

Capacities/Research Potential FP7-REGPOT-2012-2013-1

> Project No. 316254 BASTION

"From Basic to Translational Research in Oncology"

# Deliverable D3.4

Report on a new group leader and his research activities

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All reports are available on BASTION Webpage: <u>www.bastion.wum.edu.pl</u>



#### 1. Introduction

Deliverable D3.3 corresponds to the task T3.2 in WP3, that was delivered in time.

The BASTION project has been envisioned to allow Medical University of Warsaw (MUW) to become a leading research and clinical oncology center in Central Europe. One of the objectives realized in WP3 has been to organize a separate bioinformatics unit, which will support genomic analyses planned within the proposed project as well as an independent research activity aimed at development of novel bioinformatics tools and approaches to next generation sequencing (NGS). The research of the new group leader was about to be focused on personalized approaches in oncology via utilizing the bioinformatics approach (DNA and protein sequence, microarray, and biological pathways analysis).

As planned in WP3, BASTION project has recruited Dr. Radosław Zagozdzon as a highly qualified lab leader of bioinformatics unit with the ability to increase research potential in basic and translational oncology at Medical University of Warsaw. Newly employed lab leader has brought technological expertise which currently allows MUW to engage into new research direction through collaborative efforts. During the course of the BASTION project, the initial approach has further expanded via utilizing the external funds from the National Science Center (NCN), which led to creating a digital imaging facility (please see below for further information).

#### Working space:

The newly employed lab leader and his group have been provided with one office room and access to research space in the Department of Immunology. Additionally, separate two rooms have been designated for the location of a computing cluster and a digital histology slide scanner.

#### 2. Narrative overview of the activities of the bioinformatics group leader

Advances in biomedical technology in recent years resulted in a dramatic increase in the inflow of information acquired in scientific research. To cope with this flood of data, the BASTION project found it necessary to create a research group specializing in bioinformatics, systems biology, and validation of the results obtained via modern biotechniques. Indeed, such activities has been the main area of the actions carried out by the new bioinformatics group leader.

In regards to the technology, the new group has successfully established and utilized a computing cluster as a part of the bioinformatics activities under the BASTION program. This cluster is currently serving the other groups involved in the BASTION program in order to catalogue and process biological information derived from the newly created or publicly available databases. The main applications for this computing cluster is related to the support for the analysis of the Next Generation Sequencing (NGS) and transcriptomic and



epigenetic profiling assays. In addition to that, we have purchased histology slide scanner (thanks to the secured external funding from the National Science Center; Fig. 1) in order to establish a digital image analysis facility working in conjunction with the new computer cluster.

**Figure 1.** A digital histology slide scanner purchased thanks to the external funding secured by the newly hired bioinformatics group leader

Gran Agreement no:316254



In the course of the research activities under BASTION, one of the specific scientific tasks of the new group has been to evaluate the role of the enzymatic systems responsible for eliminating the effects of oxidative stress within tumor cells. We assumed that this pathway could become be a potential target for new anticancer drugs. In our study, we utilized the data generated by genomic sequencing techniques, transcriptomics and proteomics methods supported by histological and molecular biology experiments. This project is carried out in collaboration with two research centers from Ireland (University College Dublin, UCD, and Royal College of Surgeons Dublin, RCSI) and the group from China. Our efforts in this project gained additional financial support from the Polish National Science Center under the OPUS sponsorship program, as detailed below.

The efforts of Dr. Zagozdzon have resulted so far in authorships or co-authorships of several original and review publications two book chapters and one patent application, as detailed below. Moreover, the study with participation of Drs Dominika Nowis and Radoslaw Zagozdzon received a Beatson Medal award for the best presentation in the breast cancer area at the Irish Association for Cancer Research Annual Meeting; 28 February-1 March 2013, Dublin, Ireland. The award was given for the presentation given by Mr. Patrick O'Leary, a member of our partnering lab at UCD.

Our new research team, led by Dr. Zagozdzon, has also provided a number of comprehensive and versatile biotechnological approaches to the tasks delineated under the BASTION program. In more details, Drs Malgorzata Bajor and Radoslaw Zagozdzon have been responsible for generating and analyzing the biological and biomedical data. Dr Pawel Gaj has been mainly responsible for in silico analyses of the results generated within the project, provided by the collaborators or originating from the publically available datasets. Mr. Piotr Stawinski has provided the bioinformatics support for Next Generation Sequencing data acquired mainly by the group of Prof. Rafal Ploski. Mr. Slawomir Gruca has mainly been responsible for purchasing, installation and maintenance of the computer cluster and computer workstations. Additionally, Dr Zagozdzon along with Dr Dominika Nowis have also initiated a close collaboration with the Oncology Institute, Warsaw, in order to provide a bioinformatics support for the analysis the databases of clinical information from cancer patients.

Type of activity/output	Details		
Publications	Original:		
	<ol> <li>Trzeciecka A, Klossowski S, Bajor M, Zagozdzon R, Gaj P, Muchowicz A, Malinowska A, Czerwoniec A, Barankiewicz J, Domagala A, Chlebowska J, Prochorec-Sobieszek M, Winiarska M, Ostaszewski R, Golab J , Nowis D, Firczuk M. Dimeric peroxiredoxins are druggable targets in human Burkitt's lymphoma cell lines. Oncotarget (under revision)</li> </ol>		
	This work describes the dependence of Burkitt's lymphoma cell growth on functioning of the natural antioxidant enzymes, peroxiredoxins. The results of this study suggest peroxiredoxins as potential drug targets in Burkitt;s lymphoma.		
	<ol> <li>Siernicka M, Winiarska M, Bajor M, Firczuk M, Muchowicz A, Bobrowicz M, Fauriat C, Golab J, Olive D, Zagozdzon R. Adenanthin, a new inhibitor of thiol-dependent antioxidant enzymes, impairs the effector functions of human natural killer cells. Immunology. 2015 Jun 11. doi: 10.1111/imm.12494.</li> </ol>		
	This publication provides an important insight on the interplay between thiol-dependent antioxidant enzymes and anticancer activities of human immune system. Further understanding of this phenomenon can prospectively lead to fine-tuning of the novel natural killer cell-based therapeutic approaches to human disease.		
	3. Nowis D, Malenda A, Furs K, Oleszczak B, Sadowski R,		

# 3. Research activity of new group leader within BASTION project



	Chlebowska J, Firczuk M, Bujnicki JM, Staruch AD, <b>Zagozdzon R</b> , Glodkowska-Mrowka E, Szablewski L, Golab J. Statins impair glucose uptake in human cells. BMJ Open Diabetes Res Care. 2014 Apr 26;2(1):e000017.
	The results of this study can serve better understanding of physiological processes of the glucose metabolism in human cells and how these processes can be modified by statins.
4.	O'Leary PC, Terrile M, Bajor M, Gaj P, Hennessy BT, Mills GB, Zagozdzon A, O'Connor DP, Brennan DJ, Connor K, Li J, Gonzalez-Angulo AM, Sun HD, Pu JX, Pontén F, Uhlén M, Jirström K, Nowis DA, Crown JP, <b>Zagozdzon R</b> , Gallagher WM. Peroxiredoxin-1 protects estrogen receptor $\alpha$ from oxidative stress-induced suppression and is a protein biomarker of favorable prognosis in breast cancer. Breast Cancer Res. 2014 Jul 10;16(4):R79.
	These results for the first time imply a close connection between biological activity of an antioxidant enzyme, peroxiredoxin 1 (PRDX1) and regulation of estrogen-mediated signaling in breast cancer.
5.	Gaj P, <b>Zagozdzon R</b> . In silico analysis of microRNA-510 as a potential oncomir in human breast cancer. Breast Cancer Research 2014, 16:403; doi:10.1186/bcr3624
	In this study, we have analyzed the transcriptomic data regarding the expression of a microRNA-510 in breast cancer. Our results practically excluded the important role for this microRNA in the biology of human breast cancer in clinical settings.
6.	Muchowicz A, Firczuk M, Chlebowska J, Nowis D, Stachura J, Barankiewicz J, Trzeciecka A, Klossowski S, Ostaszewski R, <b>Zagozdzon R</b> , Pu JX, Sun HD, Golab J. Adenanthin targets proteins involved in the regulation of disulphide bonds. Biochem Pharmacol. 2014 May 15;89(2):210-6.
	The results of this stud indicate that and new pro-oxidant compound, adenanthin, is a mechanism-selective, rather than an enzyme-specific inhibitor of enzymes containing readily accessible, nucleophilic cysteines. This observation might be of importance in considering potential therapeutic applications of adenanthin to include a range of diseases, such as cancer, where aberrant activity of peroxiredoxins or thioredoxins is involved in their pathogenesis.
7.	Burdzinska A, Gala K, Kowalewski C, <b>Zagozdzon R</b> , Gajewski Z, Pączek L. Dynamics of acute local inflammatory response after autologous transplantation of muscle-derived cells into the skeletal muscle. Mediators Inflamm. 2014;2014:482352. doi: 10.1155/2014/482352.
	In this study, Dr Zagozdzon has contributed with his expertise within the field of in vivo digital optical imaging and data analysis. Presented results demonstrated that autotransplanted muscle-derived cells induce classical early immune reaction in the site of injection which may contribute to cellular graft elimination.



	Reviews:		
	<ol> <li>Zagozdzon R, Golab J. Cancer stem cells in haematological malignancies. Contemp Oncol (Pozn) 2015; 19 (1A): A1–A6</li> <li>Lasek W, Zagożdżon R, Jakobisiak M. Interleukin 12: still a promising candidate for tumor immunotherapy? Cancer Immunol Immunother. 2014 May;63(5):419-35. doi: 10.1007/s00262-014-1523-1.</li> </ol>		
	Book Chapters:		
	<ol> <li>Zagozdzon R, Gaj P. Modern methods of risk assessment and infections diagnosis in patients after transplantation. in 'Transplantologia praktyczna', vol. 5: 'Zakażenia w transplantologii'. Eds. Leszek Pączek, Krzysztof Mucha, Bartosz Foroncewicz; PWN, Warsaw 2013 [in Polish]</li> <li>Gaj P, Zagozdzon R. Modern biomarkers of allograft survival. in 'Transplantologia praktyczna', vol. 6: 'Wyniki odlegle transplantacji narzadow'. Eds. Leszek Pączek, Krzysztof Mucha, Bartosz Foroncewicz; PWN, Warsaw 2013</li> </ol>		
Patents	Pawel Gaj, <b>Radoslaw Zagozdzon</b> . Stratification of B-cell lymphoma cases using a gene expression signature. European Patent Application No. EP14461567.1		
Participation in external grants	See below.		
Participation in the conferences	<ol> <li>EMBO Conference, Cellular signalling and cancer therapy. 23- 27 May 2014, Cavtat, Croatia</li> <li>15th International Conference on Oxidative Stress Reduction, Redox Homeostasis and Antioxidants; June 22-24, 2015, Paris, France</li> <li>"Translational Research in Oncology in New Member State Economies" (TRON) conference, 21-22 May 2015, Warsaw, Poland</li> </ol>		
Speech/lectures/oral presentation at the conferences	<ul> <li>Passive:</li> <li>Anna Trzeciecka, Szymon Klossowski, Malgorzata Bajor, Radoslaw Zagozdzon, Pawel Gaj, Angelika Muchowicz, Agata Malinowska, Anna Czerwoniec, Joanna Barankiewicz, Antoni Domagala, Justyna Chlebowska, Monika Prochorec, Ryszard Ostaszewski, Jakub Golab, Dominika Nowis and <u>Malgorzata Firczuk.</u> Thiol-reactive peptiomimetic sk053 targets dimeric peroxiredoxins in human lymphoma cell lines. 15th International Conference on Oxidative Stress Reduction, Redox Homeostasis and Antioxidants; June 22-24, 2015, Paris, France (oral presentation by Malgorzata Firczuk)</li> </ul>		
Poster presentation at the conferences	<ul> <li>Active:</li> <li>1. Radoslaw Zagozdzon, Patrick C. O'Leary, Gaj Pawel, Bryan T Hennessy, Gordon B. Mills, Ana M. Gonzalez-Angulo, Han-Dong Sun, Fredrik Pontén, Karin Jirström, William M. Gallagher, et al. Peroxiredoxin-1 regulates estrogen receptor alpha protein content in breast cancer cells undergoing oxidative stress and is a prognostic biomarker in this disease, EMBO Conference, Cellular signalling and cancer therapy. 23-27 May 2014, Cavtat, Croatia</li> </ul>		



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3.	<ul> <li>Radoslaw Zagozdzon, Marta Siernicka, Malgorzata Bajor, Malgorzata Firczuk, Angelika Muchowicz, Malgorzata Bobrowicz, Cyril Fauriat, Jakub Golab, Daniel Olive, Magdalena Winiarska. Adenanthin, a new inhibitor of thiol-dependent antioxidant enzymes, deeply impairs the effector functions of human natural killer cells. 15th International Conference on Oxidative Stress Reduction, Redox Homeostasis and Antioxidants; June 22-24, 2015, Paris, France</li> <li>Radoslaw Zagozdzon, Marta Siernicka, Malgorzata Bajor, Malgorzata Firczuk, Angelika Muchowicz, Malgorzata Bobrowicz, Cyril Fauriat, Jakub Golab, Daniel Olive, Magdalena Winiarska. Anti-cancer effector functions of human natural killer cells are hampered by adenanthin, a new inhibitor of thiol-dependent antioxidant enzymes. TRON, 21-22 May 2015, Warsaw, Poland</li> </ul>
Passive:	
1.	Malgorzata Bajor, Agata O Zych, Patrick C O'Leary, Anna Czekalska, William M Gallagher, Jakub Golab, <b>Radoslaw</b> <b>Zagozdzon.</b> Adenanthin, a new peroxiredoxin inhibitor, induces a switch between estrogen receptor alpha-mediated and Akt- driven signaling in breast cancer cells. TRON, 21-22 May 2015, Warsaw, Poland
2.	Lech Trzeciak, Paweł Gaj, Agata Skórka, Paulina Nadkowska, Agnieszka Pollak, Joanna Kosińska, Rafał Płoski, <b>Radosław</b> <b>Zagożdżon</b> . Functional analysis of SMAD4 mutants in an in vitro system reveals upregulation of SMAD2, SMAD3 and SMAD4 by Myhre syndrome-associated variants. TRON, 21-22 May 2015, Warsaw, Poland
3.	Robert Świder, Agnieszka Perkowska-Ptasińska. Anna Stachurska, Jadwiga Fabijańska-Mitek, Radosław Zagożdżon, Sławomir Gruca, Jakub Gołąb, Marcin Poterski, Magdalena Durlik. Morphometry of the Epithelial-Mesenchymal Transition (EMT) in Subsequent Biopsies from Transplanted Kidney. 2015 American Transplant Congress, 2 <sup>nd</sup> -6 <sup>th</sup> May 2015, Philadelphia, PA, USA
4.	Malgorzata Bajor, Agata O Zych, Patrick C O'Leary, Anna Czekalska, William M Gallagher, Jakub Golab, <b>Radoslaw</b> <b>Zagozdzon.</b> Adenanthin, a new peroxiredoxin inhibitor, induces a switch between estrogen receptor alpha-mediated and Src/Akt-driven signaling in breast cancer cells. San Antonio Breast Cancer Symposium, December 9th –13th, 2014, San Antonio Texas LISA (Cancer Res May 1, 2015, 75: P5-07-09)
5.	Malgorzata Firczuk, Anna Trzeciecka, Malgorzata Bajor, Angelika Muchowicz, <b>Radoslaw Zagozdzon</b> , Joanna Barankiewicz, Antoni Domagala, Szymon Klossowski, Agata Malinowska, Justyna Chlebowska, Ryszard Ostaszewski, Jakub Golab, Dominika Nowis. Peroxiredoxins-1 and 2 Affect Proliferation and Survival of Lymphoma Cells. 56th ASH Annual
6.	<ul> <li>Meeting, 6th-9th December 2014, San Francisco, CA, USA</li> <li>Malgorzata Bajor, Patrick C. O'Leary, Pawel Gaj, Bryan T.</li> <li>Hennessy, Jakub Golab, William M. Gallagher, Radoslaw</li> <li>Zagozdzon. An antibody-based proteomic approach for identification of PRDX1 as a biomarker in estrogen receptor positive breast cancer. 10th Siena Meeting "From genome to</li> </ul>



		proteome" 20 Years of Proteomics August 31st – September
		4th 2014 Siena Italy
	7.	Malgorzata Bajor, Patrick C. O'Leary, Agata Zych, Jakub Golab, William M. Gallagher, <b>Radoslaw Zagozdzon.</b> Evaluation
		of adenanthin as an intracellular signaling modulator and potential therapeutic agent in estrogen receptor positive breast cancer. EMBO Conference, Cellular signalling and cancer
		therapy. 23-27 May 2014, Cavtat, Croatia
	8.	Martina McDermott, Lee Anderson, Liam Shields, Neil
		O'Brien, Allison Prendergast, Susan Kennedy, William
		Gallagher, Radoslaw Zagozdzon, Annette Byrne, John Crown,
		of HER2 and STARD3 in a cell line model of acquired lapatinib
		resistance. [abstract]. In: Proceedings of the 104th Annual
		Meeting of the American Association for Cancer Research;
		2013 Apr 6-10; Washington, DC. Philadelphia (PA): AACR;
		Cancer Res 2013;73(8 Suppl):Abstract nr 5634. doi:10.1158/1538-7445.0M2013-5634
	9.	PC O'Leary, DJ Brennan, DP O'Connor, BT Hennessy, AM
		Gonzalez-Angulo, J Li, GB Mills, F Pontén, K Jirström, M Uhlen,
		HD Sun, JX Pu, AM Zagozdzon, D Nowis, J Crown, <b>R Zagozdzon</b> ,
		wive Gallagner. The antioxidant enzyme, peroxiredoxin-1, protects the estrogen recentor against oxidative stress-induced
		suppression and is correlated with differential outcome of
		patients with breast cancer. Irish Association for Cancer
		Research Annual Meeting; 28 February-1 March 2013, Dublin,
		Ireland
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Participation in courses/trainings/workshops	Worksh 1.	<b>ops:</b> Workshop: Roundtable from lab to clinic, 4 <sup>th</sup> June 2013 Brussels, Belgium
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Collaboration with other research	Domestic:
teams	1. Prof. Leszek Paczek, Dr. Krzysztof Mucha, Dr. Anna Burdzinska,
	Transplantation Institute, Warsaw, Poland
	<ol> <li>Prof. Magdalena Durlik, Dr. Robert Swider, Transplantation Institute, Warsaw, Poland</li> </ol>
	3. Dr. Maciej Wiznerowicz, Greater Poland Cancer Centre,
	Poznan, Poland
	Foreign:
	1. Prof. William Gallagher, Cancer Biology & Therapeutics
	Laboratory, UCD Conway Institute, UCD School of Biomolecular and Biomedical Science, Dublin, Ireland.
	2. Prof. Bryan Hennessy, Department of Medical Oncology,
	Beaumont Hospital, Royal College of Surgeons in Ireland,
	Dublin, Ireland.
	3. Prof. Han-Dong Sun, State Key Laboratory of Phytochemistry
	and Plant Resources in West China, Kunming Institute of
	Botany, Chinese Academy of Sciences, Yunnan, China
	4. Prof. Daniel Olive, Dr. Cyril Fauriat, Research Center in
	Oncology of Marseille, France
	5. Dr. Patrick O'Leary, UCSF, CA, USA

# Other:

Media Appearances	www.youtube.com/watch?v=1TXbgMKq6Po
(links)	https://www.youtube.com/watch?v=7ET6fAvXydc
	http://czasopisma.viamedica.pl/owpk/article/viewFile/35528/25785
	http://biotechnologia.pl/biotechnologia/aktualnosci/bioinformatyka-stala-sie- dziedzina-niezbedna-rozmawiamy-z-bioinformatykami-projektu-bastion,13460 http://audycje.tokfm.pl/odcinek/Przelom-w-trzeciej-drodze-leczenia- nowotworow-O-immunoterapii-opowiada-dr-Radoslaw-Zagozdzon/27991#

# 4. External research funding:

BASTION project has not directly provided research support for the newly employed lab leader. However, he has been eligible for applying for national funding from National Science Centre (NCN), The National Centre for Research and Development (NCBiR), The Foundation for Polish Science (FNP) and Ministry of Science and Higher Education. Indeed, during the course of the BASTION project, Dr. Zagozdzon has managed to secure more than 2 million PLN funding from NCN (see the table below).

Grant number	Title	Function	Duration	Funding	Awarding institution
2012/07/B/NZ7/0 4183	Evaluation of peroxiredoxins 1 and 2 along with the thioredoxin-thioredoxin reductase system as new therapeutic targets in B cell lymphomas	Project Leader	2013-2016	987 000 PLN	National Science Center
IP2012 048172	The role of thioredoxin	Co- investiga	2013-2015	322 400 PLN	Ministry of Science and



	reductase and peroxiredoxins in multiple myeloma	tor			Higher Education
2014/13/B/NZ5/0 1354	The role for thiol-dependent antioxidant enzymes in estrogen receptor-positive breast cancer	Project Leader	2015-2018	1 213 233 PLN	National Science Center

#### 5. The course of employment of the recruited group leader:

The new lab leader has initially been employed for 30 months. Number of faculty positions at Medical University of Warsaw is regulated by a quota of teaching hours (i.e. pensum). Thus, according to the recruitment policy of Medical University of Warsaw lab leader was employed at the university as an experienced research specialist. He has been entitled to all benefits of governmental employees.

#### Changes to work-plan, delays

Although the timeline for recruitment of lab leader was relatively short we managed to employ a highly qualified candidate since 11<sup>th</sup> October 2012 for 30 months. 1 month delay was caused by a very short period for recruiting process (start of the project: September 2012 and start of the contract for lab leader: September 2012) and some administrative delays in hiring BASTION staff at MUW. Following the initial 30 months and in the light of highly successful activities of Dr. Zagozdzon, his employment under WP3 of the BASTION project has further been extended until 31<sup>st</sup> August 2015.

#### **Envisioned career path**

Thanks to the sponsorship under the BASTION program, I plan to further develop my leadership and mentoring abilities in order to establish myself in the future as an independent investigator in the cancer research area. I am very excited to be a part of the one of the Poland's leading biomedical programs and wish to devote myself to creating a state-of-art bioinformatics support for local bioresearch activities, as well as to establishing a modern digital imaging facility to work in partnership with the Polish clinical pathology centers. I will continue my work in the Department of Immunology, WUM as a part-time coordinator of two projects sponsored by National Science Center (2.5 years). Additionally, I will proceed with my clinical training in the field of clinical immunology as a volunteer in the Department of Clinical Immunology, Infant Jesus Clinical Hospital, Warsaw.

# 6. Conclusions:

By completing a successful recruitment process and hiring of a New Group Leader, we achieved Milestone 1 of the BASTION project and established a new research group at MUW. In the course of the BASTION project, the new group leader has significantly contributed to the design and the set-up of a modern bioinformatics infrastructure including equipment and specialized software to undertake new ambitious studies. Such set-up included a computing cluster for large data sets, three multi-core workstations, adequate back-up storage and database management software and specialized software for data analysis and visualization. Additionally, the newly hired group leader has successfully supervised the creation of and utilized a new digital image analysis facility at MUW. The research efforts of Dr. Zagozdzon have so far resulted in authorships or co-authorships of seven original (out of which six were already published) and two review publications, two book chapters, one patent application and several meeting reports. Following the ending of WP3, Dr. Zagozdzon will continue his employment with Medical University of Warsaw under the funding secured from the national agencies.



# Corresponding estimated/\* budget

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PER	SONNEL, TRAVEL, OTHER MAJOR D	IRECT COST ITEMS	FOR BENEFICIARY "1" FOR M19 – M36
	Item description	Amount [EUR]	Explanations
WP3 Task 3.2	Personnel costs	93,500.87	Fee of the Co-leader (0,74PM) and salary of the hired New-Group Leader (18 PM )
	Travel		
	Organization of events		
	Remaining direct costs		
TOTAL DIRECT WP3 Task T3.2 COST 93,500.87			

/\* - exact costs for M19-M36 will be presented in the II<sup>nd</sup> Period Report and Form C (October 2015)

Dr Magdalena Winiarska WP3 Leader Prof. Slawomir Majewski WP3 Co-leader

Prof. Jakub Golab BASTION Project Coordinator *Warsaw, August 2015*  ٦