

Thymidylate Synthase Polymorphisms for Use in Screening for Cancer Susceptibility

Background

Thymidylate Synthase (TS) is an important enzyme in the nucleotide biosynthetic pathway that converts dUMP to dTMP. TS is a target for a variety of chemotherapeutic agents such as 5-FU, raltitrexed (Tomudex and permtrixed (Alimta)) and inhibition of TS leads to cytotoxicity due to depletion of dTTP pool, a phenomenon dubbed as “thymine less death.”

TS also plays a critical role in cardiovascular diseases and other defects. TS and methylenetetrahydrofolate reductase (MTHFR) compete for folate in the generation of homocysteine. Folate and homocysteine have been associated with cardiovascular risk.

Polymorphisms consisting of 28 base pair repeats in the 5'-untranslated region of the TS gene have been identified in certain African and Asian populations. These polymorphisms occur as either double or triple repeat and have been shown to predict patient response to 5-FU chemotherapy. **The present invention discloses a novel single nucleotide polymorphism which could be added to existing screening tests thereby enhancing the predictive value of the tests.**

Description of the Technology

A novel single nucleotide polymorphism (SNP) in the 5' tandem repeats of the TS gene has been discovered. The SNP, which is located in the 12th nucleotide of a 28 base pair third tandem repeat of the TS gene is a variant form of the repeat. Individuals with wild-type form of 3R had higher transcription of TS than those with the variant form. In addition, the present invention also discloses a six base pair deletion in the 3' gene of TS which results in mRNA instability and decreased production of TS. It has been shown that in cancer tissues, the reduced production of TS prevents the growth and metastasis of cancerous cells. Taken together, these studies demonstrate that identification of these polymorphisms would enable the prediction of a patient's response to chemotherapy and cardiovascular disease treatments.

Applications

- To assess the risk of cancer and cardiovascular diseases
- To develop screening methods for the detection of the six base pair deletion in the 3' gene of TS
- To predict the clinical outcome of chemotherapy and anti-cardiovascular treatments
- To design therapeutic approaches based on a patient's response to chemotherapeutic and anti-cardiovascular agents
- Can be used an adjunct to existing screening tests to enhance the predictive value of the tests.

Patent Status

- PCT application filed.
- Application was published on May 6, 2004 (Publication No.: WO 2004/037852 A2)

Licensing Opportunity

File SOM 02-52/Ladner

- This technology is available for non-exclusive or exclusive license.

Contact

Peter Golikov, MS, MBA
Director, Ventures and Licensing
University of Medicine and Dentistry of New Jersey
335 George Street
New Brunswick, NJ 08901
Direct Phone: (732)-235-9355
Main Office Phone: (732)-235-9350
Facsimile: (732)-235-9358
golikope@umdnj.edu

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