**RESEARCH OBJECTIVES**

Clinical management of B-cell-derived tumors includes treatment with monoclonal antibodies, directed against CD20 antigen and combined with chemotherapy. The resistance to this therapy (affecting 30-40% of patients) is often related to decreased levels of CD20 on the surface of malignant B-cells. In particularly Chronic Lymphocytic Leukemia (CLL) is known to exhibit low levels of surface CD20. Therefore the development of new drugs or new combinations of drugs able to increase surface level of CD20 and efficacy of existing therapies, targeting this antigen, may help the relapsing and refractory patients live longer. In this project we propose to determine the activity of new derivatives of cation carriers as potential therapeutic solutions for the treatment of B-cell-derived tumors.

**PRELIMINARY DISCOVERIES**

We recently found that cation carriers (such as Salinomycin, Narasin, Nigericin) are great stimulators of *MS4A1* mRNA expression (encoding CD20 protein), leading to CD20 antigen increase on the surface of B-cell-derived tumors. When combined with the therapeutic anti-CD20 antibody Rituximab (RTX), Salinomycin (SAL) is able to effectively potentiate efficacy of RTX in assays *in vitro* and in SCID mouse model *in vivo*.

**RESEARCH PLAN**

In collaboration with group of chemists, experienced in synthesis of cation carrier derivatives, we plan to test SAL derivatives in numerous biological assays, in order to find hit compounds with potential clinical application in the future. These compounds are expected to simultaneously exhibit two important features:

1. high efficiency in inducing upregulation of surface CD20 antigen on lymphoma/leukemia cells;
2. low or no toxicity against normal healthy cells of the body.

The proposed experiments have been grouped in ten research Tasks and their implementation is expected to bring three Milestones, including:

1. List of SAL derivatives with high CD20-upregulating activity;
2. Short list of selected hit compounds with low toxicity toward normal cells, but able to upregulate CD20 on CLL patient-derived tumor cells and on mouse lymphoma/leukemia cells in tumor mouse models.
3. List of transcription factors/miRNAs and signaling pathways mediating the induction of CD20 upregulation by SAL derivatives.

The strength of this project relies on:

1. novel (previously unrevealed) discovery with therapeutic potential;
2. multidisciplinary collaboration between chemists and biologists;
3. international collaborative support from experts in UK and Italy.

**RESEARCH PROJECT IMPACT**

Identification of more effective therapeutic regimens is an urgent need in medicine. This project aims at designing and testing new approaches for the improvement of current lymphoma-directed therapies. The proposed project will be conducted by a vibrant team experienced in numerous molecular biology techniques and in studying the biology of CD20 antigen as well as the antitumor effects of anti-CD20 monoclonal antibodies. We are therefore convinced that this research can successfully provide an important molecular basis for designing improved combination therapies. The project is already strongly supported by recently obtained preliminary data. Moreover, most of the techniques as well as equipment needed to implement this project are already available in the laboratory and have been successfully used in the past. Noteworthy, advices and help in most challenging tasks will be provided in frame of the multidisciplinary national and international collaborations with the experts in the fields.