

Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease

Authors: Lamb R, Ozsvari B, Lisanti CL, Tanowitz HB, Howell A, Martinez-Outschoorn UE, Sotgia F, Lisanti MP.

Oncotarget. 2015 Jan 22. [Epub ahead of print] PubMed PMID: 25625193.

Professor Bogdan Bošković

Military Medical Academy, Clinic for Emergency and Clinical Toxicology, Belgrade, Serbia.
bogdanboskovic@gmail.com

www.impactjournals.com/oncotarget/

Oncotarget, Advance Publications 2015

Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease

Rebecca Lamb^{1,2,*}, Bela Ozsvari^{1,2,*}, Camilla L. Lisanti^{3,}, Herbert B. Tanowitz⁴, Anthony Howell^{1,2}, Ubaldo E. Martinez-Outschoorn⁵, Federica Sotgia^{1,2} and Michael P. Lisanti^{1,2}**

¹ The Breakthrough Breast Cancer Research Unit, Institute of Cancer Sciences, University of Manchester, UK

² The Manchester Centre for Cellular Metabolism (MCCM), Institute of Cancer Sciences, University of Manchester, UK

³ The Moor Allerton Preparatory School, Didsbury, Manchester, UK

⁴ Departments of Pathology and Medicine, The Albert Einstein College of Medicine, Bronx, NY, USA

⁵ The Kimmel Cancer Center, Philadelphia, PA, USA

Authors of the study, British and American oncologists propose new strategy in the treatment of various stages of carcinomas, as well as their advanced metastases. According to them, this can be achieved via the selective targeting of cancer stem cells (CSCs), also known as tumor initiating cells.

The study can be divided into three separate parts: (1) starting point of the authors; (2) what the authors have found, and (3) what the authors propose.

1. Starting point of the authors. The starting point of the authors was based on the „endosymbiotic theory of mitochondrial evolution“, since „mitochondria evolved from bacteria that were originally engulfed by eukariotic cells millions years ago“. Therefore, they have common ribosomes responsible for protein biogenesis. In other words, this theory is based on global phenotypic characteristics that were highly conserved among cancer stem cells, across multiple

tumor types, i.e. in finding an Achilles' heel in cancer stem cells for the clonal expansion and their survival.

Several classes of antibiotics inhibit mitochondrial biogenesis as a known „side-effect“ which, according to the authors of this study, can now be transformed into a „therapeutic effect“. This will be independent of cancer type, as well as of mutated, previously resistant cells to anticancer drugs. Accordingly, the assumption of the authors was that antibiotics in this case would act on cancer as a unique disease, since the survival and growth of its cells depend only on enhanced protein biosynthesis in mitochondria.

2. What the authors have found. Studies were performed *in vitro* on the cells of eight types of carcinoma: brain (glioblastoma), breast, DCIS (ductal carcinoma *in situ*), lung, melanoma, ovarian, pancreatic and prostate. Used antibiotics were: azithromycin, chloramphenicol, doxycycline, tigecycline and anti-parasitic drug pyrvinium pamoate. Antibiotics were very efficient in growth inhibition of all eight types of carcinoma. Effective concentrations of antibiotics were in micromolar range (from 1 to 250, mostly in 50 μ M) and those of pyrvinium pamoate in nanomolar range (250-500 nM). It has also been found that azithromycin, doxycycline, tigecycline and pyrvinium pamoate were highly efficient in

growth inhibition of mutated human melanoma cells A375, which were previously resistant to vemurafenib (V600E). According to the authors, this finding proves that the used antibiotics act on the cancer stem cells, independently of the type of cancer from which they emerge, as well as on previously mutated cells.

3. What the authors propose. The authors propose to treat cancer now like an infectious disease, by redirecting FDA-approved antibiotics for anti-cancer therapy, across multiple tumor types. These drugs are non-toxic for normal human cells, avoiding thus the numerous side effects of current anti-cancer medication. In this regard, a clinical trial with doxycycline in patients with advanced breast cancer and bone metastasis is already ongoing (<https://clinicaltrials.gov/ct2/show/NCT01847976>). Secondly, doxycycline trial in relapsed patients with non-hodgkin's lymphoma has also been initiated (<https://clinicaltrials.gov/ct2/show/NCT02086591>).

In any case, the study is not only of highly fundamental, but could also be of much more practical importance. Namely, if the idea of the authors is confirmed, it will enable the treatment of cancer more effective, much better tolerated and manifold cheaper, making thus discovery at least equal to that of antibiotics themselves.