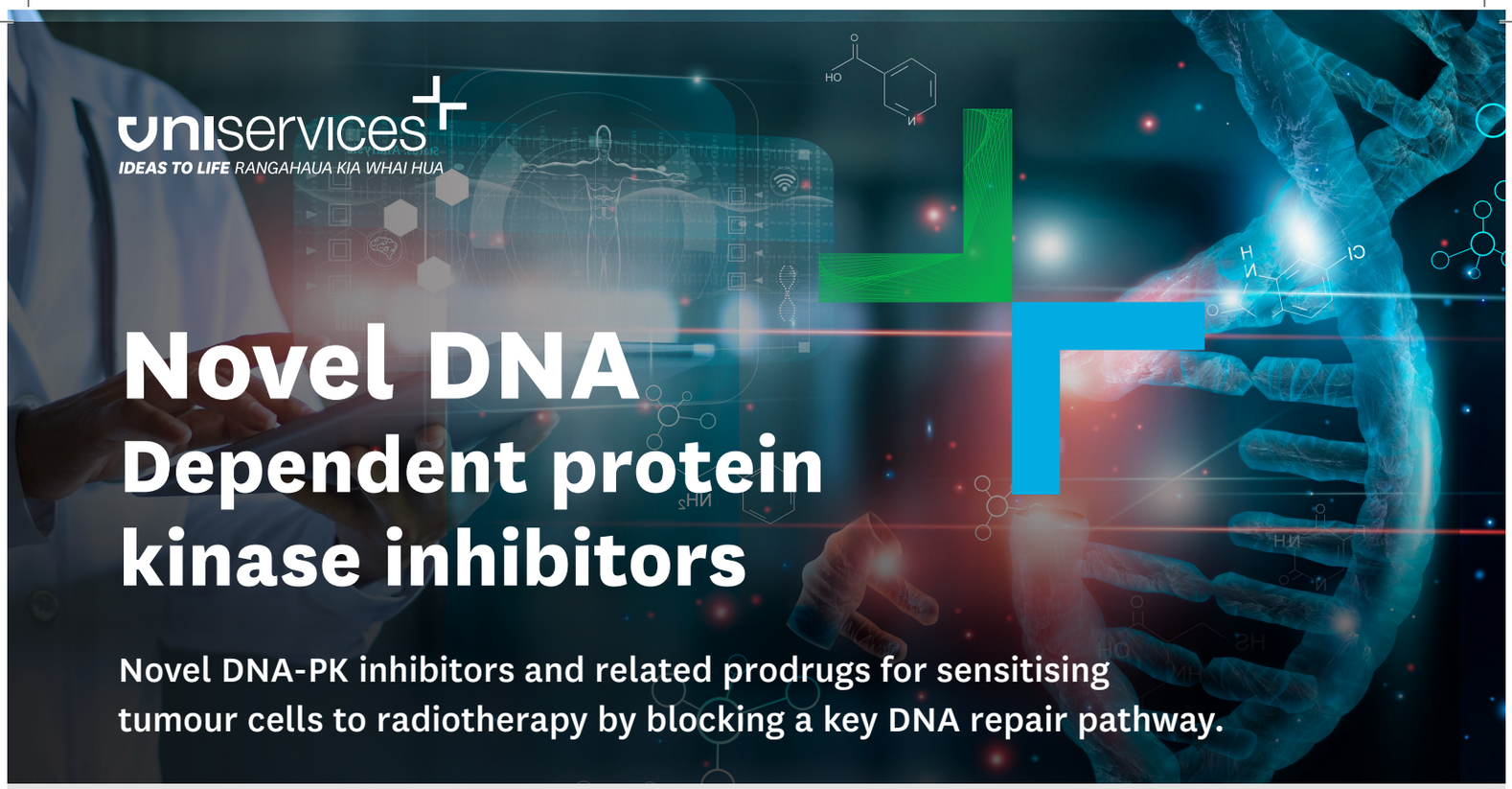

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IDEAS TO LIFE RANGAHAUA KIA WHAI HUA

Novel DNA Dependent protein kinase inhibitors

Novel DNA-PK inhibitors and related prodrugs for sensitising tumour cells to radiotherapy by blocking a key DNA repair pathway.

Background

In spite of advances in the delivery of chemoradiotherapy (CRT), its use causes considerable damage to normal (non-tumour) tissue both within and beyond the radiation field. The damage caused by CRT in normal tissue is dose limiting. To overcome radiation resistance and reduce damage to normal tissue, new cancer therapeutics are needed.

Technology

The DNA damage response (DDR) plays a key role in radiosensitisation, with DNA double strand breaks (DSB) mediating the majority of cytotoxic effects induced by radiotherapy (RT). DNA-dependent Protein Kinase (DNA-PK) is a key DSB repair enzyme and inhibition of its function results in sensitivity to radiation-induced DSBs.

We have discovered a novel class of potent and very selective DNA-PK inhibitors. We have benchmarked our unoptimised lead candidate SN39536 against the lead competitor product (AZD7648 from AstraZeneca). We have demonstrated comparable activity across a range of properties, including when used in combination with RT in an animal model of head and neck cancer.

To further differentiate our lead candidate, we are also developing a Hypoxia Activated Prodrug (HAP) of the lead compound. The HAPs are inactive until activated by oxygen-sensitive enzymatic reduction in hypoxic tissue (the tumour) to release the active DNA-PK inhibitor. This leads to radiosensition of the tumour but NOT the adjacent healthy tissue.

Major advantages of a hypoxia-activated DNA-PK inhibitor

- Greater Selectivity: Novel hypoxia-activated prodrug approach reduces off-target effects in normal cells compared to over inhibitors of DNA-PK
- Tumour Selectivity: Solid tumours often contain hypoxic cells which can reduce the treatment efficacy of many therapeutic approaches including RT. A HAP will selectively target the DNA-PK inhibitor to treatment-resistant hypoxic cells, thereby increasing the efficacy of RT.

Applications

- Tumours that receive RT and where hypoxia is a negative prognostic factor or reduces RT outcomes including:
  - HPV-ve locally advanced head and neck squamous cell carcinoma.
  - Locally advanced non-small cell lung cancer patients with stage IIB/III disease.
  - Advanced cervical carcinoma.
  - Pancreatic ductal adenocarcinoma.
  - Prostate carcinoma.
  - The use of HAP-mediated tumour-selective drug delivery would provide a considerably broader context for application of DNA-PK inhibitors.

UniServices by the numbers

Total external research funding:
$261.3M
(35% increase over 2020)

45
companies started in the past five years

$1.25BN
Total market capitalisation of companies formed

$73.5M
Net asset value of the University of Auckland Inventors' Fund

17,335 Covid-19 vaccinators trained by the Immunisation Advisory Centre in 2021

1,700
New Zealand teachers reskilled and upskilled through Tui Tuia | Learning Circle professional learning and development in 2021

3,000
clinical staff at 22 DHBs trained through teamwork-based acute care simulations designed by NetworkZ in the past five years

14,391 times that child and youth mental health workers attended Whāraurau e-modules, trainings and workshops in 2021

UniServices

UniServices is a not-for-profit company of the University of Auckland that champions research and ideas with the power to change the world. From seeking out and bringing together partners in academic institutions, industry and government to build new knowledge and solutions through research; to whakatupu (nurturing) and commercialising the ideas and intellectual property that arise from the University of Auckland's great minds, we act as the kaihono (those who join and link people to people, and people to projects) firmly entrenched in the ecosystem that bridges the world of academia with business, government and our communities.

University of Auckland

Waipapa Taumata Rau | The University of Auckland is New Zealand's largest and leading university. The name Waipapa Taumata Rau, gifted to the University by Ngāti Whātua Ōrākei, refers to the 'place of many peaks' – places to strive for, ascend to and succeed. We also rank in the top 10 globally for sustainable development impact. The University supports economic growth locally and nationally through innovation and entrepreneurship, creating quality jobs and high-value businesses, and producing graduates that contribute to our economy and society for the benefit of all.

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