Old Drugs, New Wheels
Reinvigorating natural products against cancer

Abstract
Natural products have been exploited for their medicinal properties since the beginning of human history and continue to represent a large proportion of the therapeutic arsenal available to physicians today. This influence is seen particularly clearly in cancer therapeutics, an active area of research where raw natural products are still used as first-line treatment. Despite their undeniable contribution to medicine, there has been a decline in interest in using natural products as a source of new drug that runs parallel to a general decrease in R&D output by pharmaceuticals reliant on synthetic and combinatorial strategies for drug discovery since the 90s. Perhaps due to this reduction in productivity, these irreplaceable molecules have been revitalised with modern delivery constructs.

Introduction
Natural products are secondary metabolites produced by living organisms and function in evolutionary advantage. Natural products have ‘privileged structures’:
- Occupy a small chemical space
- Bind multiple targets
- High diversity
- Natural products are considered ‘old’ drugs because we have
- This does not mean they have lost their value to
- Cytotoxic
- Metastatic
- Low toxicity
- Non
- Entering clinical trials in next two years
- Cardiotoxicity
- Broadest

Statins, immunosuppressives, antibacterials and anticancer drugs heavily rely on natural products for their therapeutic properties.

The Problem with Anticancer Drugs
- Natural products make up the vast majority of cytotoxic chemotherapy drugs.
- Chemotherapy is generally the only treatment for metastatic cancer.
- Metastatic cancer is responsible for 90% of cancer lethality.
- Cytotoxic drugs are notorious for their side effects.
- Cytotoxic (‘old’) drugs can be updated by hybridising them with targeted delivery constructs (‘wheels’), preventing the non-targeted collateral toxicity natural products induce whilst deploying their unrivalled useful properties against a tumour.

In theory, this is a very effective combination; execution, however, is no easy task. The complex is dependent on a linker that maintains integrity in circulation but dissociates inside a cell. The most successful of linkers are hydrazone, reliant on the pH change to acidic (from neutral systemic) when the complex is trafficked through the lysosomes. There are natural products, such as enediyynes, which are so potent they cannot be used alone, thus pairing them with an antibody makes use of their previously neglected cytotoxic potential. Natural products are so favored in this area (the only drugs in clinical trials) because of their structural diversity - this is essential for linker attachment.

Nanotherapeutic drug systems allow the more targeted release of a cytotoxic drug, as well as its safe passage around the body. There has been a recent wave of research into nanomedicines in the anticancer field, and this method has called upon old drugs. Nanotechnology includes nanoparticle bound drugs and, more recently, nanobubbles; gas filled microbubbles that can be injected with a cytotoxic drug, then be detected and burst on demand using ultrasound.

Antibody-Drug Conjugates (ADCs)
Antibodies complexed with a drug in the form of an ADC can transport a potent antitumour molecule to its site of action, thus affecting less healthy cells.

Advantages
- Specific targeting
- Long half-life
- Low toxicity
- Potency/efficacy
- Structural diversity

Disadvantages
- Toxicity
- Non-specificity

Conclusions
- Natural products are considered ‘old’ drugs because we have used them as a source of medicine since the beginning of human history.
- This does not mean they have lost their value to modern pharmaceuticals.
- Using sophisticated modern technology, their advantages, and generally unrivalled, properties can now be taken advantage of whilst negating their drawbacks.
- Hybridization of natural product drugs with pioneering drug delivery systems exemplifies how useful these raw drugs can still be.
- This continued value advocates a further exploration into nature as a resource for pharmaceuticals.

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Key references