notice of any delay or failure to perform that occurs by reason of force majeure. The parties shall mutually seek a resolution of the delay or the failure to perform as noted above.

9.4 <u>Notices.</u> Any consent, notice, or report required or permitted to be given or made under this Agreement by one of the notification parties hereto to the other shall be in writing, delivered personally, by email or by facsimile (and promptly confirmed by telephone, personal delivery or courier) or courier, postage prepaid (where applicable), addressed to such other party at its address indicated below, or to such other address as the addressee shall have last furnished in writing to the addressor and shall be effective upon receipt by the addressee.

If to Kinexus:

Kinexus Bioinformatics Corporation Suite 1, 8755 Ash Street Vancouver, British Columbia, Canada V6P 6T3 Attention: Dr. Steven Pelech

President & C.S.O.

Telephone: (604) 323-2547 extension 10

Facsimile: (604) 323-2548

If to the Customer:

To the Customer at the address designated at the front of this Agreement and to the attention of the duly authorized representative signing this Agreement.

- 9.5 <u>Publicity</u>. Except as required by law, the terms of this Agreement shall be treated as Confidential Information and shall not be disclosed to anyone (except for the parties' respective directors, officers, employees, consultants, agents and attorneys assisting in the review and negotiation of this Agreement and/or who have a need to know the terms of this Agreement) without the written consent of the other party, such consent which will not be unreasonably withheld. Notwithstanding the foregoing, (a) Kinexus may, without such consent, publicly announce the execution of this Agreement with the Customer and may reference the Customer as a Kinexus client.
- 9.6 No Partnership. It is expressly agreed that the relationship between Kinexus and the Customer shall not constitute a partnership, joint venture or agency. Neither Kinexus nor the Customer shall have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on the other, without the prior consent of the other party to do so.
- 9.7 <u>Applicable Law.</u> This Agreement shall be governed by, construed, interpreted and enforced in accordance with, the laws of the province of British Columbia and the laws of Canada, without reference to conflict of laws principles.

9.8 Dispute Resolution.

(a) The parties hereby agree that they will attempt in good faith to resolve any controversy or claim arising out of or relating to this Agreement promptly by negotiations. If a controversy or claim should arise hereunder, the matter shall be referred to an individual designated by the Chief Executive Officer or President of Kinexus and an individual designated by the Chief Executive Officer (or the equivalent position) of the Customer (the "Representatives"). If the matter has not been resolved within twenty-one (21) days of the first meeting of the Representatives of the parties (which period may be extended by mutual agreement) concerning such matter, subject to rights to injunctive relief and specific performance, and unless otherwise specifically provided for herein, any controversy or claim arising out of or relating to this Agreement, or the breach thereof, will be settled as set forth in Section 9.8(b).

- (b) All disputes arising in connection with this Agreement that are not resolved pursuant to Section 9.8(a) above shall be finally settled in Vancouver, British Columbia, by a single arbitrator appointed pursuant to the provisions of the *Commercial Arbitration Act* (British Columbia). Notwithstanding the above, either party has the right to bring an action in a court of competent jurisdiction against the other party for (i) any breach of such other party's duties of confidentiality pursuant to Section 5 of this Agreement; (ii) any infringement of its proprietary rights by the other party; and (iii) for interim protection such as, by way of example, an interim injunction. Judgment upon the arbitrator's award may be entered in any court of competent jurisdiction. The award of the arbitrator may include compensatory damages against either party, but under no circumstances will the arbitrator be authorized to, nor shall he/she, award punitive, consequential or incidental damages against either party. The parties agree not to institute any litigation or proceedings against each other in connection with this Agreement except as provided in this Section 9.8.
- 9.9 <u>Severability</u>. Each party hereby agrees that it does not intend to violate any public policy, statutory or common laws, rules, regulations, treaty or decision of any government agency or executive body thereof of any country or community or association of countries. Should one or more provisions of this Agreement be or become invalid, the parties hereto shall substitute, by mutual consent, valid provisions for such invalid provisions which valid provisions in their economic effect are sufficiently similar to the invalid provisions that it can be reasonably assumed that the parties would have entered into this Agreement with such valid provisions. In case such valid provisions cannot be agreed upon, the invalidity of one or several provisions of this Agreement shall not affect the validity of this Agreement as a whole, unless the invalid provisions are of such essential importance to this Agreement that it is to be reasonably assumed that the parties would not have entered into this Agreement without the invalid provisions.
- 9.10 <u>Counterparts.</u> This Agreement may be executed in counterparts, each of which when executed and delivered is an original, but both of which together shall constitute one and the same instrument.
- 9.11 <u>Fax Delivery.</u> This Agreement may be executed by the parties and transmitted by facsimile and if so executed and transmitted this Agreement will be for all purposes as effective as if the parties had delivered an executed original Agreement.

IN WITNESS WHEREOF, the parties have caused their duly authorized officer to execute and deliver this Agreement as of the Effective Date.

Printed Name of Institute or Company	KINEXUS BIOINFORMATICS CORPORATION
Per:	Per:
Signature of Authorized Representative	Signature of Dr. Steven Pelech
Name:	Dr. Steven Pelech
Title:	President and Chief Scientific Officer
Date signed:	Date signed: