UWM RESEARCH FOUNDATION

Technology Overview

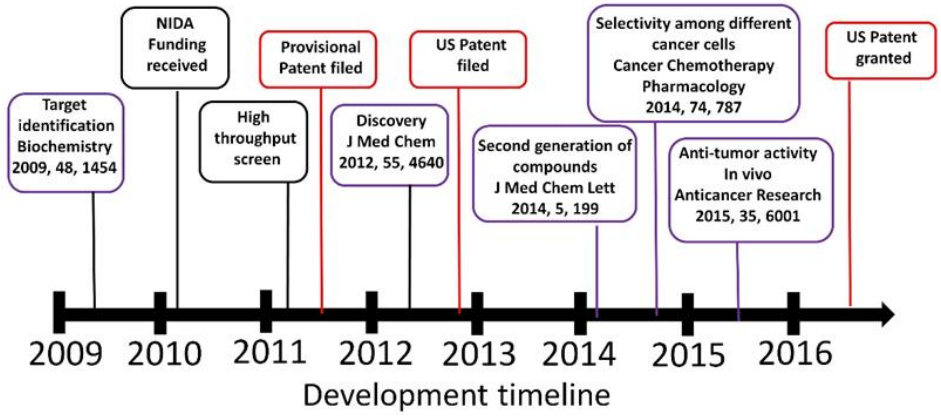
Anti-cancer prodrugs based on a novel mechanism of action

OTT ID #1250

TECHNOLOGY

Chemical biologist, Professor Arnold, has developed new anti-cancer compounds with significant anti-tumor effects for cisplatin-resistant ovarian cancer cell SKOV3-derived tumors. Ovarian cancer represents 3.7% of all female cancers and 4.2% of all cancer death in women with more than 250,000 new cases each year. The major obstacles of current cisplatin/taxane-based ovarian cancer treatments are moderate response rates of 60-80% and an almost 100% recurrence after a short remission time. The novel class of anti-cancer agents developed in the laboratory of Prof. Arnold is based on a biological chemical defense mechanism used by plants to fight herbivores. A well-known member of this class of compounds is gramine, which was isolated from P. tuberosa in the 1960s. Gramine is also known to be a precursor in the synthesis of tryptophan.

In contrast to gramine, the compound class developed in Prof. Arnold's laboratory are prodrugs that are stable under physiological conditions and interact with specific biomolecules such as the vitamin D receptor (VDR). Identified by high throughput screening and developed over years, these compounds can modulate the transcriptional function of VDR, reduce glycolysis and lipogenesis of tumors, and are effective after 2-3 weeks as demonstrated in human cancer-cell derived tumors in rodents.



FEATURES/BENEFITS

- Small molecule prodrug strategy enables the development of non-toxic but highly potent chemotherapies
- Novel mode of action is likely to increase period of remission
- Compounds have the potential to be developed for other cancers
- Easy accessibility: Synthesis only requires one step from readily available chemicals
- Proven activity *in vivo* with relative fast onset for solid tumors

INTELLECTUAL PROPERTY

US Patent Notice of Allowance 2014-0194472

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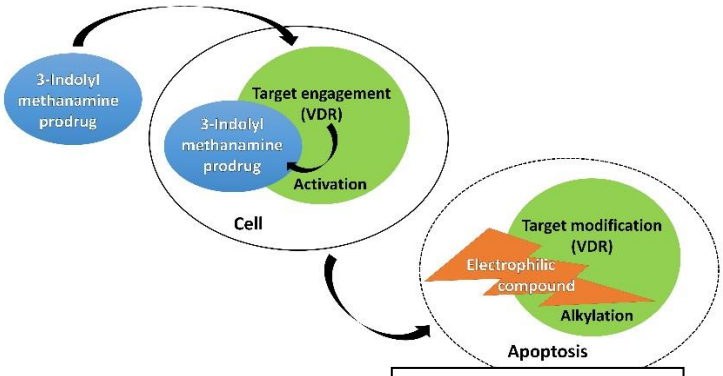
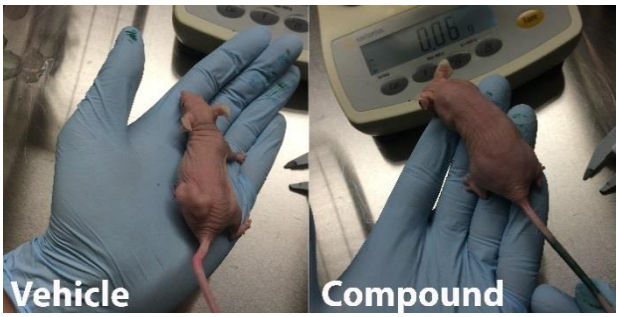
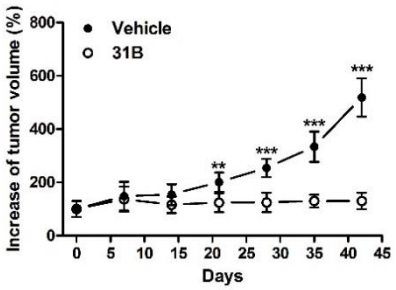
MODE OF ACTION

3-Indolylmethanamines interact with VDR and are converted into a reactive electrophilic species that will alkylate nucleophilic residues of the VDR protein or react with water forming a pharmacologically inactive compound. Alkylation of VDR induces apoptosis and cancer cell death.



In vivo activity





Antitumor activity of lead compound 31B in a SKOV3-derived mouse xenograft model. Animals were treated with i.p. with 31B at 5 mg/kg, five times a week. No toxicity was observed indicated by the absence of weight lost.

MARKETS

The therapeutic and diagnostic market for ovarian cancer was estimated at $16 billion in 2012 and is forecast to reach $34.6 billion in 2018. An unmet market need exists as current therapies are successful only for a short period of time. Remission periods are relative short and drug resistance occurs in almost 100% of patients. Thus, there is an urgent need to develop improved chemotherapies with novel mechanisms of action to overcome the limitations of cisplatin or taxanes.

INVENTOR

Prof. Arnold is an Associate Professor in the Department of Chemistry and Biochemistry and a founding member of the Milwaukee Institute for Drug Discovery. During this career, he was involved in many areas of drug discovery. Trained as a synthetic chemist under Professor Feringa and medicinal chemist at UCSF, Dr. Arnold had a leading role in the establishment of the Chemical Biology and Therapeutics department at St. Jude Children's Research Hospital. Prof. Arnold is a renowned expert in the field of vitamin D and has been working in the area of cancer research for more than eight years. In addition, he is supporting the pharmacology-driven development of new drugs for anxiety, pain, schizophrenia, depression and asthma. He is the author or more than 60 peer-reviewed articles and book chapter and is the Co-IP on four R01 grants supported by the NINDS, NIMS, and NIHLB.

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