OncoArendi Therapeutics

Warsaw, 21/06/2017

REQUEST FOR PROPOSAL

28/2017 – IPF/IBD/STRATEGMED/YKL40/ARG

I. ORDERING PARTY:

OncoArendi Therapeutics SA ul. Żwirki i Wigury 101 02-089 Warszawa VAT No. 728 27 89 248	**Contact person** Paulina Stańczak p.stanczak@oncoarendi.com tel. 798 352 548

II. OBJECT OF THE REQUEST / PROPOSAL:

Research service of testing ADMET/pharmacokinetic properties of small molecule compounds

The order carried out as a part of the projects titled:
- IBD: Preclinical and Clinical Development of a New Chemical Entity for Asthma and Inflammatory Bowel Disease (POIR.01.01.01 00-0168/15)
- IPF: Development of a first-in-class small molecule drug candidate for treatment of idiopathic pulmonary fibrosis through chitotriosidase inhibition (POIR.01.01.01-00-0551/15)
- STRATEGMED: Development of new cancer therapies based on selective antitumor immunomodulators (STRATEGMED2/265503/3/NCBR/15)
- YKL-40: Development of a first-in-class small molecule drug candidate for cancer treatment through YKL 40 inhibition (POIR.01.01.01-00-0552/16)

and because of the application process for the grant titled: **ARG** - PRE-CLINICAL AND CLINICAL DEVELOPMENT OF AN ARGINASE INHIBITOR FOR CANCER IMMUNOTHERAPY
co-financed by the National and European Union Funds and because of the competitiveness principle

III. THE FORM OF THE ORDER:

III.1 The Request is not made under the The Public Procurement Law (29/01/2004 i.e. Dz. U. z 2013 r., poz. 907 z późn. zm.).
III.2 This order is carried out in accordance with the principle of competitiveness, openness, transparency and equal access.
III.3 The Ordering Party reserves the right to cancel this procedure without providing reasons, and also to complete the procedure without choosing the winning tender.
III.4 In the course of examination and evaluation of the offers the Ordering Party may require Contractors to present explanations concerning the content of submitted bids.
III.5 The Ordering Party reserves the right to change the content of this request. If the changes can affect the content of tenders submitted in the procedure, the Ordering Party shall extend the tender

submission deadline. Any changes made shall be provided promptly to all tenderers to which the request was sent and shall be binding on them.

III.6 This procedure does not set the obligation for OncoArendi Therapeutics SA to sign any formal contracts.

III.7 It is not possible to make an offer for a part of an order.

III.8 In the case of a positive decision the Ordering Party will call the Contractor to conclude a contract for the research service on the implemented projects and to conclude a conditional contract for the future project for which the Ordering Party is applying.

IV. CONDITIONS FOR PARTICIPATION IN THE PROCEEDINGS:

IV.1 The Request for offers relates to potential Contractors whose scope of business activity is in full compliance with the subject of this Request.

IV.2 The offers may be issued by parties who:

- have the necessary qualifications and gained years of experience to carry out the described activity and have the appropriate technical potential to perform the contract,
- are in a good economic and financial standing, which assures proper execution of the project in the declared time,
- are licensed to carry out the activity in question, if this is required by law.

As a proof of the above, the Ordering Party requires that the Contractor submit, along with the tender, a statement about fulfilling conditions for participation in the proceedings. The model statement is attached as Appendix 2 to this request for proposal.

IV.3 The possibility of subcontracting studies to an additional contractor is forbidden.

IV.4 Issuing the offer represent the full acceptance of the rules set in this Request.

IV.5 Excluded from the proceedings shall be those contractors who are personally or equity related to the Ordering Part.

V. DETAILED DESCRIPTION OF THE OBJECT OF THE REQUEST:

CPV code: 73111000-3 – Laboratory research services

The subject of the service are:

1. Ames fluctuation assay, evaluating the mutagenic potential of chemicals
2. The *in vitro* micronucleus assay in CHO-K1 cells (without or with S9)
3. Cell membrane permeability test in Caco2 cell line
4. Determination of binding with plasma proteins (mouse, rat, dog, human)
5. Cell membrane permeability test (PAMPA)
6. Evaluating of *in vitro* cytotoxicity potential of chemicals (inhibition of proliferation of HepG2 cell line)
7. Determination of solubility in certain pH
8. Determination of dopamine transporter inhibition (radioligand)
9. logD assesment
10. Evaluation of hERG inhibition in patch clamp assay
11. Evaluation of Nav1.5 inhibition in patch clamp assay
12. Evaluation of GABAA inhibition in patch clamp assay
13. Evaluation of GABAA1 (alpha 1,beta 2,gamma 2) binding assay (radioligand)
14. Evaluation of Cl- channel (GABA-gated) (TBOB site) binding assay (antagonist radioligand)
15. Determination of the conjugation reaction with glucuronic acid
16. Determination of inhibition or activation of kinase panel including:

Abl kinase	FGFR3 kinase	PAK2
Akt1/PKBalpha	GSK3beta	PAK4
AurA/Aur2 kinase	HGK (MAP4K4)	PDK1
CaMK2alpha	IKKalpha	Pim2 kinase
CDC2/CDK1 (cycB)	IRAK4	PKA
CDK2 (cycA)	IRK (InsR)	PKCbeta 2
CHK1	JAK3	PLK1
CHK2	JNK1	RAF-1 kinase
c-Met kinase	KDR kinase (VEGFR2)	ROCK1
EGFR kinase	Lck kinase	SGK1
EphA2 kinase	MAPKAPK2	SIK
EphA3 kinase	MARK1	Src kinase
EphB4 kinase	MNK2	TAOK2 (TAO1)
ERK2 (P42mapk)	MST4 kinase	TRKA
FGFR1 kinase	NEK2	
FGFR2 kinase	p38alpha kinase	

17. Evaluation of metabolic stability using microsomes (human, rat, mouse, dog).
18. Evaluation of metabolic stability using hepatocytes (human, rat, mouse, dog).
19. Evaluation of cytochromes inhibition including:

CYP1A	CYP2C9	CYP2E1
CYP2B6	CYP2C19	CYP3A
CYP2C8	CYP2D6	CYP3A

20. Evaluation of cytochromes induction including:
    CYP1A
    CYP2B6
    CYP3A4
21. Inhibition of drug transporters including:

P-gp	OAT1	OCT2
BCRP	OAT3	ASBT
MRP1	OATP1B1	NTCP
MRP2	OATP1B3	
MRP3	OCT1	

22. Determination of inhibition or activation of diversity profile including following assays:

GPCRs	
Adenosine	A1 (antagonist radioligand)
	A2A (agonist radioligand)
	A3 (agonist radioligand)
Adrenergic	alpha1 (non-selective) (antagonist radioligand)
	alpha2 (non-selective) (antagonist radioligand)
	beta2 (agonist radioligand)
	beta1 (agonist radioligand)

Angiotensin-II	AT1 (antagonist radioligand) AT2 (agonist radioligand)
Bradykinin	B1 (agonist radioligand) B2 (agonist radioligand)
Cannabinoid	CB1 (agonist radioligand) CB2 (agonist radioligand)
Cholecystokinin	CCK1 (CCKA) (agonist radioligand) CCK2 (CCKB) (agonist radioligand)
Corticotropin releasing factor	CRF1 (agonist radioligand)
Dopamine	D1 (antagonist radioligand) D2S (antagonist radioligand) D3 (antagonist radioligand) D4.4 (antagonist radioligand)
Endothelin	ETA (agonist radioligand) ETB (agonist radioligand)
Histamine	H1 (antagonist radioligand) H2 (antagonist radioligand) H3 (agonist radioligand)
Leukotrienes	BLT1 (LTB4) (agonist radioligand) CysLT1 (LTD4) (agonist radioligand)
Melanocortin	MC4 (agonist radioligand)
Melatonin	MT1 (ML1A) (agonist radioligand)
Muscarinic	M (non-selective) (antagonist radioligand)
Neurokinin	NK1 (agonist radioligand) NK2 (agonist radioligand) NK3 (antagonist radioligand)
Neuropeptide Y	Y (non-selective) (agonist radioligand)
Opioid and opioid-like	opioid (non-selective) (antagonist radioligand) NOP (ORL1) (agonist radioligand)
Prostanoid	EP2 (agonist radioligand)

	IP (PGI2) (agonist radioligand)
Purinergic	P2Y (agonist radioligand)
Serotonin	Serotonin (5-Hydroxytryptamine) 5-HT1, Non-Selective
Thyrotropin releasing hormone	TRH1 (agonist radioligand)
Vasopressin	V1a (agonist radioligand) V2 (agonist radioligand)
Steroid nuclear receptors	AR (agonist radioligand) ER (non-selective) (agonist radioligand) PR (agonist radioligand) GR (agonist radioligand)
Non-steroid nuclear receptors	PPARgamma (agonist radioligand)
GABA	GABA (non-selective) (agonist radioligand)
Imidazoline	I2 (antagonist radioligand)
Nicotinic	N neuronal alpha4beta2 (agonist radioligand)
Sigma	sigma (non-selective) (agonist radioligand)
Ca2+ channels	Ca2+- L (dihydropyridine site) (antagonist radioligand) Ca2+- L (diltiazem site) (benzothiazepines) (antagonist radioligand) Ca2+- L (verapamil site) (phenylalkylamine) (antagonist radioligand)
K+ channels	KATP (antagonist radioligand) KV (antagonist radioligand) SKCa (antagonist radioligand)
Na+ channels	Na+- site 2 (antagonist radioligand)
GABA Channels	BZD (central) (agonist radioligand) Cl- channel (GABA-gated) (antagonist radioligand)
Glutamate Channels	AMPA (agonist radioligand) kainate (agonist radioligand) NMDA (antagonist radioligand)

	PCP (antagonist radioligand)
Purinergic Channels	P2X (agonist radioligand)
Choline	choline transporter (CHT1) (antagonist radioligand)
Dopamine	dopamine transporter (antagonist radioligand)
GABA	GABA transporter (antagonist radioligand)
Norepinephrine	norepinephrine transporter (antagonist radioligand)
Serotonin	5-HT transporter (antagonist radioligand)
AGC	PKCalpha
DNA repair & mitotic enzymes	CENP-E Eg5
HDACs	HDAC3 HDAC4 HDAC6 HDAC11 sirtuin 1 (inhibitor effect) sirtuin 2 (inhibitor effect)
Phosphatases	phosphatase 1B (PTP1B) phosphatase CDC25A
Phosphodiesterases	PDE1B PDE2A1 PDE3A PDE4D2 PDE5 (non-selective)
Monoamine & neurotransmitter synthesis & metabolism	acetylcholinesterase COMT (catechol-O-methyl transferase) GABA transaminase MAO-A MAO-B tyrosine hydroxylase
ATPase	ATPase (Na+/K+)

Lipoxygenases	5-lipoxygenase
Cyclooxygenases	COX1
Cyclases	adenylyl cyclase (activator effect) guanylyl cyclase (activator effect)

23. Metabolite identification *in vitro* (Liver microsomes, S9, hepatocyte)
24. *In vivo* metabolite analysis in plasma or tissue from in-life studies
25. *In vivo* pharmacokinetic profile of compound analyzed in mice or rat with renal or biliary clearance

VI. EVALUATION OF THE OFFERS:

VI.1 Price – weight: 90% (90 pts.)

In this criterion point will be calculated according to the formula below:

$$\text{Points received} = \quad Pc = \frac{C_{min}}{C_{evaluated}} \times 90$$

where:

Pc – Points received
C_{min}– the smallest Net price
$C_{evaluated}$ – Net price of the offer being evaluated
90– weight of the criterion (90%)

The total contract value is a sum of costs for all individual studies. The studies were priced based on the information specified in the Request for the Offer

VI.2 Payment deadline – weight: 10% (10 pts.)
up to 7 days - 0 pts.
8 – 14 days – 3 pts.
15 – 21 days – 5 pts.
22 – 30 days – 7 pts.
more than 30 days – 10 pts.

10 – weight of the criterion (10 %)

VI.3 In the case of two or more tenders with equal number of points awarded, to guarantee performance of the contract in a manner favorable to the environment, by providing minimize the consumption of materials, raw materials, energy, etc. any environmental certifications will be taken into consideration (eg. ISO).

If the abovementioned does not allow to choose the best offer, the Ordering Party shall call Contractors who submitted equally evaluated offers to submit, within the period specified, additional offers. Contractors cannot offer higher prices than those offered in the tenders.

VII. HOW TO PREPARE AND SUBMIT THE OFFER:

IX.1. The offer should be signed by the person authorized to represent the institution.
IX.2. Each contractor may submit only one offer.

IX.3. The Contractor should make the offer in Polish or English.
IX.4. The costs of the offer preparation shall be incurred by the offering party.
IX.5. Offers must be submitted no later than: **28/06/2017, 23:59** and must be written on the form as in Appendix 1 to the request for proposals
IX.6. Offers shall be issued via email to: **p.stanczak@oncoarendi.com**
IX.7. Offers that do not meet the deadline will not be taken into consideration.
IX.8. Any questions concerning the Object of the tender should be addressed to p.stanczak@oncoarendi.com no later than 26/06/2017, 15:00. Contact person is: Paulina Stańczak
IX.9. The offer should be valid for at least 30 days from its submission.
IX.10. The price should be set in both Net and Gross.
IX.11. The offer shall not be presented in price variants.

VIII. TENDER RESULTS

The winner will be informed via e-mail address, Formal results will be also published on the Ordering Party's website (www.oncoarendi.com) and on public domain called Baza Konkurencyjności.

IX. MOST IMPORTANT PROVISIONS OF THE AGREEMENT

IX.1. Supplier will be obligated to enter into the agreement including all conditions presented in the Request for the Offer.
IX.2. It is not possible to introduce significant changes to the content of the agreement in relation to the content of the offer, which was the base for the Service Provider selection, unless:

a) the amendments concern performing additional services by the Service Provider, not covered by the basic contract, provided they are necessary and the following conditions are met:
   i. the change of the Service Provider cannot be made due to economic or technical reasons, in particular concerning the interchangeability and interoperability of equipment, services or installations, ordered as part of the basic contract,
   ii. the change of the Service Provider would cause significant inconvenience or substantial cost increase to the Ordering Party,
   iii. the value of any subsequent changes do not exceed 50% of the basic contract value,
b) the amendment does not lead to a change in the nature of the contract and the following conditions are met:
   i. the need for the contract change is brought about by circumstances which the Ordering Party, acting with due diligence, could not foresee,
   ii. the value of a change does not exceed 50% of the basic contract value,
c) the amendment does not lead to a change in the nature of the contract and the total value of changes is less than 209 000 EUR, and at the same time is less than 10% of the basic value
d) If the modification of clinical study plan become a matter of necessity, the order description and the Clinical Study Synopsis will be adjusted. The current study plan will be reviewed and validated after analyzing all preclinical toxicology and safety pharmacology data.

If the clinical study plan changes, the contract value will be amended.

Any contract amendment must be done in writing, otherwise will not be valid.

IX.3. Information regarding contractual penalties:
a) If the offered project execution time (as defined in Section VI.2.) extends for at least 15 days, the Service Provider shall pay the Ordering Party a contractual penalty of 5% of the net offer price for exceeding the time limit, and then another 5% of net offer price for each additional 30 days of delay. Moreover, the Ordering Party will gain a right to withdraw from the contract if the project execution time is exceeded by at least 60 days.

b) Due to the termination or withdrawal from the Agreement by either Party for reasons caused by the Service Provider, the Ordering Party will charge a contractual penalty of 25% of net offer price.
c) The formal basis for charging contractual penalties will be a debit note the Ordering Party delivers to the Service Provider. The Ordering Party shall be entitled to deduct contractual penalties from payments due to the Service Provider.
d) The Ordering Party has the right to claim damages in the amount exceeding contractual penalties based on general principles.
e) Contractual penalties will be paid within 7 days form the debit note receipt date.

Appendices:

1. The offer form
2. Statement concerning fulfillment of all the requirements set out in part IV of the Request for offers
3. Statement concerning personal or/and capital connections between the Service Provider and the Ordering Party