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Licensing Opportunity

STW Technology Foundation



Vitamin D3 as treatment strategy for tumors of the proximal gastrointestinal tract

The invention

► Very few effective treatment strategies are available for pancreatic cancer and other tumors of the proximal gastrointestinal tract (esophagus, stomach, duodenum). The relatively high incidence (10 in every 10000 persons for pancreatic cancer each year in Western countries) and lack of adequate treatment strategies call for novel therapeutic options. Research performed at the AMC recently showed that the well known compound (pro-)vitamin D3 is the naturally occurring antagonist for smoothened, the activating receptor of the hedgehog pathway. This pathway is causal in the development of a large number of malignancies and (pro-)vitamin D3 has been shown to inhibit the growth of these tumors. A patent application describing this finding has been filed in 2006. The present invention relates to a pharmaceutical composition comprising an inhibitor of the enzyme 7-dehydrocholesterol reductase

(DHCR7) together with a pharmaceutically acceptable carrier or excipient. This pharmaceutical composition is active against various types of cancer, in particular but not limited to adenocarcinomas of the upper gastrointestinal tract. The invention also relates to a method of preparing a pharmaceutical composition suitable for the treatment of an adenocarcinoma.

Advantages of this treatment

Using (pro-)vitamin D3 for the treatment of proximal GI tract tumors offers several advantages over other known treatment strategies;

- Vitamin D3 is a naturally occurring molecule in the human body. This limits chances of side effects.
- Vitamin D3 is the physiological inhibitor of the Hh pathway.
- Vitamin D3 is known to be safe. It has been added to certain foodstuffs for decades without any negative consequences and high amounts of vitamin D3 are known to be well tolerated.
- The inhibitory action on *in vitro* tumor cell

viability by vitamin D3 is strong, and epidemiological data support this effect on cancer cell growth.

- Despite previously demonstrated non-Hh specific effects of vitamin D3 on tumor cell growth, studies done at the AMC showed that the growth-inhibitory effect of vitamin D3 is specific for those cells that are dependent on an overly active Hh pathway.

What this invention can mean for you company

Because of the abovementioned advantages, the presented invention can mean the following for commercial application:

- The known safety of- and long experience with administering high doses of vitamin D3 leave very little in the way of a clinical trial
- In phase I trials with other Hh-inhibitors (like cyclopamine), significant off-target effects were found. This makes vitamin D3 an interesting alternative.
- A clinical trial using vitamin D3 will be soon be started at the AMC

Commercial information

- The patent application is available for licensing or assignment
- An option right in exchange for financial support of further research is negotiable.

Introduction/clinical problem

► The median survival prognosis for untreated pancreatic cancer after diagnosis is 3 to 5 months. Treatment strategies are limited to resection, for which only few patients qualify (10-15%, after which 30% survival), and chemotherapy, which shows very limited efficacy. The most effective chemotherapy, gemcitabine, raises 1-year survival by only 18%. Radiotherapy has even been described to have a deleterious effect on survival; therefore it is clear that the existing treatment options are not adequate.

Underlying mechanism

In the development of pancreatic cancer as well as other tumors of the proximal GI tract, an excessively activated hedgehog (Hh) pathway has been shown to be causative. This Hh pathway is mainly known for its role in patterning events in the developing embryo, however recently, its involvement in regulating proliferating tissue in adults has become clear, but also -as mentioned- its role in tumorigenesis.

Cyclopamine: an obsolete golden standard

The potent action of the "golden standard" inhibitor cyclopamine on the Hh pathway and the know causality of an overactive Hh pathway in the development of proximal GI tract tumors have led several pharmaceutical companies to trial cyclopamine as a drug. *In vitro* studies showed promising results, but unfortunately, administering cyclopamine to humans resulted in seizures and disappointing efficacy. The reasons for this are yet unknown.

A new therapeutic option

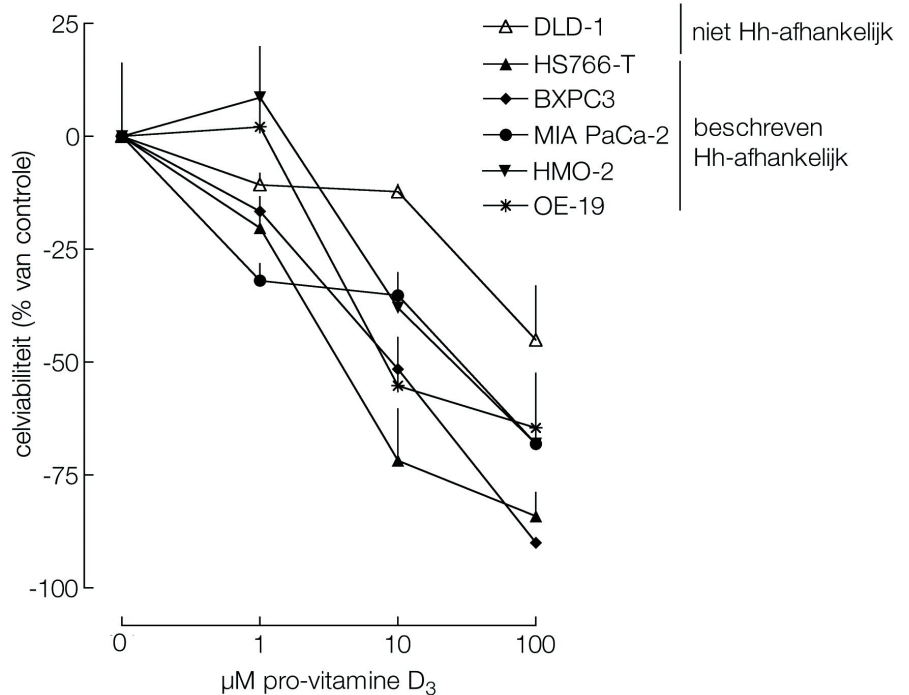
Research performed at the AMC recently showed that the well known compound (pro-) vitamin D3 is the naturally occurring antagonist for smoothened, the activating receptor of the Hh pathway. The other receptor for the pathway (there are two), patched, exerts an inhibitory action on smoothened and uses (pro-)vitamin

D3 to do so. This finding thus identifies the naturally occurring inhibitor for the Hh pathway rather than a compound isolated from plants (cyclopamine). Besides the scientific implications of the identification of the endogenous inhibitor of the Hh pathway, the clinical targets anticipated for cyclopamine now seem eligible for treatment with vitamin D3. More specifically, the inhibition of tumor cell growth is an interesting target for (pro-)vitamin D3.

figure 1. Inhibition of tumor cell growth/viability by pro-vitamin D3. Cell lines isolated from various tumors (DLD-1, colon; HS766-T, pancreas; MIA PaCa-1, pancreas; HMO-2, stomach; OE-19, esophagus) were incubated in increasing concentrations of pro-vitamin D3 and cell viability was assessed. A significant reduction in cell viability can be seen at 10 μ M pro-vitamin D3.

In *figure 1*, a clear inhibition by pro-vitamin D3 of cell growth can be seen for those cells from tumors known to be dependent on excessive Hh pathway activation (inhibition in the same order of magnitude as cyclopamine, not shown in *figure*). The clinical implications of this inhibition are potentially enormous.

figuur 1.



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