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Mediator: the missing link in amyloid precursor protein nuclear signalling

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The amyloid cascade hypothesis—in which the age-dependent accumulation of the amyloid β-peptide (Aβ) is proposed to be the trigger for Alzheimer disease—has provided a huge impetus for research into disease mechanisms and contributed to the focusing of research on to Alzheimer disease therapeutics. Aβ itself is derived from the transmembrane amyloid precursor protein (APP), the gene for which was the first to be linked with early onset Alzheimer disease exactly 20 years ago (Goate *et al*, 1991). Most subsequent therapeutic strategies have focused on modifying the formation, aggregation or removal of Aβ. Yet, two decades on, treatments remain limited and they are palliative, rather than curative for the disease. This suggests a missing link in the chain from disease initiation to cognitive decline and death. The focus on amyloid accumulation has therefore detracted from attempts to understand the normal functions of APP. It might be that a loss of normal APP metabolism and physiology, as much as a gain in Aβ toxicity, could contribute to the development of Alzheimer disease and hence provide new approaches to therapy.

Aβ is only one of several metabolites of APP that result from the actions of a set of proteases collectively referred to as secretases, which comprise the disease-promoting β- and γ-secretases (generating Aβ), as well as the neuroprotective (non-amyloidogenic) α-secretase. These produce the soluble ectodomains sAPP-β and -α, respectively, and a cytoplasmic fragment of 50–59 amino acids known as the APP intracellular domain (AICD), all of which are fundamental to understanding the pathological effects of APP dysregulation. However, theories about the role and mechanism of action of AICD have been controversial.

AICD was originally suggested to function in transcriptional activation analogously to the Notch intracellular domain, but the detection of AICD has been problematic, in part because of its rapid turnover. However, a consensus is emerging that AICD is formed and translocated to the nucleus in a retrograde manner, predominantly in a β-secretase-dependent manner, which involves a lipid-raft-mediated, endosomal processing pathway (Goodger *et al*, 2009; Belyaev *et al*, 2010). Several target genes have been proposed for AICD, but the best characterized is the neprilysin (*NEP*) gene that encodes a metalloprotease that is itself involved in Aβ degradation (Pardossi-Piquard *et al*, 2005; Belyaev *et al*, 2009). We have further proposed that neuronal specificity is imposed on this gene-regulatory mechanism by the preferential involvement of the 695 neuronal isoform of APP, when compared with the ubiquitously expressed isoforms (APP751 and APP770) (Belyaev *et al*, 2010).

General acceptance of AICD as a transcriptional regulator has foundered, however, owing to the lack of a more detailed mechanistic understanding. Although we have shown a direct interaction between AICD and the NEP promoter (Belyaev *et al*, 2009, 2010), a more specific target within the general transcriptional apparatus has been lacking, as well as validation of a subset of AICD-responsive genes. The missing link seems to be the MED12 protein (Xu *et al*, 2011), which forms part of Mediator—a large protein complex of 30 subunits that transduces signals from specific transcription factors to RNA polymerase II (pol II). Although the Mediator complex seems to be a requirement for transcription of most, if not all, eukaryotic pol II promoters, individual subunits are recruited to control specific transcriptional programmes, usually leading to transcriptional activation. In this context, MED12 is particularly important in relation to the nervous system, as it was previously implicated in neuronal development and cognitive impairment (Wang *et al*, 2006; Clark *et al*, 2009). Xu *et al* (2011) have now identified MED12 as a protein that interacts with the carboxy-terminal tail of APP family members, by using a yeast two-hybrid screen to map the interaction region to a specific PQL domain on MED12. Two proteins that have been previously implicated in AICD-dependent gene regulation—Fe65 and Tip60—immunoprecipitated with MED12, but only in the presence of co-expressed AICD. Furthermore, AICD was shown to recruit the Mediator complex to AICD-responsive promoters, depending on the presence of MED12.

In addition to *NEP*, several other genes were confirmed as being MED12/AICD-dependent including aquaporin 1—previously identified by Huysseune *et al* (2009)—fibronectin 1 and microtubule-associated monooxygenase (*MICAL2*). Of the many Mediator subunits, MED12 seems to be specifically linked to neural development and disease; it provides a mechanistic route through its intracellular domain for the involvement of APP in gene regulation.

Given that mutations in MED12 lead to cognitive and behavioural dysfunction in humans, Xu *et al* (2011) speculate that polymorphisms in MED12 might also contribute to the development of Alzheimer disease. It is our view that a fuller knowledge and validation of the genes regulated by AICD might open up new therapeutic avenues in Alzheimer research. Furthermore, delineating the fine detail of the cellular site of production of AICD, its neuronal

specificity and its nuclear transport will guide future strategic directions for the Alzheimer-disease research community.

REFERENCES
Belyaev ND *et al* (2009) *EMBO Rep* **10:** 94–100
Belyaev ND *et al* (2010) *J Biol Chem* **285:** 41443–41454
Clark RD *et al* (2009) *Genet Med* **11:** 769–775
Goate A *et al* (1991) *Nature* **349:** 704–706
Goodger ZV *et al* (2009) *J Cell Biol* **122:** 3703–3714
Huysseune S *et al* (2009) *FASEB J* **23:** 4158–4167
Pardossi-Piquard R *et al* (2005) *Neuron* **46:** 541–554
Wang X *et al* (2006) *Proc Natl Acad Sci USA* **103:** 17284–17289
Xu X *et al* (2011) *EMBO Rep* **12:** 216–222

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Microbial rights?

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Synthetic biology and the increasing complexity of molecular biology have brought us to the stage at which we can synthesize new microorganisms. This has generated pressing questions about whether these new organisms have any place in our system of ethics and how we should treat them.

The idea that microbes might have some moral claims on us beyond their practical uses or instrumental value is not a new question. Microbiologist Bernard Dixon (1976) presciently asked whether it was ethical to take the smallpox virus to extinction at the height of the attempts of the World Health Organization in the 1970s to eradicate it. There is no unambiguous answer. Today, we might still ask this question, but we might extend it to ask whether the destruction or extinction of a synthetic microbe that was made by humans is also ethically questionable or is such an entity—in that it is designed—more like a machine, which we have no compunction in terminating? Would two lethal pathogens, one of them synthetic and one of them natural, but otherwise identical, command the same moral claims?

In a colloquial way, we might ask whether microbes have rights. In previous papers (Cockell, 2004) I have discussed the 'rights' of microbes and further explored some issues about the ethics we apply to them (Cockell, 2008). Julian Davies, in a recent opinion article in EMBO *reports* (Davies, 2010) described my assertion that they should have constitutional rights as 'ridiculous'. Although I did suggest that environmental law could be changed to recognize the protection of microbial ecosystems—which would imply statutory rights or protection—nowhere have I claimed that microbes should have 'constitutional' rights. Nevertheless, this misattribution provides a useful demonstration of the confusion that exists about exactly how we should treat microbes.

Few people are in any doubt that microbes should be conserved for their direct uses to humans, for example, in food and drug production, and their indirect uses such as the crucial role they have in the health of ecosystems. Indeed, these motivations can be used to prioritize microbial conservation and protection efforts (Cockell & Jones, 2009). The crucial question is whether microbes have 'intrinsic value' beyond their practical uses. If the answer is 'no', then we should have no guilt about deliberately driving microbes to extinction for our benefit. However, there are people who feel uneasy with this conclusion, a feeling that calls forth more complex ethical questions.

The question is whether microbes have some sort of 'interests' that make demands on our treatment of them that go beyond a mere utilitarian calculation. These arguments themselves question what we define as 'interests' and whether interests make demands on us. A microbe has no future plans or thought processes; the sorts of interests that are accepted as being of sufficient scope to place demands on our treatment of other human beings, for instance. However, microbes do have biological interests. A halophilic microbe might eventually die if it is dropped into freshwater. Does our knowledge of what is in the biological interests of a microbe mean that we must show it any consideration beyond practical uses? The answer is not obviously negative (Taylor, 1981), but even if we decide that it is, this does not let us off the hook quite yet.

There are other intrinsic value arguments that are more obscure, particularly those around the notion of 'respect'; the idea that we should show empathy towards the trajectory, however deterministic, of other life forms. These unquantifiable and controversial arguments might, nevertheless, partly explain any unease that we have in watching a group of people smash up and destroy some exquisite microbial mats, just because they were bored.

Clearly, human instrumental needs do trump microbes at some level. If they did not, we could not use bleach in our houses, an absurd end-point raised in a 1970s science fiction story that explored the futuristic ramifications of full microbial rights, in which household bleaches and deodorants are banned (Patrouch, 1977).

However, we should not be so quick to ridicule ideas about microbial ethics and rights. Although it might be true that phages kill a large percentage of the bacterial population of the world every few days, as Julian Davies points out, human society has achieved an unprecedented capacity for destruction and creation. Our ability to poison and disrupt habitats has been unquantified, with respect to the loss of microbial species. Both synthetic biology and bioterrorism raise the spectre of creating new organisms, including pathogens, which we might need to control or deliberately pursue to extinction. Dixon's dilemma about the smallpox virus, raised more than 30 years ago, has become an urgent point of discussion in the ethics of molecular biology and microbiology.

REFERENCES
Cockell CS (2004) *Interdiscip Sci Rev* **29:** 141–150
Cockell CS (2008) *Ethics Environ* **13:** 23–39
Cockell CS, Jones HL (2009) *Oryx* **43:** 520–526
Davies J (2010) *EMBO Rep* **11:** 721
Dixon B (1976) *New Scientist* **26:** 430–432
Patrouch J (1977) *Analog Science Fiction and Fact* **97:** 167–169
Taylor P (1981) *Environmental Ethics* **3:** 197–218

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