New therapy for the treatment of childhood bone cancer

Cancer in children and young adults is rare, with survival rates being very high, mainly depending on the treatment. The biggest proportion of this diagnosis will be on leukaemia and brain tumours, with just about 3% of them, related to bone cancer, mainly osteosarcoma and Erwing's sarcoma. Bone cancer affects children of growing age, if it has not spread from the tumour site, survival rate are around 60-80% but this is highly affected by diagnosis stage (with early diagnosis being more favourable), tumour's size and location. Treatment generally involves some type of surgery, and the stage of the cancer will determine which type of surgery will be used - this can be from removing only the area affected in the bone to amputation of the limb. Further treatment can include radiotherapy and chemotherapy with it affecting the rate of remission, produce delays in recovery times or cause long term effects such as fertility problems. Biological therapies, such as antibodies or cytokines, aiming at encouraging the immune system to attack the bone cancer, are currently being evaluated in clinical trials. Despite great advances in research for some forms of cancers, we are still lagging behind in offering new treatments for the non-so-prevalent cancers in children.

In our group we mainly work with flavonoids and terpenoids, but we also explore natural extracts from plants and invertebrates and mimic bio-inorganic compounds using a range of synthetic methods. For this project, we have gone to basics; we looked at Nature and searched for potential small structures. Being interested in flavonoids led us to look into the synthetic intermediates and what biological activities they might show. Dibenzoyl-methane derivatives are known to be present in tea and mangosteen fruit, and have been used in traditional medicine to treat several conditions ranging from infection to rheumatic diseases and as antioxidants, though no pathways have been fully elucidated.

In our quest, we used an elegant though simple reaction to produce the skeleton of the dibenzoyl-methane and later modified it, with the most interesting one replacing the carbonyl oxygens by sulphurs. After testing the family of compounds on different cells, we discovered the thionylated version was active and most important, selective for Saos-2 (Sarcoma osteogenic). This cancer cell line possesses several osteoblastic features that make it extremely useful as a permanent line of human osteoblast-like cells for drug discovery and as a source of bone-related molecules.

We went go further to analyse the mode of action. Cell cycle and mRNA expression studies gave us a window into how it works. Arresting the cells at subG1-phase indicated disruption of the mechanism of control, with the expression of MYC, CDK4 and CDK6 being greatly reduced. This would seem to indicate this new compound is an inhibitor for cyclin dependant kinases. More work is currently being done for combination therapy studies and evaluate this compound as a new anticancer agent.

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