

The role of receptor tyrosine kinases in Brain Tumour Diagnosis and Therapy (RTKBT)

Project Director: Prof. Univ. dr. Anica Dricu

Scientific Report III (1st of January to 5th of December, 2013)

General objectives

1. Evaluation of the cytotoxic effect of Helianthine on brain tumors
2. Elaboration of „in vitro” experimental models for screening, using combined treatments of tyrosine kinase inhibitors, on which „in vivo” combined treatments can be developed.
3. Continue the collection and processing of biological materials from patients, in accordance with medical ethics for the maintenance of the Brain Tumor bank started in 2006.

Objectives of the execution phase:

- a. Acquisition of equipment and reagents/consumables
- b. Continuing the experimental phase
- c. Processing and presentation of preliminary results
- d. Analysis and interpretation of existing material
- e. Summary of preliminary theoretical findings in the study
- f. Dissemination of research results

Introduction

The current study aims to discover and improve methods of diagnosis and therapy, able to improve the prognosis of patients diagnosed with brain tumors. In brain tumors signaling pathways are frequently altered by growth factors and may contribute to uncontrolled cell growth by autocrine and paracrine tumor mechanisms. Excessive stimulation of growth factor receptors may also lead to excessive activity of the Ras signaling pathway, which is frequently aberrant in brain tumors. Inhibition of tyrosine kinase receptors using antireceptor monoclonal antibodies and antisense oligonucleotides are currently under investigation, as a means for regulating aberrant signaling pathways of growth factor in brain tumors. In recent years, we are witnessing a

revolutionary development of therapeutic agents targeting angiogenic growth factors and their signaling pathways.

The latest in targeted therapy of cancer stem cells consists in using several receptor tyrosine kinase inhibitors including imatinib mesylate (Gleevec), gefitinib (Iressa) and erlotinib (Tarceva) which have entered in clinical trials for patients with high grade glioma. Farnesyl transferase inhibitors, such as tipifarnib (Zarnestra) which is affecting proRas processing and inhibits Ras signaling pathway, have also entered clinical trials for patients with malignant gliomas. You may need further development and evaluation of targeted therapies by clinical trials of these new agents in order to improve the survival and quality of life of patients with brain tumors. Because of the genotypic and phenotypic heterogeneity of brain tumors, the constitution of a brain tumor bank is difficult.

Results

In this first phase of the project we achieved:

1. To buy necessary supplies for carrying out the objectives;
2. To continue collecting tumor samples from patients with brain tumors by surgery at Emergency Hospital "Bagdasar-Arseni", Department of Neurosurgery, to expand the bank of brain tumors
3. To evaluate the cytotoxic effect of Heliantin as single treatment and in combination with different chemotherapy on different tumor lines established from brain tumors.
4. To determinate some serum molecules (insulin, ferritin) in order to use them as tumor markers in the diagnosis of brain tumors.
5. To determine the cytotoxic effect of tyrosine kinase inhibitor combined with chemotherapy, in order to find effective treatment models and with minimal side effects.
6. To test the cytotoxic effect of a tincture extract of "Ligustrum vulgare flower" on glioblastoma cells.
7. To start analyzing the cytotoxic effect of AG1024, AG1433 and AG 556 in combination with classical therapy in brain tumor cell lines, then analyzing the cumulative effect of the treatment.

IDB Articles:

1. O.M. Neamțu, M.C. Neamțu, E. Avramescu, L. Tătăranu, D. E. Bieru, Ș.O. Purcaru, O. Daianu, D.E. Tache, A.M. Popescu, A. Dricu. Brain tumors incidence related to the tumor type, age group and geographical regions: a biobank-based study. *Current Health Sciences Journal. Supplement*, 2013, pag. 22-26
2. O.M. Neamțu, M.C. Neamțu, E. Avramescu, L. Tătăranu, S.O. Purcaru, O. Daianu, D.E. Tache, A. Dricu. Biobank-based statistical study of brain cancer. *Current Health Sciences Journal. Supplement*, 2013, pag. 29-32
3. Alisa Madalina Popescu, Ștefana Oana Purcaru, B. Stoleru, Ligia Tataranu, Daniela Elise Tache, Monica Daniela Dosa, Anica Dricu, Angiogenesis and Vascular Endothelial Growth Factor in malignant gliomas, *Current Health Sciences Journal*, 2013, Vol. 39, No. 1, ISSN 1454-6876, pag. 5-10
4. Bogdan Stoleru, Alisa Madalina Popescu, Daniela Elise Tache, Oana Maria Neamtu, Ghazaleh Emami, Ligia Gabriela Tataranu, Alice Sandra Buteica, Anica Dricu, Ștefana Oana Purcaru, Tropomyosin-Receptor-Kinases Signaling in the Nervous System, *Mædica J Clin Med* 2013, Vol 8(11), No 1, ISSN:1841-9038, eISSN: 2069-6116, pag. 43-48

ISI Articles:

1. Biobanking in a Constantly Developing Medical World, Stefan-Alexandru Artene, Marius Eugen Ciurea, Ștefana Oana Purcaru, Daniela Elise Tache, Ligia Gabriela Tataranu, Mihaela Lupu and Anica Dricu. *The Scientific World Journal*, Volume 2013, Article ID 343275,

International Conference presentations

1. Sandra Alice Buteica, George Dan Mogoșanu, Ștefana Oana Purcaru, Daniela Elise Tache, Ghazaleh Emami and Anica Dricu, The effect of *Ligustrum vulgare* flower hydroalcoholic extract on *Glioblastoma cells* in vitro * The Tumour Models, 2-4 dec. 2013, London, England
2. S.O. Purcaru, S.A. Buteica, G.D. Mogoșanu, D.E. Tache, and A. Dricu, Hydroalcoholic Extract Of *Ligustrum Vulgare* Flower Induces Cytotoxic Effect On Glioblastoma Cells *In Vitro*. *Recent Advances in Molecular and Cellular Pathology* , 6 Dec. 2013, London, England
3. Conferința Oana Alexandru, Laurentiu Ene, Ligia Gabriela Tătăranu, Vasile Ciubotaru, Alisa Popescu, Ada Maria Georgescu and Anica Dricu. Glucose and insulin expression in various types and grades of brain tumors. Abstract book, pg 88. The 39th International Congress of the Romanian Society of Neurosurgery, 18-21 sept 2013. Bucharest.

4. Ligia Tataranu, V. Ciubotaru, B. Dumitrescu, Anica Dricu. Our last 10 years experience in treatment of tuberculom sellae meningiomas. Abstract book, pg 17. The 39th International Congress of the Romanian Society of Neurosurgery, 18-21 sept 2013. Bucharest, ISSN 2285 – 5939, ISSN-L 2285 – 5939
5. V. Ciubotaru, D. Paunescu, Ligia Tataranu, M. Chelsoi, Anica Dricu. Current Surgical Treatment And Prognosis of S U Pratorientorial Low Grade Gliomas In Adults, Abstract book, pg 47. The 39th International Congress of the Romanian Society of Neurosurgery, 18-21 sept **2013**. Bucharest, ISSN 2285 – 5939, ISSN-L 2285 – 5939
6. Ligia Tataranu, Adriana Dediu, V. Ciubotaru, Alisa Popescu, Anica Dricu. Analysis of 136 patients with intracranial glioblastoma: clinical characteristics, management and prognostic factors. Adults Abstract book, pg 52. The 39th International Congress of the Romanian Society of Neurosurgery, 18-21 sept **2013**. Bucharest, ISSN 2285 – 5939, ISSN-L 2285 – 5939
7. Ligia Tataranu, Alice Buteica, Dan Mihaescu, Ion Mandrila, Oana Stefana Purcaru, Daniela Tache, Cristian Neamtu, Anica Dricu. The effect of ferite nanoparticles on brain tumours *in vitro*. The 3-the National Conference of Neuro-Oncology. 16-20 April. 2013 Cluj Napoca

Oral Presentations:

1. V. Ciubotaru, D. Paunescu, Ligia Tataranu, M. Chelsoi, Anica Dricu, Current Surgical Treatment And Prognosis Of Supratentorial Low Grade Gliomas In Adults, The 39th International Congress of the Romanian Society of Neurosurgery, 18-21 sept 2013. Bucharest
2. Ligia Tataranu, Adriana Dediu, V. Ciubotaru, Alisa Popescu, Anica Dricu. Analysis of 136 patients with intracranial glioblastoma: clinical characteristics, management and prognostic factors. The 39th International Congress of the Romanian Society of Neurosurgery, 18-21 sept 2013. Bucharest

28. 12. 2013

Project director

Prof. Univ. dr. Anica Dricu