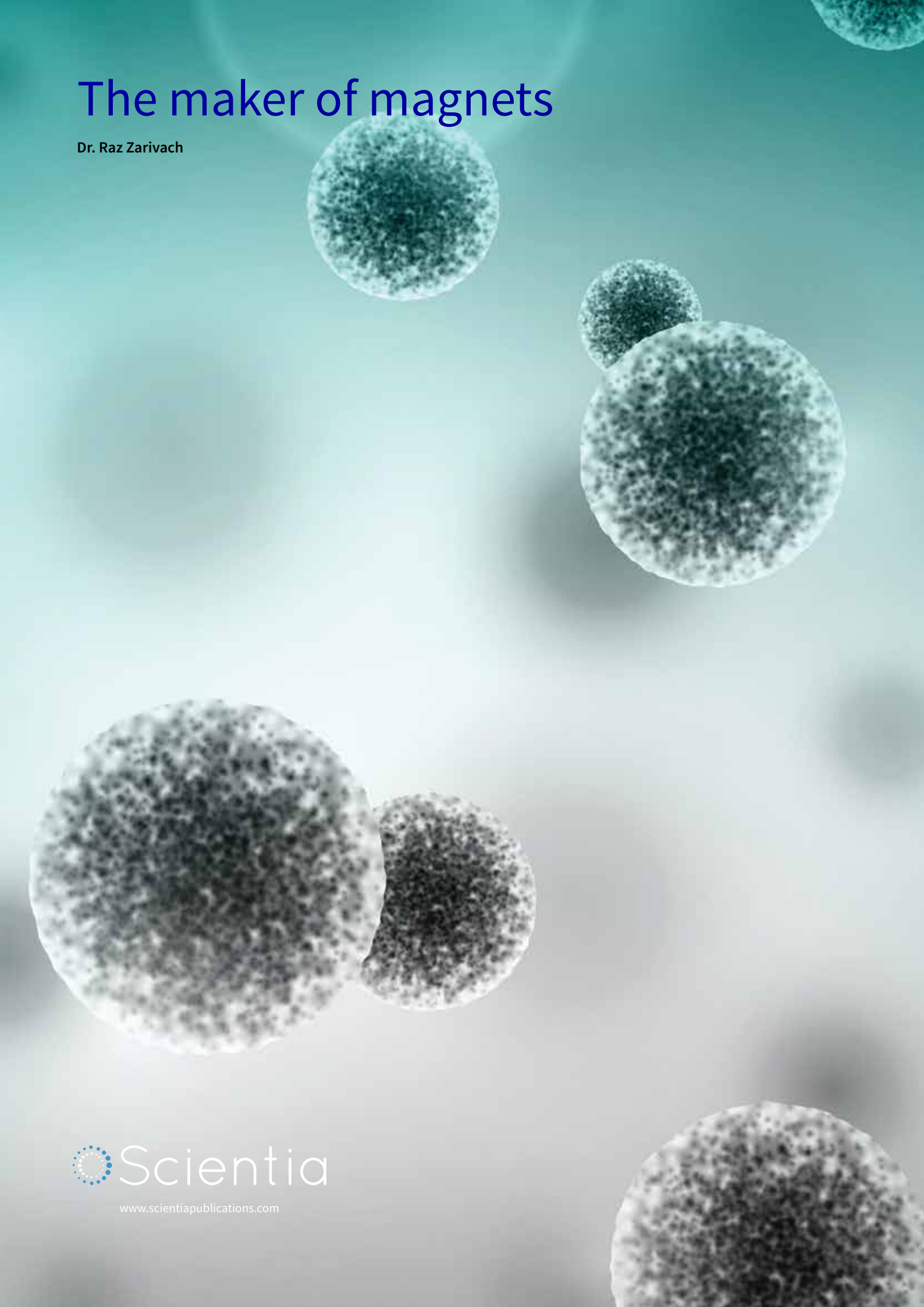
The maker of magnets

Dr. Raz Zarivach

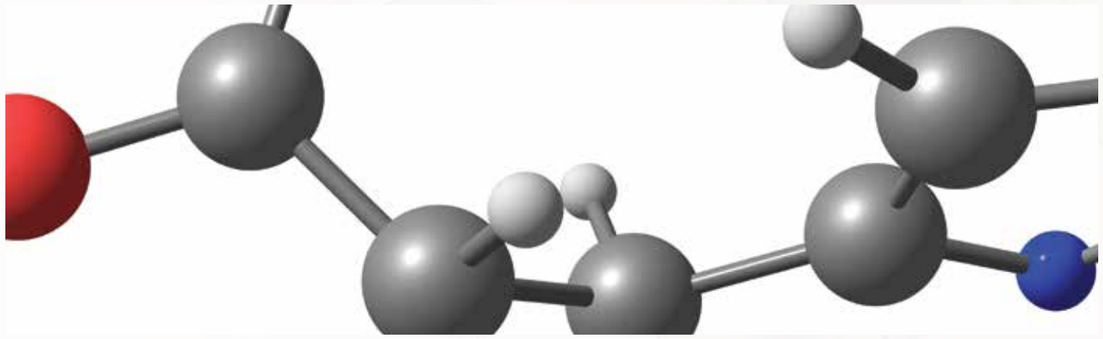


Scientia

www.scientiapublications.com

The maker of magnets

Dr Raz Zarivach is a leading expert in the structural biology of magnetosome-associated proteins. We ask him about his current research.



How did you end up in your current role?

I got here via a conventional route: I started as a chemist during my first degree, then went into doing a PhD in Structural Biology, which I had previously really liked as a topic. By mistake or by chance I did my PhD in the lab of Ada Yonath, the group that determined the molecular structure of the ribosome and in doing so won the 2009 Nobel Prize. I was actually working on this topic as a PhD student, continued in structural biology during my Postdoc, and then afterwards I was selected for the position here in Ben-Gurion University of the Negev.

What brought you into the magnetosome world?

Moving into the magnetosome world was different, because this is a very specialized topic. I had already heard about biomineralization during my first year as a PhD student – and it somehow always stayed with me, including hearing about the magnetosome and magnetic / magnetotactic bacteria. It intrigued me as to how things were being done, but of course I was already doing my PhD on another, very specific field. When I finished my Postdoc on bacterial pathogenicity mechanisms, with a strong focus on bacterial secretion systems, I really wanted to move my lab onto a new topic. At this point I recalled my excitement upon hearing of work with magnetic bacteria – and this is taking into account that even after 10 years I was still interested.

You have had quite an international career; do you think it has shaped the way you perform research?

I'm not sure it's actually because it was an international career, so much as that I was exposed to good researchers. I learned many 'best practices' – how one should conduct research, how work should be done patiently and correctly, how to look at things in a different way. I don't think it's the location of where I have worked; it's more who I have met and worked with.

What do you think will be 'the' big finding in magnetosome research?

I think there are many big findings. One direction is always towards biotechnology, one that many groups are taking – this is what brings money into the field. However there are also very big questions regarding protein-mineral interaction, how do you control a mineral using biological components? We use bacteria as they are much easier to study and simply see how it goes.

Is it possible to transfer the entire magnetosome production system to a foreign host?

It has been tried many times. One of my collaborators has actually managed to do that in a bacterial strain that is very closely related to magnetotactic bacteria. His name is Dr. Dirk Schuler and his work was actually published in Nature Nanotechnology, but that was the only time that someone has managed to transfer the magnetosome into another organism.

Do you think it will be possible to integrate foreign proteins into magnetite crystals?

There are currently many attempts to cover magnetite crystals with proteins. In a way this is not hard, once you find an appropriate protein from the magnetotactic bacterial genome (one that can bind biomagnetite), then you can use that to cover magnetite with your desired protein. This is something we do, and this is something that our collaborators are doing, so we are all heading in this direction.

Can this replace the current techniques using labelled magnetic-beads?

I think so. The idea is not just to cover magnetite, you can also do this using current techniques. Instead the idea is to control the size and shape of magnetite, then process them to obtain uniform, controlled, and tightly-bound protein surface coatings.

Do you see yourself moving some of these discoveries into the commercial sphere? Are you encouraged by your experience with companies such as SmartZyme?

I'm a member of the National Institute for Biotechnology in Israel, and we are looking in the direction of patenting and spin-offs, i.e. commercialising our ideas. As a shareholder of SmartZyme, and as someone on the Scientific Directive Board, I'm always exposed to the 'industrial' world. Having these connections is really important, allowing me to take my work in other directions. However I do see a distinction between my life as a scientist (where I'm looking at the very basic scientific questions), and that involvement in the industrial world (in which I act as an advisor, as someone with ideas, as someone with different opinions that can be taken). Scientists in pure research are really looking at these very fundamental questions, which cannot necessarily be easily translated across.

The race to the Pole

The Department of Life Sciences at Ben-Gurion University conduct cutting edge research into a wide range of biological fields. It is located within Beer Sheva, the largest city in the Negev desert of southern Israel.

There is a moment in every child's life when they take a couple of magnets off the fridge and hold them close to each other. They then marvel as those magnets somehow push or pull back and forth without any visible sign that something is happening. At least, no visible sign to our eyes. But what if you could detect magnetic fields, see them curving through space and follow them as you wanted to? When people hear this idea their thoughts normally jump straight to homing pigeons, but bacteria have been perfecting this skill for millennia.

Magnetotactic bacteria sense magnetic fields to navigate the chaotic depths of the ocean. How? Read on…

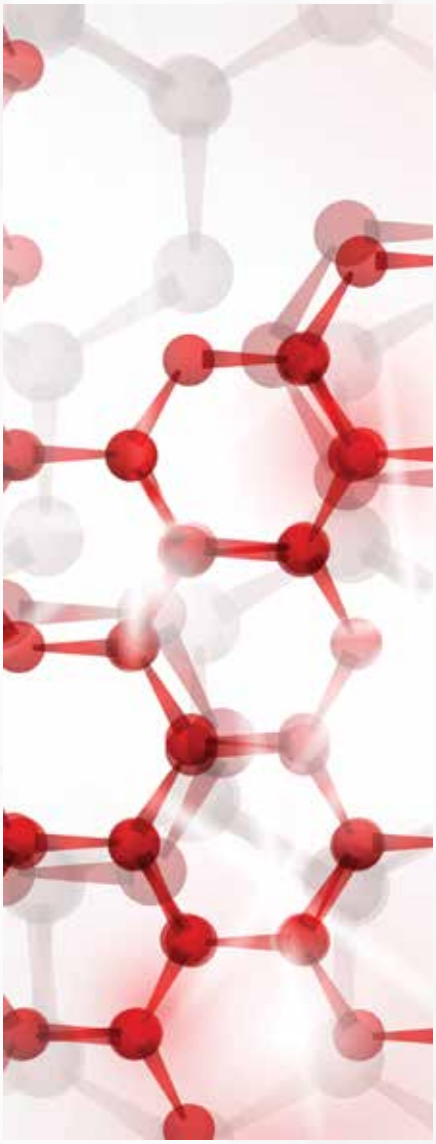
This seems a rather odd ability for a single-celled microorganism to have, but in fact aquatic 'magnetotactic' bacteria can use magnetic field lines to determine 'up' and 'down', no small feat when you are floating in the middle of the ocean. But how can you detect a magnetic field? The answer lies in a specialised organelle known as the magnetosome, which consists of a lipid bilayer surrounding an iron crystal known as magnetite. By producing a number of these magnetosomes and lining them up, end to end, the bacteria essentially become a single (very small) magnet, which then lines up alongside the Earth's magnetic field. Held in this orientation, magnetotactic bacteria simplify the chaotic ocean movement into a simple Go Up/Go Down choice (as the magnetic field dips in towards the earth's core). They then use this knowledge to choose their goal: the oxygen-filled surface zone or the anaerobic depths.

While this seems simple enough, actually forming the magnetosome is a remarkably complex process requiring the formation of the organelle from cell membranes, filling it with iron precursors, nucleating, and then controlling crystal growth. As such, a number of specialised proteins known as magnetosome-associated proteins (MAPs) are involved in the magnetosome production process. The majority of these proteins were identified using proteomic approaches – while they are known to play a role in magnetosome formation, just what that role is often remains a mystery.

MYSTERIOUS MAGNETISM

Understanding these roles is where scientists such as Dr. Raz Zarivach from Ben-Gurion University come in. As a structural biologist, his expertise lies in determining the shape of proteins at the molecular level, using that to identify just how they perform their designated jobs. Skills honed during a PhD in the lab that successfully determined the structure of the ribosome (which eventually brought the lab head a Nobel Prize) provided him with the basis for a long, multinational career in structural biology.

The research goals of the Zarivach group focus on identifying the roles these MAPs play, one at a time, by examining their molecular



structure. Proteins often contain typical 'motifs' or 'domains', combinations of structure and chemistry that provide a particular effect, for example a Zinc Finger is involved in binding DNA, while a GxxxG region promotes binding of proteins within membranes. By examining the structure of MAPs they intend to identify magnetosome-specific domains, then determine how they work.

This process is harder than it sounds, naturally. The gene for each MAP needs to be cloned and expressed in a simpler bacteria, such as E. coli (yet more complications, E. coli use different coding systems for their DNA-protein translation process, requiring the use of specially modified strains). These MAPs then need to be purified in large amounts and turned into crystals, a slow process full of trial and error – made even worse by the need to crystallise in the presence of magnetite. However, once all of this is done, the researchers can see the structure of the protein – right down to the atomic level.

A MAGNET FOR CASH

While this kind of research sounds quite abstract, it has some unexpectedly important outcomes for biotechnology. Of the many examples, let's look at the purification of a single protein or biomolecule from a large mixture, a process which often uses magnetic beads. Polymer beads have long been used as a solid support for biomolecule capture, usually by attaching an antibody, mixing everything together, and then centrifuging it all – the relatively heavy beads will form a pellet at the bottom of the tube, hopefully with your biomolecule attached. The downside is the need to centrifuge, which is slow, hard to scale up, and cannot be used in continuous flow systems. Enter the magnetic bead, which can be directly pulled from the solution by applying a magnetic field, no centrifugation required.

Ok, but where do magnetosomes come in? Currently, magnetic beads are produced chemically, a process that can lead to a mixture of a variety of shapes and sizes. By contrast, magnetosomes produced by bacteria are the same size and shape every time – a huge boost in quality, if only it can be applied at an industrial scale. First, however, scientists need to figure out what each protein does, and whether the whole system can be moved into a simpler bacteria, such as the E. coli beloved by biotech groups everywhere. This is where the research performed by Professor Zarivach, his group, and his wide ranging collaborators come in.

Dr. Zarivach is no stranger to commercialisation. He has served for several years on the advisory board of SmartZyme, a biotech company in the field of enzyme development, based just outside Tel Aviv, which is itself a known hotbed of biotech start-ups. He credits this experience with showing him the myriad possibilities for expanding scientific developments, possibilities which sadly pass by the majority of research focused academic groups.

Despite this, however, his heart remains in pure research, in the chase after knowledge. As he says "this is what really powers me – the structure of biology, and how you connect that knowledge to so many different things: from pure analysis, to creating new drugs, to modifying the protein's function". Luckily for him, the field of magnetosome research has enough unknown connections to keep even a researcher of Dr. Zarivach's calibre busy for a while.

Researcher Profile

Dr. Raz Zarivach
Associate Professor, Chair of the Macromolecular Crystallography Research Centre
Ben-Gurion University of the Negev

Dr. Zarivach is the head of the Zarivach Laboratory for Structural Biology, as well as the Chair of the Macromolecular Crystallography Research Centre (MCRC) at Ben Gurion University. His work involves X-ray crystallography, which his group uses to determine the structures of proteins involved in magnetosome formation, as well as those involved in effector secretion by pathogenic bacteria. A PhD completed in a Nobel-Prize winning lab led to a successful career, and he has been part of over 45 publications, including several in Nature and Cell.

CONTACT

E: zarivach@bgu.ac.il
T: +972-8-64-61999
W: http://lifeserv.bgu.ac.il/wb/zarivach

FUNDING

Marie Curie Actions
Israel ministry for Science, Technology and Space
German-Israeli Foundation for Scientific Research and Development
Israel Science Foundation
Ben Gurion University of the Negev
National Institute of Biotechnology in the Negev
EMBO

The Zarivach Laboratory for Macromolecular Crystallography