RESEARCH OBJECTIVES

Recent advances in immunotherapy, including immune checkpoint blockade and adoptive cell therapy, have revolutionized tumor treatment. Only recently, researchers have begun to understand that cancer-fighting immune cells can get "exhausted," reach a dysfunctional state, or die inside the tumor due to either the persistent antigen exposure over time or factors present in the tumor microenvironment, which shut off the anti-tumor activity of immune cells. Therefore, the key factors influencing the activity of immune cells and the efficiency of adoptive cell therapy have recently become the subject of very intensive study. For example, the ion level in TME, particularly of potassium (K^+) and sodium (Na^+), appears to influence the activity of T cells strongly. Moreover, an "ionic checkpoint" has recently been identified that blocks T cell function in tumors. In this project, we propose to test a new strategy with the potential to boost the NK cells and T cell's anti-tumor efficacy for the benefit of cancer patients and analyze the molecular mechanisms leading to such improvement.

PRELIMINARY DISCOVERIES

Numerous preclinical studies have reported the beneficial antitumor activity of a group of compounds functioning as cation carriers. However, our research group has recently found a unique feature of cation carriers, which is valuable for treating leukemias and lymphomas. Considering that these compounds are promising drug candidates to be combined with immunotherapies, and they certainly lead to changes in ion balance, we plan to study their effect on the anti-tumor activity of immune cells, such as T and NK cells. In particular, we expect that the "ionic checkpoint," blocking T cell function in tumors, can be successfully eliminated by the treatment with cation carriers. Estimation of the effect of cation carriers on the activity of immune cells and the efficacy of immunotherapies seems to be an essential and urgent task.

RESEARCH PLAN

In this project, we propose to determine whether the cation carriers reprogram the transcriptional and metabolic status of immune cells, notably T and NK cells, influencing or improving their antitumor activity as effectors of immunotherapies. The proposed project is interdisciplinary and will be implemented in collaboration with experts in chemistry and metabolomics.

Collectively, the strength of the proposed project relies on:

- novel discovery with immunotherapeutic potential;
- multidisciplinary collaboration between chemists and biologists;
- international collaborative support from experts in the UK.

RESEARCH PROJECT IMPACT

Identification of more effective therapeutic regimens is an urgent need in medicine. This interdisciplinary project aims to identify, design, and test new approaches to improve cancer immunotherapies. The project is also strongly supported by the preliminary data. It will be conducted by a team experienced in numerous molecular biology techniques and supported by national and international experts. We are therefore convinced that this research can successfully provide an important molecular basis for designing improved combination therapies and bringing benefits to cancer patients.