Vedecká grantová agentúra Ministerstva školstva SR a Slovenskej akadémie vied

Scientific Grant Agency of the Ministry of Education of Slovak Republic and the Academy of Sciences

GRANT APPLICATION

REGISTRATION NUMBER
Draft

Confidental

Commisions of S.G.A.

9 VEGA commission for medical and pharmaceutical sciences

Title of the project

Prevention of irinotecan induced diarrhea by probiotics

Key words

irinotecan, diarrhea, probiotics

Duration of the project (m/y)					
From	01	2011	to	12	2013

Number of	- researchers	5
	- graduate students	0

SUMMARY OF THE FINANCIAL MEANS REQUESTED	1st year	2nd year	3rd year	4th year
	(IN EUROS - €)			
INVESTMENTS (equipment)	0	0	0	0
NON-INVESTMENTS COSTS (travels expences including conferences, energies, communications, minor material/immaterial items, consumables, maintenance, services, sub-contracts)	6 100	6 650	6 650	0

PRINCIPAL INVESTIGATOR ***(surname, first name, title):***

Mego Michal,

List of scientific co-workers

Drgoňa Luboš
Mardiak Jozef
Obertová Jana
Vranovsky Andrej

Date ..... **Signature of the principal investigator** .....

Project summary

Irinotecan is one of key drug used in the treatment of colorectal cancer. The incidence of irinotecan induced diarrhea varies between 60-90%, with severe diarrhea in 20-40%. The main cause of diarrhea is one of irinotecan metabolites, SN-38 which is in the liver glukuronated and subsequently expelled into the intestine. Due to the bacterial enzyme beta-D-glukuronidase in intestinal lumen it is dekonjugated. This form causes direct damage of intestinal mucosa associated with malabsorption and the development of diarrhea. It is known that probiotic bacteria, reduse activity of intestinal beta-D-glukuronidase and therefore these bacteria could be applied in the prevention of diarrhea in patients treated by this drug. Given their low toxicity, good tolerability, probiotics may be an important part of supportive therapy. This is a first study aimed to determine the effectiveness of the probiotics in the prophylaxis of irinotecan induced diarrhea due to reduction intestinal beta-D-glukuronidase activity.

Scientific goals for whole period of this project

Study hypothesis
We hypothesize that administration of probiotic formula Colon Dophillus to cancer patients tretaed by irinotecan based chemotherapy, will prevent irinotecan induced diarrhea due to reduction intestinal beta-D-glukuronidase activity.
Primary objective
To determine the efficacy (as measured by prevention of grade 3/4 diarrhea) of probiotic formula Dophillus given orally to patients with colorectal cancer started new line of irinotecan based chemotherapy.

Secondary Objectives

To describe incidence of any grade of diarrhea, other gastrointestinal symptoms and safety/toxicity in patients with colorectal cancer started new line of irinotecan based chemotherapy. To determine stool beta-D-glucuronidase activity and serum cytokines level and their correlation to clinical outcomes.

End-points
Primary end-point: □□Prevention of grade 3/4 diarrhea
Secondary end-points:□Prevention of any grade of diarrhea
□□□□ Other gastrointestinal symptoms
□□□□ Safety/toxicity
□□□□ Stool beta-glucuronidase activity
□□□□ Serum cytokines

Realisation outputs and output user

Colorectal cancer is one of the most prevalent cancer in Slovakia, with approximately of 2300 newly diagnosed patients per year. Irinotecan is main drug used in the treatment of metastatic colorectal cancer. This treatment is associated with significant morbidity and also mortality. Prevention of irinotecan induced diarrhea by probiotics could be non-expensive approach how to deal with this problem. This approach could save significant amount of indirect cost associated with irinotecan based therapy due to spare cost for supportive medication (antidiarrheal drugs, antibiotics, infusion therapy, hospitalization), could help to maintain dose intensity of chemotherapy as well as maintain quality of life of colorectal cancer patients treated by chemotherapy. The succesfull study results could lead to patent application, and successful execution of this study could be usefull in planning multicenter trials within Slovak cancer community in future.

International scientific co-operation

This is a multicenter study that will be perfomed in several oncology centers in Slovakia, international cooperation is unlikely.

Description of the project ***(range - maximum 5 pages)***

a) Present state of subject
b) Particular contribution expected
c) Proposal of the ways to reach the project goals, including timetable for each individual year of research
d) Working group (comment on the choice of the research group)
e) Description of applied methods and their explanation

X X X X X

a) Present state of subject:
Diarrhea is a relatively common complication in patients with cancer. At its inception, participated several mechanisms; malabsorption on the basis of mucositis induced by chemotherapy, dysmicrobia induced broad-spectrum antibiotic and a predisposition to infectious diarrhea in immunocompromised patients. Some cytostatics and their metabolites also induce diarrhea directly due to effect on the intestinal mucosa.
Use of probiotics in prevention and treatment of diarrhea relies on both the theoretical assumptions and the results of several clinical trials. Lactic acid bacteria involved in the treatment dysmikrobia, compete for substrate with pathogenic bacteria, produce bacteriocins, increases transepithelial resistance (Resta-Lenert et al, 2003). Their enzymatic activity affects the activation or deactivation of metabolites that cause diarrhea. Production of fatty acids with short chains, which are important for the maintenance of intestinal mucosal cells also contributes to their antidiarrhoical effect (Batt, 1996).
Meta-analysis of 9 randomized, placebo-controlled trials showed a significant reduction in the incidence of antibiotic associated diarrhea in children (D'Souza, 2002). Another meta-analysis in which 23 studies were included showed a significant reduction in risk of infectious diarrhea (Allen, 2004). Most of these studies was carried out with the probiotic strains Lactobacilus GG.
In phase II study performed in NCI Slovakia preventive administration of Enterococcus faecium probiotic strain M-74 with selenium was associated with a low incidence (14%) and severity (all grade 1), diarrhea, despite the fact that half of the patients received induction therapy (Mego et al., 2005). We noted safety of probiotic strain during the 370 days of severe neutropenia Gr 3-4 (Mego et al, 2005).
The incidence of irinotecan induced diarrhea varies between 60-90%, with severe diarrhea is 20-40%. In phase II studies, its incidence was 17% in NCI Slovakia (Šálek et.al, 2002), but irinotecan dose was reduced by 25% in all patients. Diarrhea is an important factor in morbidity and mortality during irinotecan based chemotherapy (Michael et al. 2004). Predisposing factors are age over 65 years, ECOG PS of 1 and previous abdominopelvic radiation. One of irinotecan metabolites, SN-38 (7-ethyl-10 hydroxycamptotehecin), which is in the liver glukuronated and subsequently expelled into the intestine is main cause of diarrhea. Due to the bacterial enzyme beta-D-glukuronidase in intestinal lumen it is dekonjugated again. This form causes direct damage of intestinal mucosa associated with malabsorption of water, electrolytes and the development of diarrhea.
Among the ways to avoid irinotecan induced diarrhea included reduction of activity of intestinal beta-D-glukuronidase using broad-spectrum antibiotics and/or beta-D-glukuronidase inhibitors (Sakata 1994). Promising results were shown using activated charcoal, which has resulted in the absorption of SN-38 (Michael et al). Several other procedures have been studied only in phase II trials. It is known that probiotic bacteria, reduse activity of intestinal beta-D-glukuronidase (Goldin, BR., Et al. 1984, Ferenčík, et al, 1999), and therefore these bacteria could be applied in the prevention of diarrhea in patients treated by irinotecanom based therapy.
Given their low toxicity, good tolerability, probiotics may be an important part of supportive therapy. The objective of this phase III. trial is to determine the effectiveness of the probiotic formula Colon Dophillus in the prophylaxis of irinotecan induced diarrhea due to reduction intestinal beta-D-glukuronidase activity.
References:
1. Allen SJ et al. In The Cochrane Library, Issue 2,2004. Chichester, UK: John Wiley &Sons, Ltd.

(item - continued)

2. Batt RM et al. J Small Anim Pract 1996, 37: 261-267
3. D´Souza AL et al., BMJ, 2002, 324: 1361
4. Ferencík M et al. Bratisl Lek Listy, 1999, 100:238–245
5. Goldin BR. Ann.Med, 1990, 22:43-48
6. Mego M et al. Neoplasma, 2005; 52: 159-164
7. Mego M et al. Support Care Cancer, 2006; 14: 285-290
8. Michael M et al. JCO, 2004; 22: 4410-4417
9. Resta-Lenert et al. Gut, 2003, 52: 988-97
10. Sakata Y et al. Proc Am Soc Clin Oncol, 13: 394, (Abstr. 1578)
11. Salek T et al. Proc.Am.Soc.Clin.Oncol, 2002, 21:2378

b) Particular contribution expected:
The main benefit from the study could be prevention of significant morbidity and mortality of chemotherapy induced diarrhea in colorectal cancer patients. This could be achieved by relatively simple and non-toxic administration of probiotics concurrently with chemotherapy. Successful prevention of diarrhea could lead to decrease cost for patient care (hospitalization, antibiotics, treatment of dehydratation due to severe diarrhea), better quality of life. Prevention of irinotecan induced diarrhea could help to maintain dose intensity of chemotherapy and this could lead to better patients outcome.
Translational data could help to explore the immunostimulatory effect of probiotics in chemotherapy treated patients as well as to correlate these data with important clinical endpoints (response rate, progression-free survival, and other chemotherapy induced toxicity). Correlation of beta-D-glukuronidase activity with concentration of probiotics in stool and clinical outcome could assess, on the molecular level, the validity of tested hypothesis and could generate new data, which could be tested in future in clinical or in experimental setting

c) Proposal of the ways to reach the project goals, including timetable for each individual year of research:
1.1.2011 - 31.12.2011
Study initiation (approval of competent authorities, study registration), patient accrual, treatment of probiotics, collecting of biological material

1.1.2012 - 31.12.2012
Patient accrual, treatment of probiotics, collecting of biological material

1.1.2013 - 31.12.2013
Analysis of study results, preparing publication, presentation of study results at national and international meetings, analysis of biological material and correlation of translational data to clinical outcome.

Potential limitations and alternative approaches:
The main risk of this project is sufficient accrual of study patients and cooperation of study centers. To achieve compliance of clinician with study, we initiated Slovak cooperative group within Slovak Cancer Society. Investigator`s meeting will be performed on regular basis to maintain high motivation of investigators. The other potential problems could be compliance of patients with translational part of study (willigness to collect stool and to offer the blood for translational research). To ensure data consistency, patient`s safety and compliance to good clinical practice, study centers will be monitored on regular basis.

d) Working group (comment on the choice of the research group):
Department of Medical Oncology of National Cancer Institute of Slovakia and 2nd Department of Medical Oncology, School of Medicine, Comenius University (LFUK) in collaboration with the Department of Cancer Genetics, Cancer Research Institute, Slovak Academy of Sciences cooperate for several years in research concerning the application of probiotics in the prevention of cancer treatment induced adverse events. The second main cooperation is focuse on exploration of the role of intestinal bacteria in colorectal cancer and prevention of colorectal cancer by probiotics. Achieved results were presented and published on national and international level and were cited extensively (Mego M et al. Neoplasma, 2005; 52: 159-164, Mego M et al. Support Care Cancer, 2006; 14: 285-290, Mego M and Zajac V. Via practica. 2008, 5: 206-210. Mego M and, Zajac V. Gastroenetrologia pre prax. 2007; 6: 28-32, Mego M and Zajac V. Klinická onkologie, 2006; 19: 167-171, Mego M et al. Folia Microbiologica, 2005; 50: 443-447, Mego M. Via practica 2005; 2: 354-357).
Recently established Translational Research Unit, as a specialized facility of 2nd Department of Medical

(item - continued)

Oncology, NCI, Bratislava provides translational research, i.e. knowledge transfer of basic research into clinical practice as well as back, solving significant problems in clinical oncology using experimental approaches in vitro and in vivo on animal models.

Composition of research team:
MUDr. Michal Mego, PhD – study co-chair, study coordination, patient`s accrual
MUDr. Ľuboš Drgoňa, CSc – study co-chair, study coordination, patient`s accrual
RNDr.Daniela Světlovská, PhD – study monitoring, administrative procedures, data analysis
Doc. RNDr. Vladimír Zajac, CSc – basic science researcher, analysis of biological material
Doc. MUDr. Jozef Mardiak, CSc - clinician, patients` accrual, treatment of patients with study drug, data analysis
MUDr. Zuzana Hlavatá – clinician, patients` accrual, treatment of patients with study drug
MUDr. Iveta Andrezalová-Vochyanová - clinician, patients` accrual, treatment of patients with study drug
MUDr. Patrik Palacka, PhD - clinician, patients` accrual, treatment of patients with study drug
PharmDr.Dagmar Mikusová - administrative support
MUDr.Mária Rečková - clinician, patients` accrual, treatment of patients with study drug

e) Description of applied methods and their explanation:
1 Trial Design
Randomized, double blind, multicentre phase III trial trial to assess efficacy (as measured by prevention of grade 3/4 diarrhea) of probiotic formula Dophillus given orally compared to placebo to patients in patients with colorectal cancer started new line of irinotecan based chemotherapy. See section 5 for specific details. Several cancer centers in Slovakia will be involved in this study.

2 Main patient selection criteria
2.1. Inclusion criteria
1) signed written informed consent, 2) age > 18 years, 3) histologically proven colorectal cancer patients started new line of chemotherapy based on irinotecan, 4) ECOG PS 0 – 1 at study entry, 5) life expectancy more than 3 months

2.2. Exclusion Criteria:
1) impossibility to take oral medication, 2) active infection treated by antibiotic therapy, 3) hypersensitivity to study drug, 4) serious concomitant systemic disorders or diseases incompatible with the study (at the discretion of investigator)

3.1. Randomization
Patient will be centrally randomized. Following sign of informed consent, patient will receive study number and investigator will call to randomization center and will be allocated to one of the treatment group. Patients will be stratified according age (<65 vs >65 years) and according treatment with cetuximab (irinotecan with cetuximab vs. without cetuximab), because these represent potential confounders.

4. Treatment Plan
4.1. Drug Administration
Probiotic formula Colon Dophillus, will be administered at a dose of 3x1 tbl per day orally. One cycle of therapy consists of 42 days. In the first cycle the starting dose is 3x1 tbl per day. In other cycles the starting dose is 3x1 tbl per day, or the dose according to dose adjustments from the previous treatment cycle. No premedication or patient monitoring after administration of probiotic formula is required. Probiotic formula may be taken after meals or snacks to reduce stomach upset.

5. Statistical considerations
5.1 Statistical design
Statistical and Analytical Plan
This is a phase III study to investigate the efficacy of probiotic formula Dophillus given orally compared to placebo to patients in patients with colorectal cancer started new line of irinotecan based chemotherapy. Because we presume 10% rate of inegibility total 220 patients will be accrued. Primary endpoint of this study is prevention of grade 3 diarrhea.

Study Design, Significance level and Power

(item - continued)

H(0) - absence of grade 3-4 diarrhea = 75% of patients
H(A) – absence of grade 3-4 diarrhea = 90% patients

Group sample sizes of 100 in group one and 100 in group two achieve 82% power to detect a difference between the group proportions of 0,1500. The proportion in group one (the treatment group) is assumed to be 0,7500 under the null hypothesis and 0,9000 under the alternative hypothesis. The proportion in group two (the control group) is 0,7500. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targetedat 0,0500. The significance level actually achieved by this design is 0,0494. Because of expected 10% of ineligibility, proposed number of study patients will be 220.

Accrual and Duration of Study
The estimated accrual for this study is 10 patients per month. Thus, patient accrual is expected to be completed within 24 months. Additional time is required to allow the response data to mature. All of the patients registered in the study will be accounted for follow up. The number of patients who were not evaluable, who died or withdrew before treatment began will be specified. The distribution of follow-up time will be described and the number of patients lost to follow-up will be given.

6 Translational research
Plasma analysis
From each patient, 5 ml of blood drawn in heparin tube, will be drawn at baseline, after cycle 1 and 2 to provide a frozen blood plasma sample for conducting cytokine profiling, and/or microRNA analysis. Sample for plasma proteomics must remain frozen and should be transferred on dry ice for long term storage at -70C.
Cytokine profiling will be initiated on appropriate subsets of the plasma samples when clinical activity of Colon Dophillus has been established in sufficient number of patients from the study. Due to technical reason, only patients treated in NCI Slovakia and St` Elisabeth Cancer Institute, Slovakia will be subject for this research. Cytokine profiling will be done using Luminex assay or other appropriate assay. The plasma samples may also be used to confirm findings by application of alternative Technologies eg. microRNA profiling.

Stool analysis
From each patients stool will be subject for evaluation of gut colonization by probiotic bacteria as well as for beta-glucuronidase activity. Stool will be collected at baseline, after cycle 1 and 2 cycle of therapy and will be processed using appropriate microbiological technique at Cancer Research Institute of Slovakia. Due to technical reason, only patients treated in NCI Slovakia and OUSA Slokavia will be subject for this research.

PRINCIPAL INVESTIGATOR **Enclosure A**

Surname, first name, title	Highest degree & year		Age	
Mego Michal,		PhD. 2006		33

Institution and adress (street, postal code, city)
Lekárska fakulta UK
Špitálska 24
813 72 Bratislava 1

Selection of 5 most important works of the principal investigator (whole period). Please quote the total numbers of citations / numbers of citations for the last five years with each work.

1) Mego, Michal - Májek, J. - Končeková, R. - Ebringer, Libor - Čierniková, S. - Rauko, P. - Kováč, M. - Trupl, Ján. - Slezák, P. - Zajac, V. : Intramucosal Bacteria in Colon Cancer and Their Elimination by Probiotic Strain Enterococcus faecium M-74 with Organic Selenium, Folia Microbiologica. - Vol. 50, No. 5 (2005), s. 443-447
2) Mego, Michal - Končeková, R. - Mikušová, E. - Drgoňa, Ľuboš - Ebringer, Libor - Demitrovičová, Ľ. - Nemová, I. - Trupl, Ján - Mardiak, Jozef - Koza, Ivan - Zajac, Vladimír : Prevention of febrile neutropenia in cancer patients by probiotic strain Enterococcus faecium M-74 : Phase II study. Supportive Care in Cancer. - Vol. 14, No. 3 (2006), s. 285-290
3) Mego, Michal - Rečková, Mária - Obertová, J. - Syčová - Milá, Z. - Brozmanová, K. - Mardiak, Jozef: Increased cardiotoxicity of sorafenib in sunitinib - pretreated patients with metastatic renal cell carcinoma. Annals of Oncology. - Vol. 18, No. 11 (2007), s. 1906-1907
4) Mego, Michal - De Giorgi, U. - Broglio, K. - Dawood, S. - Valero, V. - Andreopoulou, E. - Handy, B. - Reuben, J. M. - Cristofanilli, M. : Circulating tumour cells are associated with increased risk of venous thromboembolism in metastatic breast cancer patients. British Journal of Cancer. - Vol. 101, No. 11 (2009), s. 1813-1816
5) Mego, Michal - De Giorgi, U. - Hsu, L. - Ueno, N. T. - Valero, V. - Jackson, S. - Andreopoulou, E. - Kau, S. W. - Reuben, J. M. - Cristofanilli, M. : Circulating tumor cells in metastatic inflammatory breast cancer. Annals of Oncology. - Vol. 20, Iss. 11 (2009), s. 1824-1828

Selection of 5 most important works of the principal investigator in last 5 years - quote the survey of the citations of the most frequently cited work from this selection in the Appendix 1.

1) Mego, Michal - Májek, J. - Končeková, R. - Ebringer, Libor - Čierniková, S. - Rauko, P. - Kováč, M. - Trupl, Ján. - Slezák, P. - Zajac, V. : Intramucosal Bacteria in Colon Cancer and Their Elimination by Probiotic Strain Enterococcus faecium M-74 with Organic Selenium, Folia Microbiologica. - Vol. 50, No. 5 (2005), s. 443-447
2) Mego, Michal - Končeková, R. - Mikušová, E. - Drgoňa, Ľuboš - Ebringer, Libor - Demitrovičová, Ľ. - Nemová, I. - Trupl, Ján - Mardiak, Jozef - Koza, Ivan - Zajac, Vladimír : Prevention of febrile neutropenia in cancer patients by probiotic strain Enterococcus faecium M-74 : Phase II study. Supportive Care in Cancer. - Vol. 14, No. 3 (2006), s. 285-290
3) Mego, Michal - Rečková, Mária - Obertová, J. - Syčová - Milá, Z. - Brozmanová, K. - Mardiak, Jozef: Increased cardiotoxicity of sorafenib in sunitinib - pretreated patients with metastatic renal cell carcinoma. Annals of Oncology. - Vol. 18, No. 11 (2007), s. 1906-1907
4) Mego, Michal - De Giorgi, U. - Broglio, K. - Dawood, S. - Valero, V. - Andreopoulou, E. - Handy, B. - Reuben, J. M. - Cristofanilli, M. : Circulating tumour cells are associated with increased risk of venous thromboembolism in metastatic breast cancer patients. British Journal of Cancer. - Vol. 101, No. 11 (2009), s. 1813-1816
5) Mego, Michal - De Giorgi, U. - Hsu, L. - Ueno, N. T. - Valero, V. - Jackson, S. - Andreopoulou, E. - Kau, S. W. - Reuben, J. M. - Cristofanilli, M. : Circulating tumor cells in metastatic inflammatory breast cancer. Annals of Oncology. - Vol. 20, Iss. 11 (2009), s. 1824-1828

SURVEY OF THE CITATIONS

Citattions are in the attachment

SCIENTIFIC CO-WORKERS

Surname, first name, title	Highest degree & year		Age	
Drgoňa Luboš,		PhD. 1995		43

Institution and adress (street, postal code, city)

Lekárska fakulta UK
Špitálska 24
813 72 Bratislava 1

Selection of 5 most important works of the co-worker in the last 5 years

Drgona, L, Paul M, Bucaneve G, Calandra T, Menichetti F: The need for aminoglycosides in combination with betalactams for high-risk, febrile neutropaenic patients with leukaemia. Eur J Cancer Supplements 2007; 5, 2, 13-22.
Jan Pachl, Lubos Drgona, Ruth Matthews, for the Mycograb Invasive Candidiasis Study Group:A Randomized, Blinded, Multicenter Trial of Lipid-Associated Amphotericin B Alone versus in Combination with an Antibody-Based Inhibitor of Heat Shock Protein 90 in Patients with Invasive Candidiasis. Clinical Infectious Diseases 2006;42:1404-1413
Bartáková, H.; Cetkovský, P.; Drgoňa, Ľ.; et al.: Invazivní aspergilóza: současné možnosti diagnostiky (guidelines). Vnitr Lek 2007; 53 (Suppl): S1-S34.
Mego, M.; Ebringer, L.; Drgoňa, Ľ; et al.: Prevention of febrile neutropenia in cancer patients by probiotic strain Enterococcus faecium M-74. Pilot study phase I. Neoplasma, 2005, 52, 2, p. 75-80.
Mego M, Koncekova R, Mikuskova E, Drgona L, Ebringer L, Demitrovicova L, Nemova I, Trupl J, Mardiak J, Koza I, Zajac V: Prevention of febrile neutropenia in cancer patients by probiotic strain Enterococcus faecium M-74. Phase II study. Support Care Cancer. 2006 Mar;14(3):285-90.

SCIENTIFIC CO-WORKERS

Surname, first name, title	Highest degree & year		Age	
Mardiak Jozef,				57

Institution and adress (street, postal code, city)

Lekárska fakulta UK
Špitálska 24
813 72 Bratislava 1

Selection of 5 most important works of the co-worker in the last 5 years

Gore ME, Griffin CL, Hancock B, Patel PM, Pyle L, Aitchison M, James N, Oliver RT, Mardiak J, Hussain T, Sylvester R, Parmar MK, Royston P, Mulders PF.Interferon alfa-2a versus combination therapy with interferon alfa-2a, interleukin-2, and fluorouracil in patients with untreated metastatic renal cell carcinoma (MRC RE04/EORTC GU 30012): an open-label randomised trial. Lancet. 2010 Feb 20;375(9715):641-8. Epub 2010 Feb 10. PubMed PMID: 20153039; PubMed Central PMCID: PMC2835851.
2: Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarbá JJ, Chen M, McCann L, Pandite L,Roychowdhury DF, Hawkins RE. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010 Feb 20;28(6):1061-8. Epub 2010 Jan 25. PubMed PMID: 20100962.
3: Mego M, Reckova M, Obertova J, Sycova-Mila Z, Brozmanova K, Mardiak J.Increased cardiotoxicity of sorafenib in sunitinib-pretreated patients with metastatic renal cell carcinoma. Ann Oncol. 2007 Nov;18(11):1906-7. PubMed PMID: 17993633.
4: Mardiak J, Sálek T, Sycová-Milá Z, Obertová J, Recková M, Mego M, Hlavatá Z, Brozmanová K, Risnyovzská Z, Svetlovská D, Koza I. Paclitaxel, bleomycin,etoposide, and cisplatin (T-BEP) as initial treatment in patients with poor-prognosis germ cell tumors (GCT): a phase II study. Neoplasma. 2007;54(3):240-5. PubMed PMID: 17447857.
5: Mardiak J, Sálek T, Sycová-Milá Z, Obertová J, Hlavatá Z, Mego M, Recková M, Koza I. Paclitaxel plus ifosfamide and cisplatin in second-line treatment of germ cell tumors: a phase II study. Neoplasma. 2005;52(6):497-501. PubMed PMID: 16284696.

SCIENTIFIC CO-WORKERS

Surname, first name, title	Highest degree & year		Age	
Obertová Jana,				39

Institution and adress (street, postal code, city)

Lekárska fakulta UK
Špitálska 24
813 72 Bratislava 1

Selection of 5 most important works of the co-worker in the last 5 years

1) Mego M, Rejlekova K, Reckova M, Sycova-Mila Z, Obertova J, Rajec J, Mardiak J. Kinetics of tumor marker decline as an independent prognostic factor in patients with relapsed metastatic germ-cell tumors. Neoplasma. 2009;56(5):398-403.
2) Rejlekova K, Mego M, Sycova-Mila Z, Obertova J, Rajec J, Salek T, Mardiak J. Prognostic factors in patients with relapsed or primary refractory germ cell tumors. Neoplasma. 2009;56(3):215-23.
3) Mego M, Sycova-Mila Z, Rejlekova K, Rychly B, Obertova J, Rajec J, Hes O, Mardiak J. Sunitinib in the treatment of tubulocystic carcinoma of the kidney. A case report. Ann Oncol. 2008 Sep;19(9):1655-6.
4) Mego M, Reckova M, Obertova J, Sycova-Mila Z, Brozmanova K, Mardiak J. Increased cardiotoxicity of sorafenib in sunitinib-pretreated patients with metastatic renal cell carcinoma. Ann Oncol. 2007 Nov;18(11):1906-7.
5) Mego M, Recková M, Sycova-Mila Z, Obertova J, Brozmanova K, Salek T, Mardiak J. Bevacizumab in a growing teratoma syndrome. Case report. Ann Oncol. 2007 May;18(5):962-3. Epub 2007 Apr 13. PubMed PMID: 17434900.

SCIENTIFIC CO-WORKERS

Surname, first name, title	Highest degree & year		Age	
Vranovsky Andrej				43

Institution and adress (street, postal code, city)

Lekárska fakulta UK
Špitálska 24
813 72 Bratislava 1

Selection of 5 most important works of the co-worker in the last 5 years

1: van Oers MH, Tönnissen E, Van Glabbeke M, Giurgea L, Jansen JH, Klasa R, Marcus RE, Wolf M, Kimby E, Vranovsky A, Holte H, Hagenbeek A, van der Reijden BA. BCL-2/IgH Polymerase Chain Reaction Status at the End of Induction Treatment Is Not Predictive for Progression-Free Survival in Relapsed/Resistant Follicular Lymphoma: Results of a Prospective Randomized EORTC 20981 Phase III Intergroup Study. J Clin Oncol. 2010 Apr 5. [Epub ahead of print] PubMed PMID: 20368567.
2: Ballova V, Ladicka M, Vranovsky A, Lakota J. Autologous stem cell transplantation with selected CD34+ cells and unmanipulated peripheral blood stem cells in patients with relapsed and refractory Hodgkin's lymphoma: a single centre experience. Neoplasma. 2008;55(5):428-36. PubMed PMID: 18665754.
3: Vranovsky A, Ladicka M, Lakota J. Autologous stem cell transplantation in first-line treatment of high-risk aggressive non-Hodgkin's lymphoma. Neoplasma. 2008;55(2):107-12. PubMed PMID: 18652043.
4: van Oers MH, Klasa R, Marcus RE, Wolf M, Kimby E, Gascoyne RD, Jack A, Van't Veer M, Vranovsky A, Holte H, van Glabbeke M, Teodorovic I, Rozewicz C, HagenbeekA. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. Blood. 2006 Nov 15;108(10):3295-301. Epub 2006 Jul 27. PubMed PMID: 16873669.
5: Zámecníková A, Vranovský A, Hlavcák P. Coexistence of Philadelphia-positive chronic granulocytic leukemia and diffuse large B-cell lymphoma at initial diagnosis. Leuk Lymphoma. 2002 Feb;43(2):429-31. PubMed PMID: 11999582.

Graduate students involved in the project (for each of them list selected works, if any and different from those listed by the project leader or scientofic co-workers):