To develop 3D bioPRINTed osteoinductive constructs that deliver CHEMOtherapeutics within large bone defects that are surgically created when removing bone tumours.

Sprawozdania

Informacje na temat projektu

PRINT-CHEMO

Identyfikator umowy o grant: 839150

Strona internetowa projektu

DOI
10.3030/839150

Projekt został zamknięty

Data podpisania przez KE
2 Kwietnia 2019

Data rozpoczęcia
1 Lipca 2019

Data zakończenia
30 Czerwca 2022

Finansowanie w ramach
EXCELLENT SCIENCE - Marie Skłodowska-Curie Actions

Koszt całkowity
€ 257 561,28

Wkład UE
€ 257 561,28

Koordynowany przez
THE PROVOST, FELLOWS, FOUNDATION SCHOLARS & THE OTHER MEMBERS OF BOARD, OF THE COLLEGE OF THE HOLY & UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN
Ireland

Periodic Reporting for period 2 - PRINT-CHEMO (To develop 3D bioPRINTed osteoinductive constructs that

deliver CHEMOtherapeutics within large bone defects that are surgically created when removing bone tumours.)

Okres sprawozdawczy: 2021-07-01 do 2022-06-30

Podsumowanie kontekstu i ogólnych celów projektu

Patients who are diagnosed with osteosarcoma today, will receive the same standard-of-care regimen, that was first introduced in the late 1970s — tumour resection and chemotherapy — resulting in dismal prognosis. The use of tissue engineering strategies after malignant tumour resection remains a subject of scientific controversy. As a result, there is limited research that focuses on bone regeneration postresection. Furthermore, although chemotherapy is effective in controlling cancer cell growth, it also significantly hinders the bone's ability to regenerate. Therefore, any bone regeneration strategy that would enhance bone regeneration, would be of great interest to these young patients. Motivated by this, this MSCA fellowship investigated if localised delivery of miR-29b —which has been shown to promote bone formation by inducing osteoblast differentiation and also to suppress prostate and glioblastoma tumour growth—would suppress osteosarcoma tumour growth and enhance the therapeutic potential of chemotherapy whilst simultaneously providing the surrounding damaged bone the necessary cues for repair.

The scientific team developed a formulation of miR-29b:nanoparticles that were delivered via an injectable system which crosslinked in situ to enable local and sustained release of the therapy. The study's main findings showed that when miR-29b was delivered along with systemic chemotherapy, compared to chemotherapy alone, the therapy provided a 45% decrease in tumour burden, a significant increase survival, and a 75% reduction in bone osteolysis caused by the tumour and/or chemotherapy. This anti-cancer and pro-osteogenic effect of miR-29b delivery may extend to other types of cancer. As bone is one of the most common locations of cancer cell metastasis, any therapeutic that inhibits bone tumour growth whilst simultaneously aiding in bone regeneration while the patient is undergoing chemotherapy would significantly benefit not only osteosarcoma patients but any cancer patient with bone metastases.

Prace wykonane od początku projektu do końca okresu sprawozdawczego oraz najważniejsze dotychczasowe rezultaty

Work Package 1: Understanding the divergent relationship between tumour elimination and bone regeneration in Osteosarcoma
Recently, there has being increasing interest in the use of 3D cultures to study the interactions between tumour cells and other cellular or acellular components of the tumour microenvironment as the results better correlate with results seen in vivo. Therefore, we developed a 3D spheroid model of early and late-stage osteosarcoma, consisting of a direct co-culture of both osteosarcoma cells and MSCs. As MSCs are an integral player in osteosarcoma progression, but also are well known to play an important role in bone regeneration, it was vital that these were included in the model. We

validated the clinical relevancy of the model using FDA-approved chemotherapeutic Doxorubicin. Following validation with Doxorubicin, we were able to use this model to further understand the paradoxical relationship between tumour elimination and bone regeneration. Specifically, our model validated that osteogenic supplements have stimulatory effect on the stromal cells, but minimal effect of cancer cell growth. However, when these osteogenic supplements are delivered along with chemotherapeutics this stimulatory effect is completely abolished. Taken together, we have developed and validated a model that mimics the vital relationship between stromal and osteosarcoma cells as well as models their response to chemotherapeutics and regenerative cues, providing vital information that can inform the design of future therapies for these young patients. This work culminated in a paper in Advanced Healthcare Materials in 2021.

Work package 2: Investigate the tumour promotive/regenerative potential of BMP-2 delivery in an immunocompetent orthotopic model for osteosarcoma.
The results generated from WP1 clearly demonstrate that there is a fine balance with regenerating the damaged tissue without causing tumour recurrence. With this in mind, I first established an orthotopic model for osteosarcoma which metastasises to the lung. Next, we conducted our in vivo study to understand the effect BMP-2 delivery alone or in combination with Doxorubicin would have on tumour progression and bone formation. The results from this study show that BMP-2 delivery did not accelerate tumour progression in a pre-clinical osteosarcoma orthotopic model, when compared to non-treated or doxorubicin alone groups. Interestingly, when treated locally with a hydrogel containing BMP-2 alone ectopic bone formation was observed surrounding the tibia However, when treated with the same hydrogel and concentration of BMP-2 in combination with systemic chemotherapeutics this stimulatory effect was significantly diminished (see Figure 1). Taken together, these results indicate that although BMP-2 delivery does not exert any tumour-promoting effects as previously feared, it is not an effective therapy to aid with the regeneration, while the patient is undergoing chemotherapy.

Work Package 3: Investigate if localised delivery of miR-29b would suppress osteosarcoma tumours whilst simultaneously normalising the dysregulation of bone homeostasis caused by osteosarcoma. We developed a formulation of miR-29b:nanoparticles that were delivered via a novel hyaluronic-based hydrogel to enable local and sustained release of the therapy, and to study the potential of attenuating tumour growth whilst normalising bone homeostasis. We found that when miR-29b alone, compared to chemotherapy alone, our therapy provided a significant decrease in tumour burden, increase in mouse survival, and a significant decrease in osteolysis thereby normalising the dysregulation of bone lysis activity caused by the tumour (Figure 2). This work is currently under review in Advanced Materials.

All of this work was presented at 5 international conferences (3 poster presentations 2 podium presentations). There will also be 3 journal publications in leading journals including Advanced Healthcare Materials and Trends in Molecular Medicine.

Innowacyjność oraz oczekiwany potencjalny wpływ (w tym dotychczasowe znaczenie społeczno-gospodarcze i szersze implikacje społeczne projektu)

Due to the young age of initial diagnosis, the management of osteosarcoma is a challenging and costly exercise, which has a significant socioeconomic cost, it is estimated to be €14.7 billion in Europe in the last 18 years. Despite the resonating clinical urgency for newer and more effective treatment options, thus far, no major changes in treatment and outcome have been achieved since the 1970s. Furthermore, as the global oncology drugs market is expected to grow from $80.92 billion in 2020 to $84.38 billion in 2021, the discovery of druggable targets and development of innovative therapies for inhibiting metastatic progression could have significant economic implications. The results gained from this proposal will provide pharmaceutical companies a cost-effective platform for testing potential new drugs or combinations.

I have set up a hastag on twitter for the project #PRINTCHEMO and will begin heighten awareness of medical research and MSCA actions in the public through it.

I have took in European Researcher night and was spotlighted #meettheresearchers each year.

I was highlighted in a series on women in bioprinting - online article about my work.

I was also awarded New Investigator Recognition Award from the Orthopeadic Research Society.

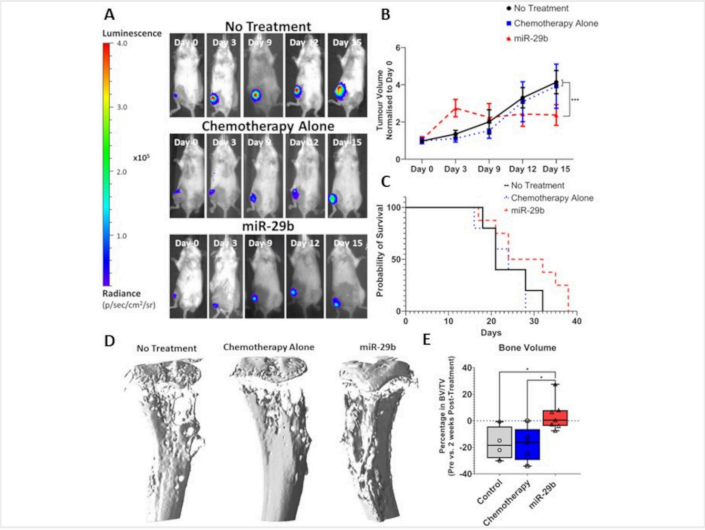

Figure 2: Investigating the therapeutic potential of miR-29b delivery

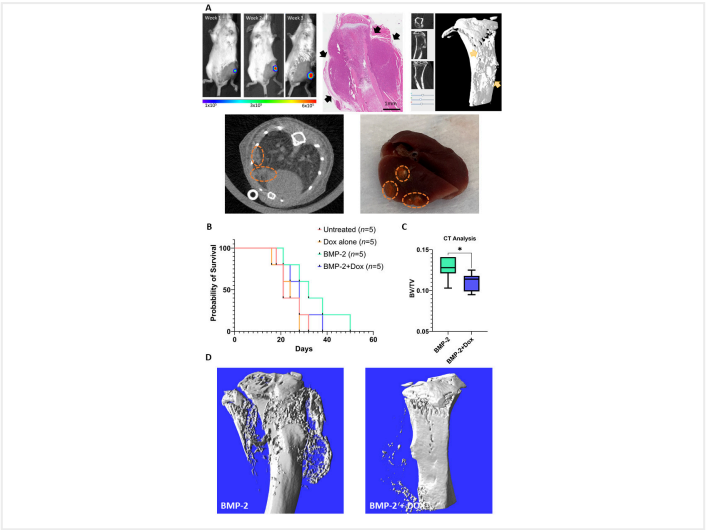

Figure 1: Investigating the therapeutic potential of BMP-2 delivery

Ostatnia aktualizacja: 9 Maja 2024

Permalink: https://cordis.europa.eu/project/id/839150/reporting/pl