Discovering a new generation of small molecule cancer treatments

Malignant melanoma is the most dangerous form of skin cancer, accounting for approximately 75% of skin cancer deaths. With the number of cases diagnosed annually on the increase, the development of a curative agent is an urgent unmet medical need. While recent immunotherapies have shown impressive duration of efficacy in diseases such as cancer where aberrant cell division occurs, microtubules provide an excellent target for therapeutic intervention.

The components of microtubules are two protein subunits of pairs of these two protein subunits. The target site for the compounds being developed by Dr Li and Dr Miller is a region on these tubulin subunits. Unlike other established cancer therapies, their compounds are designed to bind to the colchicine binding site. The site is named after the first compound discovered to bind to tubulin, which is derived from the autumn crocus. Although the site was discovered many decades ago, this approach remains very challenging in cancer drug development.

Dr Li and Dr Miller’s new series of novel tubulin inhibitors disrupt microtubule formation within cells, and therefore preventing tumour growth

Dr Wei Li and Dr Duane Miller conduct collaborative research at the University of Tennessee Health Science Center, USA, with a focus on the development of new compounds for cancer treatment. Their new series of novel tubulin inhibitors disrupt microtubule formation within cells, therefore preventing tumour growth.

Cells contain a cytoskeleton of interlinking tubules and filaments. Microtubules are one of the key structures within this network, playing a role in a wide array of cellular functions, including transport and structural support. They are also essential to the process of cell division, rearranging to form the mitotic spindle structure that facilitates the movement and segregation of chromosomes. When cell division is halted by a drug, the cells can then proceed to undergo programmed cell death. Therefore, in diseases such as cancer where aberrant cell division occurs, microtubules provide an excellent target for therapeutic intervention.

The components of microtubules are two building blocks known as α- and β-tubulin. Together they assemble into long filaments of microtubules. These compounds the researchers analysed were high potency against cancer cells targeting to the colchicine site in tubulin and showed great promise for treating numerous other cancers.

Collaborating with Dr Dalton, Dr Li and Dr Miller initially synthesised a series of microtubule destabilisers: substituted methoxybenzoyl-ary-thiazole (SMART) compounds. By binding to the colchicine binding site of tubulin, they inhibit the polymerisation of the subunits into microtubules. These compounds circumvent the drug resistance issues that have caused other microtubule-stabilising drugs to become ineffective. The first line of drugs are aimed at disrupting microtubule polymerisation of the subunits into microtubules. These compounds are designed to bind to the colchicine binding site.

Figure 1: Structural modifications from the initial thiazole (SMART) analogue produced several new scaffolds (ABIs, RAIs, PATs, IBAs). These new scaffolds were designed to improve aqueous solubility, metabolic stability and bioavailability while maintaining their targeting to the colchicine site in tubulin and high potency against cancer cells in vitro and tumour growth in vivo.

LACK OF EFFECTIVE THERAPEUTICS SPARKS NOVEL DRUG DEVELOPMENT

Researchers have traditionally favoured other sites as targets – such as that for the widely used chemotherapeutic taxane class of drugs. These and many other anti-cancer drugs are aimed at disrupting microtubule structure and dynamics, either by stabilising or destabilising them. Although existing chemotherapeutic drugs with this mechanism of action have been successful in treating many cancers, and in recent years several new tubulin inhibitor drugs have been developed, treatment options remain inadequate. Their success is generally short term as drug resistance often develops and the drugs become highly toxic. This has led Dr Li and Dr Miller to shift their focus towards the colchicine binding site, one of the most important for the destabilisation of tubulin polymers into microtubules.

Malignant melanoma is a highly invasive form of skin cancer, with a high propensity for metastasis via the lymph nodes to other organs. Currently, there is no known curative therapy as the cancer is extremely resistant to most existing therapeutics. Although advances have recently been made in immunotherapy and targeted chemotherapeutics, the prognosis following diagnosis remains poor for the majority of melanoma patients.

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levels of toxicity. Therefore, to overcome this obstacle and increase the bioavailable lifetime of the compound, Dr Li and Dr Miller pushed forward with research and development.

The result was a new set of SMART analogues, aryl-2-benzoyl-endoazolines (ABIs) compounds, improving on the properties of the parent compound. ABIs and subsequent new analogues potently target tubulin, proving to be an effective disrupter of the assembly of tubulin into microtubules. However, systemic administration of any compound that potently disrupts cell function is hazardous. For this reason, most conventional chemotherapeutics result in serious toxic side effects. Therefore, to optimise drug delivery, Dr Li and Dr Miller have been working with Dr Mahato at UNMC to develop a drug delivery system that works in combination with their novel inhibitor.

SMART DRUG DELIVERY
In collaboration with Dr Mahato at UNMC, they tried encapsulating the drug into nanoparticle formulations. This significantly reduced the toxicity while effectively targeting tumour tissue. Despite this, Dr Li, Dr Miller, and Dr Mahato deemed these initial nanoparticle formulations suboptimal, due to their relatively low drug-loading capacity and fast rate of drug release than desired. To improve on these factors and further mitigate toxic effects, they conjugated SMART-OH (a new SMART analogue) and a polymer to create P-SMART.

Unlike other established cancer therapies, Dr Li and Dr Miller’s compounds are designed to bind to the colchicine binding site. Although discovered many decades ago, this approach remains very challenging in cancer drug development.

What led to your collaboration on this project?
This project sprung from an earlier collaborative project between Dr Miller and Dr Dalton. Dr Li joined the project in 2004 and has been working with Dr Miller and Dr Dalton. Currently, Dr Li is responsible for most of the efforts in the project.

Why has drug development thus far been challenging for the colchicine binding site compared with others?
While colchicine itself is an approved drug for gout treatment, it is not FDA approved for cancer treatment due to its high toxicities. There have been a number of new compounds developed targeting the colchicine binding site. However, none of these agents targeting this binding site have obtained FDA approval. The main challenges are the toxicities associated with many of the existing compounds and that the structural requirement for colchicine binding is very exquisite.

How reliable are mouse models of malignant melanoma as a predictor of human tumour response?
Traditionally, human cell lines implanted in nude mice are used for malignant melanoma. They are good models for initial efficacy studies, but are limited by their lack of human melanoma tumour heterogeneity and potentially altered genetic profile. Recently, patient-derived xenograft (PDX) models are becoming widely used since these compounds provide a more predictive of human tumours. We are beginning to work with Dr Meenhard Herlyn at the Wistar Institute to test our tubulin inhibitors and their combinations with targeted drugs in PDX models.

Do you think polymer-conjugated drugs are the future of drug delivery methods instead of the compounds in isolation?
We think so. Due to its mechanism of action, it will be challenging to develop a tubulin inhibitor without side effects. Therefore, any drug delivery method that allows specific targeting of tumour cells will be helpful in increasing the therapeutic index. Polymer-conjugation is one of the approaches for tumour-selective delivery. We are also working on attaching these compounds to antibodies to create antibody–drug conjugates (ADC) to minimise potential systemic toxicities.

What are your plans for testing your novel compounds on other cancers?
We have established collaborations with other cancer researchers to test our novel compound that pancreatic cancer, prostate cancer, colon cancer, and breast cancer. Preliminary data are very promising. In fact, the company who currently licenses these compounds, The Female Health Company (FHC) and Aspen Park Pharmaceuticals, Inc. (APPI), are developing these compounds for metastatic prostate cancer. If we can develop a really good compound, it can potentially be used for a number of cancer types.

What are the future prospects of your research?
Dr Li and Dr Miller are set to achieve their goal of creating a new generation of small molecule tubulin inhibitors. They can be easily synthesised in the laboratory, and combined into an optimised nanoparticle formulation for drug delivery and future clinical trials. Excitingly, early research has also shown that the SMART and ABI compounds possess anticancer properties against breast, ovarian, colon and prostate cancer. Further trials, with a focus on utilising the compounds to treat these cancers, are on the horizon.