

# Magnetotactic Bacteria – Trends for the Future Research

Denis Grouzdev, Veronika Koziaeva, Boris Kuznetsov † and Konstantin Skryabin\*

Research Center of Biotechnology of the Russian Academy of Sciences, 33, bld. 2. Leninsky Ave., Moscow 119071, Russian Federation

## \*Correspondence to:

Konstantin Skryabin  
Research Center of Biotechnology of the Russian  
Academy of Sciences, 33, bld. 2. Leninsky Ave.  
Moscow 119071, Russian Federation  
Tel: +7 (499) 135-73-19  
E-mail: [office@biengi.ac.ru](mailto:office@biengi.ac.ru)

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## Abstract

Magnetotactic bacteria (MTB) are interesting for their ability to produce size-narrowed and chemically pure magnetic nanoparticles, which are the promising new nanomaterial useful for a number of biotech applications – drug delivery, cell sorting, DNA/RNA extraction, etc. The only difficulty hampering the practical recruitment of bacterial magnetosomes is the low level of their production by bacteria. The ways to get over this problem are discussed in the paper.

## Keywords

Magnetosomes, Nanoparticles, Magnetospirillum

## Letter to the Editor

Magnetotactic bacteria were discovered by Salvatore Bellini in freshwater ecosystems near Pavia, Italy [1]. Bellini observed bacteria moved towards the north pole of the magnet and proposed that there are small magnetic compasses inside their cells [2]. Later such magnets were described. The first TEM pictures of the magnetic crystals chain inside *Magnetospirillum magnetotacticum* MS-1 revealed that each electron-dense particle is surrounded by one or several layers of organic material, and Blakemore hypothesized that this layer could be a lipid membrane, which was confirmed a few years later when the lipid analysis of purified magnetosomes was undertaken [3]. Further studies revealed a vast diversity of magnetosome nanoparticles in their forms - cuboctahedral, elongated hexagonal prismatic and bullet-shaped morphologies were reported [4].

Why MTB need to synthesize magnetosomes? The common answer is that the presence of a magnetosome chain inside MTB cell allows it to orient themselves passively by the geomagnetic field. It accelerates and facilitates the search of the preferable layer in the oxic-anoxic transition zone of the aquatic bottom sediments [5]. If it is the sole function of magnetosomes or they possess any other function, remains discussable, but the presence of a magnetic needle inside bacterial cell offers us a tool to guide MTB with external magnetic force [6].

Bacterial magnetosomes are made from magnetite  $\text{Fe}_3\text{O}_4$  or greigite  $\text{Fe}_3\text{S}_4$  and surrounded by a lipoprotein membrane. *De novo* magnetite synthesis techniques mostly allow production of crystals which are either too small (and thus being superparamagnetic) or too large (possessing multiple domain crystals) for biomedical applications. Magnetite crystals produced by MTB are strikingly consistent in size and shape and always fall within the single magnetic domain range (30–120 nm in length) and confer a permanent magnetic dipole moment to the cell. In MTB, magnetite is conveniently produced at ambient temperature and under atmospheric pressure. The first studies on the practical application of magnetosomes appeared in late 80's and early 90's when magnetosomes were used

for mRNA extraction and purification [7]. Magnetosomes also comprise the promising material for the development of early stage diagnostics techniques and therapy of social significant diseases including oncological ones [8-10]. Magnetosomes are of particular interest as the therapeutic tool due to the absence of toxic influence on recipient organism [11]. Magnetosomes were also proposed for a number of practical applications: as biosensors [12], non-destructive domain analysis of soft magnetic materials [13], in nanorobotics [14] and as a material for computer memory chips [15]. But the successful practical application of magnetosomes is limited by the fact that all MTB deposited in culture collections possess the low productivity in magnetosome synthesis. In natural ecosystems, MTB inhabit the thin layer of the bottom sediments and their requirements to substrates and environmental conditions for efficient growth remain unclear due to inability to measure these parameters in labile redox zone of their preferred habitats *in situ*. As a result, the problems appear in cultivation of MTB in biotech reactors and the yield of MTB biomass remains at low levels.

In our own study we met just the same problem – low production of magnetosomes by the *Magnetospirillum* strain used (*Magnetospirillum caucaseum* SO-1). Being highly stable with its magnetic genotype (in comparison with commonly used *Magnetospirillum* strains, where magnetosome gene island determining the ability to produce magnetosomes is spontaneously removed from the genome), *M. caucaseum* SO-1 synthesized 25 nanocrystals per cell and its productivity was about 10 mg per 1 liter of liquid culture. We were able to find the way to display IgG antibodies on the magnetosome membrane [10] and the resulted functionalized magnetosomes were highly efficient in magnetic ELISA application and potentially could be useful in drug delivery or tumor magnetic detection as a tomography contrast agent. Moreover, the obtained magnetosomes occurred to be the promising material for magnetic DNA extraction/purification procedure (unpublished data), but the only obstacle for the further practical application became the low level of magnetosome production in *Magnetospirillum* strains.

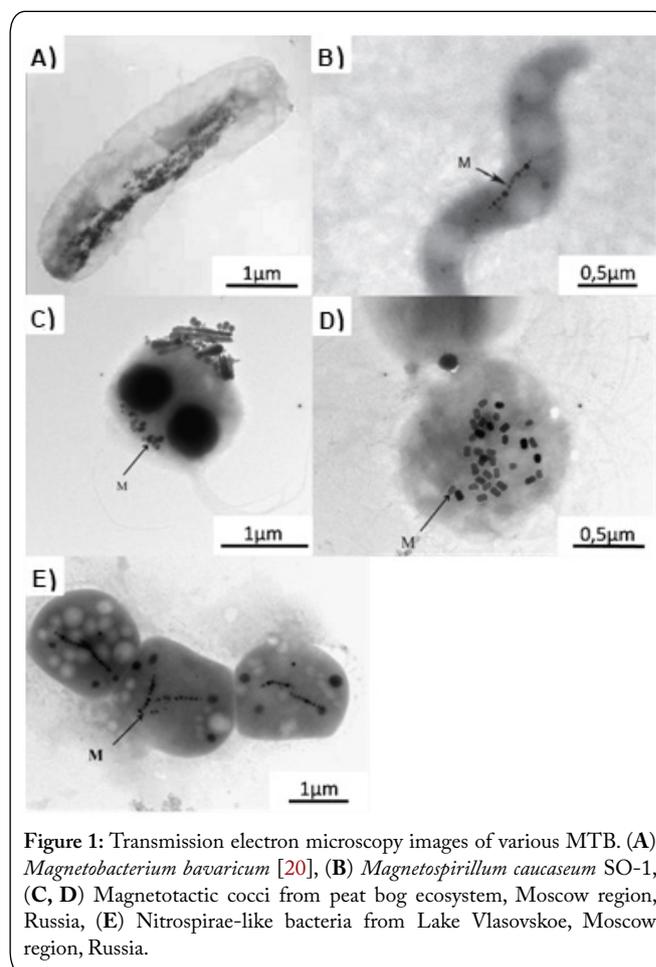
There are several ways to increase the production of biogenic substances by bacteria – genetic engineering manipulations, mutagenesis and selection, the search of new promising magnetosome producing strains. As magnetosome production is concerned, the first way was studied using two approaches. The first strategy for the overexpression of magnetosome biosynthesis genes in the alphaproteobacterium *Magnetospirillum gryphiswaldense* included chromosomal multiplication of individual and multiple magnetosome gene clusters via transposition [16]. The resulted mutant strain had more than 100 magnetosomes per cell (wild-type – 25 magnetosomes per cell), but the mean size of crystals was slightly increased, to 39 nm. Besides, authors observed that cell division was slightly impaired in cells, as indicated by the presence of conspicuously elongated cells that often remained connected by deformed separation sites at advanced stages of constriction. The conclusion of the paper was that the cell size in the case of *Magnetospirillum gryphiswaldense* could be a natural limit in increasing its productivity and the best way

could be a transfer of genes encoding magnetosome formation to an alternative host.

Another approach is the search for new promising magnetosome producer in natural habitats among the unknown bacteria. This way is extensively applied for, and many of new MTB are described every year. The application of NGS and metagenomics, in this case, looks the most attractive, and the most promising results could be obtained using new long-read sequencers like PacBio RS II (Pacific Biosciences, Menlo Park, USA) and nanopore-based sequencers (Oxford Nanopore Technologies, Oxford, UK). Long reads are expected to be helpful for reconstructing genomes from metagenome data. By this approach, the searching and describing the new MTB look very promising.

Species of magnetotactic bacteria are found in diverse Gram-negative phylogenetic groups, including the *Alphaproteobacteria*, *Gammaproteobacteria*, *Deltaproteobacteria* and *Nitrospira* classes and the candidate phyla *Latescibacteria* (also known as candidate division WS3) and *Omnitrophica* (also known as candidate division OP3) [17]. Only a few magnetotactic bacteria strains have been isolated in pure cultures by now, so there is worldwide increase in the efforts to find some new cultivable strains that are able to produce magnetosomes.

The obvious way to search a new magnetosome producer is isolation of the MTB synthesizing the increased number of magnetosomes per cell as it takes place in *Candidatus*



**Figure 1:** Transmission electron microscopy images of various MTB. (A) *Magnetobacterium bavaricum* [20], (B) *Magnetospirillum caucaseum* SO-1, (C, D) Magnetotactic cocci from peat bog ecosystem, Moscow region, Russia, (E) Nitrospirae-like bacteria from Lake Vlasovskoe, Moscow region, Russia.

*Magnetobacterium bavaricum* (Figure 1A). Our results obtained in studies on the biodiversity of MTB in freshwater ecosystems in Russia, allowed us [18] to find and describe four new species of *Magnetospirillum* genus (Figure 1B), but these MTB possessed just the same levels of magnetosome production as the previously described *Magnetospirillum*. A common scheme for the isolation of new MTB species from natural habitats includes the following steps: (i) the sampling from the studied source, (ii) microcosm formation, (iii) magnetic separation of MTB, (iv) enrichment of magnetically separated MTB fraction using 'race-track' method, (v) inoculation of final dilutions in elective media, (vi) growing, microscopic analysis of cultures, (vii) secondary inoculation from the enrichment cultures, new growing and analysis repeating (this cycle could occur many times until the pure culture/or failure resulted). The complete time spent on this process could take years. With this scheme MTB with low motility will be lost, but these bacteria are the most promising for the production of magnetosomes. The 16S rRNA-targeted NGS screening of some additional ecosystems (peat bogs, psychrophilic sea lagoons) revealed the presence of substantially increased MTB species diversity. Among the candidates for new species we found MTB with the elevated number of magnetosomes per cell, phenotypically similar to cocci (Figure 1C and 1D) and the representatives of Nitrospirae phylum (Figure 1E). In the future, the combination of metagenomics, genome analysis and new visualizing techniques combining optical, electron microscopy and FISH (Fluorescent *In Situ* Hybridization) [19] will result to the explosion in discovering and isolating new unusual species of MTB.

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