Functional annotation of dementia-related miRNAs using Gene Ontology

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Overview
To understand the basis of disease it is crucial to know the functions of the genes involved and the pathways they act in. The role of microRNAs (miRNAs) in the regulation of developmental and cellular processes is a relatively new field of study, however, the data generated from such research has, so far, not been organised optimally to allow inclusion of this data in pathway and network analysis tools. The association of proteins with terms from the Gene Ontology (GO) has proven to be highly effective for large-scale analysis of functional data, but the equivalent data is currently lacking for miRNAs. The GO resource provides dynamic, controlled vocabularies that allow consistent descriptions of the functional attributes and subcellular localisations of all gene products. We are now focused on the annotation of microglial proteins implicated in neuroinflammatory processes relevant to dementia and the miRNAs that regulate expression of these proteins.

GO curation of dementia-related miRNAs
We capture both the role of the miRNA in gene silencing and the effect that the silencing event has on the cell or organism (Table 1), enabling researchers to easily find the roles of a miRNA and interpret large datasets.

Network analysis of miRNAs
An analysis of Alzheimer’s disease-relevant miRNAs (Figure 3) identifies that the network is highly connected with many miRNAs having common mRNA targets (for example both miR101-3p and miR-155-5p target RIPK1). In addition, the network demonstrates that a single mRNA may be regulating the expression levels of multiple Alzheimer’s-associated proteins (for example both APP and RIPK1 are targets of miR101-3p).

Table 1. GO annotation of the experimentally verified roles of miRNAs.

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<tr>
<th>miRNA</th>
<th>GO annotation of miRNA role in gene silencing</th>
<th>dementia-relevant mRNA targets</th>
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<tr>
<td>miR-338-3p</td>
<td>Gene silencing by miRNA</td>
<td>Regulates expression of SMO</td>
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<tr>
<td>miR-145-5p</td>
<td>Cellular response to amyloid-beta</td>
<td>Occurs in neuron</td>
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miRNA Gene Ontology annotation
GO annotations and their contextual information can only go so far in describing a process or pathway. The GO Consortium have developed a tool, Noctua, which can be used to link together GO annotations and their associated evidence in order to give a more complete picture of the biological roles and activities of gene products (Figure 2).

CONCLUSION
We have pioneered the GO annotation of miRNA relating to dementia. We have shown how our functional annotations can be used to visualise the roles of individual miRNAs in a dementia-relevant molecular interaction network, thereby demonstrating that this resource will be a valuable addition to the advancement of miRNA research and may be used to predict proteins with a role in dementia. This work will support the rapid evaluation of new neurological data.