

Gene Ontology annotation of microglial proteins associated with dementia

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Background and Objectives

This project is a continuation of our Gene Ontology (GO, geneontology.org) annotation initiative, funded by Alzheimer's Research UK (ARUK), aimed at capturing biological information relevant to dementia and Alzheimer's disease.

We previously used GO to annotate proteins, which have been shown to interact with amyloid-beta and the microtubule-associated protein tau¹. We are now focused on annotation of microglial proteins² implicated in neuroinflammatory processes relevant to dementia and microRNAs³ that regulate expression of these microglial proteins.

¹ Kramarz B, Roncaglia P, Meldal BHM, Huntley RP, Martin MJ, Orchard S, Parkinson H, Brough D, Bandopadhyay R, Hooper NM, Lovering RC. **Improving the Gene Ontology Resource to Facilitate More Informative Analysis and Interpretation of Alzheimer's Disease Data.** *Genes.* 2018 Nov 29. PMID:30501127

² ARUK Conference 2019 Poster P12.3

³ ARUK Conference 2019 Poster P12.9

ARUK-UCL Gene Ontology Development Examples

If an area of biology has not yet been comprehensively annotated using GO, then during annotation of proteins and microRNAs curators sometimes identify a lack of suitable GO terms. In order to ensure high accuracy and precision of GO annotations, this is addressed by expanding relevant branches of GO and adding more descriptive GO terms. GO terms contributed as a part of this initiative are acknowledged in the GO browsers as ARUK-funded (Figure 2). The resulting new GO terms can be accessed in GO browsers (QuickGO and [AmiGO 2](http://AmiGO2)), and they can be used by any GO curator for annotation of proteins or microRNAs.

GO:0150076

neuroinflammatory response

Biological Process

Definition ([GO:0150076 GONUTS page](#))

The immediate defensive reaction by neural vertebrate tissue to infection or injury caused by chemical or physical agents. PMID:10981966 PMID:11099416 PMID:18164423

GO:0061900

glial cell activation

Biological Process

Definition ([GO:0061900 GONUTS page](#))

A change in morphology and behavior of a glial cell resulting from exposure to a cytokine, chemokine, cellular ligand, or soluble factor. PMID:18723082

Figure 2. Examples of new terms contributed to GO by this ARUK-UCL project. (Image from QuickGO).

Gene Ontology: a dictionary for biology

- Gene Ontology (GO): a collaborative effort to provide freely-available, standardised, consistent descriptions of physiological roles of proteins and microRNAs across all biomedical fields and species.
- GO comprises three types of structured controlled vocabularies that describe gene products in terms of their associated molecular functions (F), biological processes (P), and localisation to cellular components (C).
- Originally developed in 1998, GO has grown to include over 49,700 terms, arranged as a hierarchy, describing a wide range of concepts to differing levels of specificity, and linked by different types of relationships (Figure 1).
- GO is an essential resource for high-throughput data analysis, facilitating the grouping of genes into common pathways, functions and cellular locations.

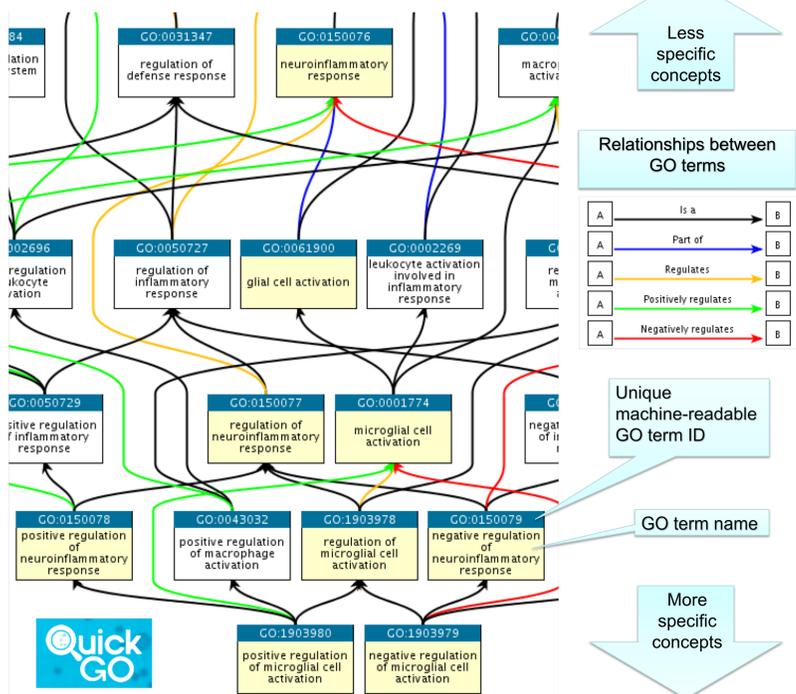


Figure 1. A fragment of GO hierarchy showing 'neuroinflammatory response' and some of its descendants. (Image adapted from QuickGO; 8 February 2019).

ARUK-UCL Gene Ontology Annotation Examples

ARUK-UCL biocurators search literature for experimental data about microglial proteins relevant to dementia and neuroinflammation, and capture this information in the form of GO annotations. This neuroinflammation-focused annotation project has so far resulted in 2341 GO annotations to over 320 proteins, or protein-containing complexes; of these, 1620 GO annotations were made to over 290 human proteins, or human protein-containing complexes (Data from QuickGO; 5 March 2019). These GO annotations are available in QuickGO and [AmiGO 2](http://AmiGO2), and, as they are imported into other resources, e.g. UniProt, and analysis tools, e.g. g:Profiler, these GO annotations can now be used by any researcher for analyses and interpretation of their datasets.

Gene Product	Symbol	Qualifier	GO Term	Evidence	Reference	With / From	Taxon	Assigned By	Annotation Extension
UniProtKB:F1M670	Fpr2	involved_in	GO:0048143 astrocyte activation	ECO:0000316 IGI	PMID:18723082	UniProtKB:P05067:PRO_0000000092	10116 Rattus norvegicus	ARUK-UCL	part_of (GO:1904646)
UniProtKB:F1M670	Fpr2	involved_in	GO:0001774 microglial cell activation	ECO:0000316 IGI	PMID:18723082	UniProtKB:P05067:PRO_0000000092	10116 Rattus norvegicus	ARUK-UCL	part_of (GO:1904646)
UniProtKB:P08473	MME	part_of	GO:0045121 membrane raft	ECO:0000314 IDA	PMID:22183801	Amyloid-beta 1-42	9606 Homo sapiens	ARUK-UCL	Cellular response to amyloid-beta
UniProtKB:P08473	MME	part_of	GO:0045121 membrane raft	ECO:0000314 IDA	PMID:15100223		9606 Homo sapiens	ARUK-UCL	part_of (GL:0000540)
UniProtKB:P78423	CX3CL1	involved_in	GO:0001774 microglial cell activation	ECO:0000250 ISS	GO_REF:0000024	UniProtKB:O51545 Fractalkine	9606 Homo sapiens	ARUK-UCL	neuron

Figure 3. Examples of ARUK-UCL GO annotations contributed to the GO resource (Image from QuickGO).

ARUK-UCL Gene Ontology Annotation Progress

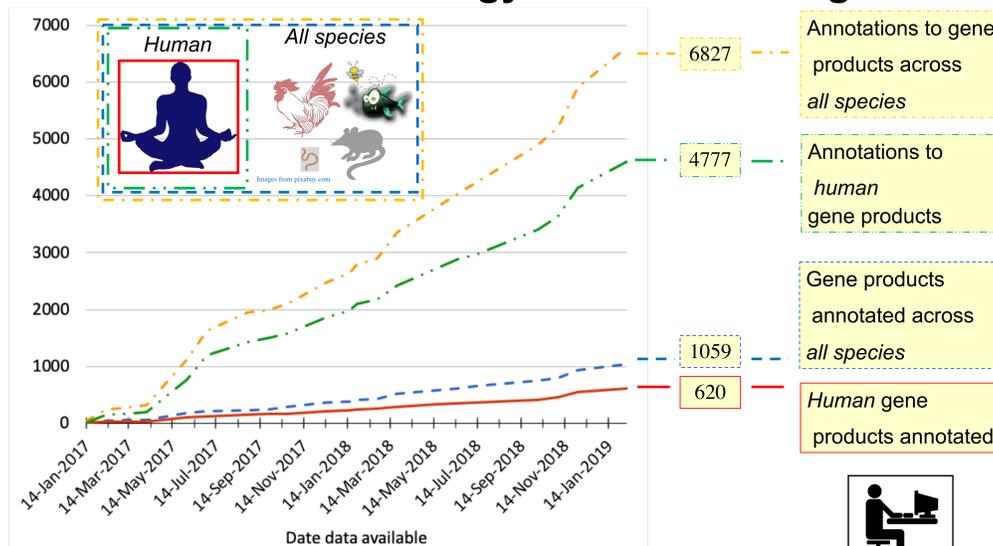


Figure 4. The number of annotated gene products and GO annotations for human and all species, contributed by all ARUK-UCL projects (Data from QuickGO; 5 March 2019).

Gene Ontology Methods

Scientific curators manually search literature, using gene symbols/names and keywords, e.g. 'microglia', to capture biological information using GO terms and develop ontology. GO annotations and new terms are regularly submitted to GO databases: QuickGO and AmiGO.



Conclusions and Future Prospects

Gene Ontology (GO) is among major resources fundamental to informative analyses of 'big data' from biomedical studies. Yet, prior to this ARUK-UCL annotation initiative, dementia-relevant neurological processes had not been comprehensively curated, limiting the applicability of GO to this research domain. Our focused and systematic contribution to GO in this niche will have improved this resource to facilitate the analyses of Alzheimer's disease datasets.