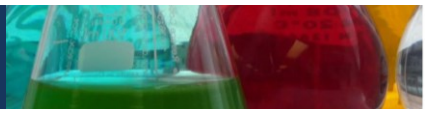

Metals in Biology: Elements of the Bioeconomy

At the beginning of 2014 the UK Biotechnology and Biological Sciences Research Council (BBSRC) established thirteen Networks in Industrial Biotechnology and Bioenergy[1]. An aim of these networks is to reduce the barriers for initiating collaborations between the academic and business communities, especially in the arena of Industrial Biotechnology. One of the networks entitled "Metals in Biology: The elements of Biotechnology and Bioenergy"[2], has seven themes: *Metals in bioprocessing, metals in the environment, metal-related nutrition and supplements, metallo-enzyme engineering, tools for metals in biology, metal circuits for synthetic biology and metal-related antimicrobials*. Here this network is introduced, giving background to two themes with events planned this year.

Metals are used as industrial catalysts to drive reactions that produce valuable chemicals. Metals also catalyze a substantial proportion of the reactions of life[3]. Using cellular enzymes whose structures are known as a representative sub-set, nearly a half (47%) of enzymes are estimated to need metals. The different proportions of the individual elements which make-up this surprisingly large fraction have been calculated and graphically represented[3]. A second key observation is that metal-requiring enzymes readily bind to wrong metals in preference to the metals needed for activity[4]. This creates the potential for enzymes to become inactivated by mismetalation. In this respect life seems perilously ill-designed, but in truth it has not been designed at all, rather it has evolved in the face of changing metal supply. This has selected for 'circuits' to assist proper enzyme metalation. Over the past three or more decades, many of the genes encoding components of these circuits have been discovered: Genes that encode proteins which import specific metals into cells, others which export, store or deliver metals and yet more which sense metal sufficiency or deficiency[4]. These discoveries now create opportunities to engineer metal-circuits to enhance the metalation of desirable enzymes to the benefit of industrial biotechnology. Although beyond the scope of industrial biotechnology, this knowledge also makes it possible to study how these circuits fail in numerous chronic diseases and to devise ways to subvert metal circuits to eliminate unwanted cells for therapeutic purposes. As an aside, a common observation from the BBSRC NIBB is that fundamental knowledge of life processes tends to spark innovation across the entire bioeconomy including biomedicine, bioenergy, agritechnology, nutrition, health, ecosystem management and not solely restricted to one sector such as industrial biotechnology.

Metal circuits for synthetic biology: **I**sobutanol is an industrial feedstock which is typically manufactured from fossil fuels. It can also be made biologically through the action of enzymes such as Dihydroxy Acid Dehydratase (DHAD)[5]. In many organisms this enzyme uses iron in the form of iron sulfur clusters and cells have a specialised machinery for assembling and distributing these clusters[5,6].To generate a commercial fermentation process for the sustainable production of isobutanol, DHAD has been engineered into yeast cells. Patents document how the iron-sensing circuitry of yeast can be adjusted to ensure a sufficient supply of iron sulphur clusters to support the extra demand created by the introduced DHAD[5]. With so-many enzymes needing metals, this exemplifies an opportunity to engineer wide-ranging metal circuits in order to enhance metalation of chosen enzymes to boost targeted reactions in support of the bioeconomy. For example, key enzymes required for the capture and utilisation of C_1-gases (carbon dioxide, carbon monoxide and methane) have exotic metal demands including the nickel-containing F430 cofactor and cobalt in vitamin B_{12}. In November 2015, there will be a joint event between the Metals in Biology and the C1Net BBSRC NIBB[7] to

consider improving C_1 gas capture by manipulating metals.

Metal-related antimicrobials:

Historically, some unpleasantly hazardous metals have been used to treat infections, such as mercury for syphilis, arsenic and antimony for Leishmania. In agriculture, copper sulphate in Bordeaux mixture is an effective fungicide for treating vines, and hospital trusts have replaced steel fixtures and fittings with copper ones, since copper surfaces (unlike those containing iron) are antimicrobial barriers. A range of products contain metal chelants such as Ethylene Diamine Tetra Acetic acid (EDTA) with preservative, antimicrobial action. A well known shampoo, which generates multiple billions of dollars of revenue each year, contains Zinc Pyrithione (ZPT) which interferes with the iron handling circuitry of fungi through an intricate sequence of biochemical interactions which also involve copper[8]. ZPT treats dandruff which is triggered by the fungal microflora of the scalp. But there is a much longer history of using metals to fight microbes, because immune systems have evolved to exploit metals to combat infections. This is emerging as a new sub-discipline called nutritional immunity[9].

Iron often limits life, from restricting primary productivity in the oceans to a most prevalent human dietary deficiency, anaemia[10,11]. Microbial pathogens fight to obtain this valuable element from hosts, often releasing iron scavenging siderophores. This has triggered an evolutionary arms race fought on a battle ground of iron, with hosts producing defensive siderocalins to bind siderophores, in turn selecting for stealth siderophores which the siderocalins fail to recognise, combatted by stealth siderocalins from adapted hosts and so on. Host immune cells such as macrophages engulf microbes whereupon a specialised protein, Natural Resistance Associated with Macrophage Protein 1 (NRAMP1), helps to kill the entrapped invader. Some years after its discovery, NRAMP1 was found to pump vital metals such as iron from the microbe-containing compartment, presumably to starve it of essential elements. The compartment subsequently fills with a toxic dose of copper. Calprotectin is liberated from other immune cell types, classes of neutrophils, to scavenge zinc and manganese, starving microbes of these essential elements[9].

As details of the cell biology of metals are uncovered, it becomes possible to tailor more precise antimicrobial treatments by design, not just stumbled upon empirically or by evolution. Metals, and by implication chelants, ionophores, and agents that interfere with the metal-handling systems of microbes and hosts, are increasingly recognized among the promising candidates for new antimicrobials[12]. Another BBSRC NIBB event in November 2015 will highlight advances in understanding metal-handling systems of microbes and hosts, explore why metals are a microbial “Achilles heel”, and encourage innovation at this academia-business interface.

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Nigel J Robinson (Director)
Metals in Biology BBSRC NIBB
metals.bbsrcnibb@durham.ac.uk
https://mib-nibb.webspace.durham.ac.uk/
@METALSBBSRCNIBB

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