Capturing amyloid-ß-relevant knowledge with Gene Ontology

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Background

The goal of this six-month project, supported by a grant from Alzheimer's Research UK (ARUK), is to annotate proteins involved in clearance of amyloid-ß (Aß) and mediating the neurotoxicity of Aß oligomers (AßO) using Gene Ontology (GO, geneontology.org).

The project is based on work by Jarosz-Griffiths *et al.*, summarised in their recent (2016) review '**Amyloid-β Receptors: The Good, the Bad, and the Prion Protein**' (PMID: 26719327).

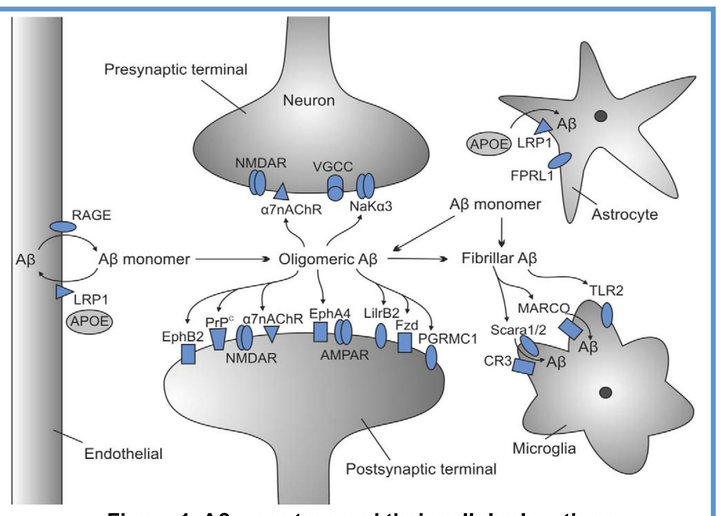
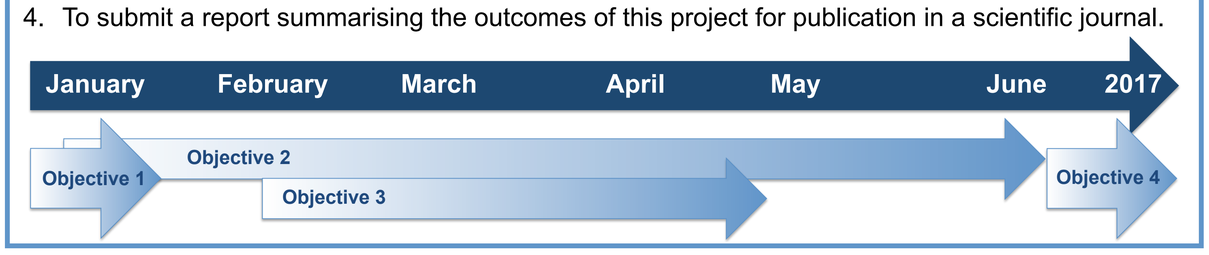


Figure 1. Aβ receptors and their cellular locations.
(Figure from Jarosz-Griffiths *et al.*, 2016, *JBC*).

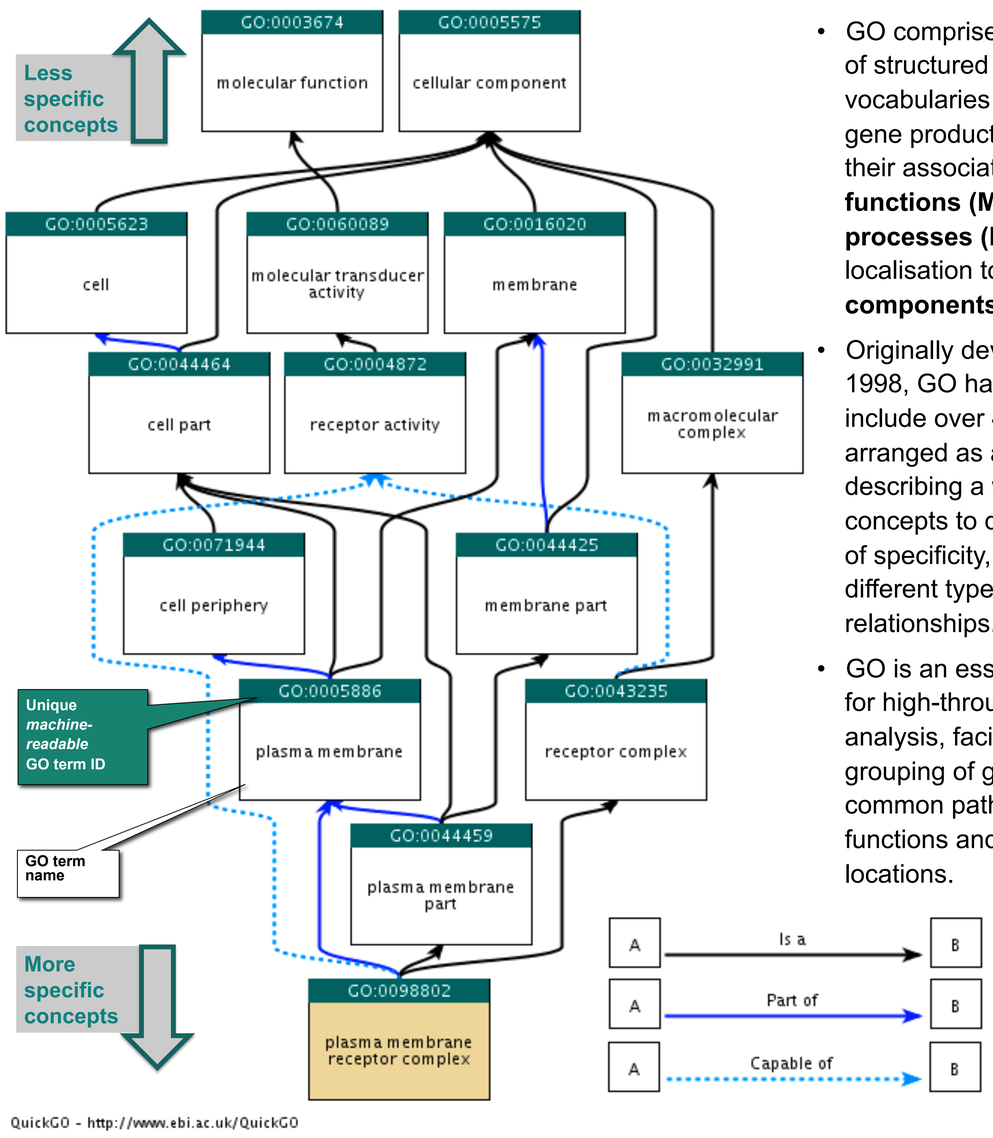
Project Objectives

1. To assign UniProt identifiers to Amyloid-ß Receptors, named in Table 1 of the Jarosz-Griffiths *et al.* review, and to establish annotation priorities.
2. To annotate research articles referenced by Jarosz-Griffiths *et al.* using Gene Ontology (GO), focusing firstly on papers cited in context of the prioritised UniProt identifiers.
3. In order to enable the GO annotation of biological roles of Aß dimers and/or oligomers (and not Aß monomers), it is our aim to collect evidence for Aß oligomerisation to aid in generation of protein complex identifiers by the EBI for structurally different Aß dimer and oligomer complexes.
4. To submit a report summarising the outcomes of this project for publication in a scientific journal.



Gene Ontology: a dictionary for biology

- Gene Ontology (GO): a collaborative effort to provide freely-available, standardised, consistent descriptions of gene products' physiological roles 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 (MF), biological processes (BP)**, and localisation to **cellular components (CC).**
- Originally developed in 1998, GO has grown to include over 44,400 terms, arranged as a hierarchy, describing a wide range of concepts to differing levels of specificity, and linked by different types of relationships.
- GO is an essential resource for high-throughput data analysis, facilitating the grouping of genes into common pathways, functions and cellular locations.

Figure 2. A fragment of GO hierarchical structure and key to relationship arrows (modified from QuickGO).

Gene Ontology Annotation

Gene Ontology (GO) curators manually search literature for experimental data using gene symbols and/or keywords, here e.g. 'amyloid-ß'. Curators subsequently read the selected articles to extract information about biological processes (BP), molecular functions (MF), and cellular components (CC) and capture the biological information using the universal GO terms. The resulting GO annotations are periodically submitted to GO databases (QuickGO and AmiGO), and they are next exported to other biological databases, such as UniProt, Ensembl, or NCBI Gene.

Objective 1 outcomes – proteins prioritised for annotation

A total of sixty UniProt identifiers have been assigned to the Amyloid-β Receptors reviewed by Jarosz-Griffiths *et al.* Eighteen of these have been prioritised for annotation and are listed below.

Table 1. Amyloid-β Receptors prioritised for annotation.

	Gene Symbol	UniProt ID	Name
1	CHRNA7	P36544	α7-Nicotinic acetylcholine receptor (α 7nAChR)
2	APOE	P02649	Apolipoprotein E (apoE)
3	CLU	P10909	Clusterin (ApoJ)
4	PRNP	P04156	Prion protein (PrPC)
5	EPHA4	P54764	Ephrin A4 (EphA4)
6	EPHB2	P29323	Ephrin B2 (EphB2)
7	FCGR2B	P31994	Fcγ receptor IIb (FcγRIIb)
8	LILRB2	Q8N423	Leukocyte immunoglobulin-like receptor B2 (LilrB2)
9	LILRB3	O75022	Leukocyte immunoglobulin-like receptor B3 (PirB)
10	ATP1A3	P13637	Na+/K+-ATPase neuron-specific α3 subunit (NaKα3)
11	NLGN1	Q8N2Q7	Neuroligin-1
12	GRIN1	Q05586	Glutamate receptor ionotropic, NMDA 1
13	GRIN2A	Q12879	Glutamate receptor ionotropic, NMDA 2A
14	GRIN2B	Q13224	Glutamate receptor ionotropic, NMDA 2B
15	GRIN2C	Q14957	Glutamate receptor ionotropic, NMDA 2C
16	GRIN2D	O15399	Glutamate receptor ionotropic, NMDA 2D
17	NGFR	P08138	p75 neurotrophin receptor (p75NTR)
18	PGRMC1	O00264	Sigma-2/PGRMC1

Objectives 2 and 3 – on-going progress (1 Jan – 28 Feb)

Table 2 provides a selection of annotations created whilst collecting experimental evidence in support of generation of Aß dimer and oligomer complex identifiers by the EBI.

Table 2. Amyloid-β Monomer annotations. Key: UniProt identifiers used for annotation of human Aß monomers: Aß40, P05067:PRO_0000000093; Aß42, P05067:PRO_0000000092. IPI, Inferred from Physical Interaction; IDA, Inferred from Direct Assay.

Entity	GO Term	Evidence	With	Reference
Aß40	protein homodimerization activity (MF)	IPI	Aß40	PMID:18568035
Aß42	protein homodimerization activity (MF)	IPI	Aß42	PMID:18568035
Aß40	protein heterodimerization activity (MF)	IPI	Aß42	PMID:18568035
Aß42	protein heterodimerization activity (MF)	IPI	Aß40	PMID:18568035
Aß40	protein homooligomerization (BP)	IDA	n/a	PMID:15447668
Aß42	protein homooligomerization (BP)	IDA	n/a	PMID:23386614
Aß40	protein complex (CC)	IPI	Aß40	PMID:22179788
Aß40	protein complex (CC)	IPI	Aß42	PMID:18568035
Aß42	protein complex (CC)	IPI	Aß42	PMID:23386614
Aß42	protein complex (CC)	IPI	Aß40	PMID:18568035

Objective 2 – on-going progress (1 Jan – 28 Feb)

A selection of annotations created for Aß oligomer (AßO) complexes (but not for Aß monomers) are listed in Table 3. These annotations have not yet been submitted to GO databases, as curation efforts are currently on-going at the EBI to generate Aß oligomer complex identifiers for these.

Table 3. Amyloid-β Oligomer annotations. Key: Aß40O, human Aß40 oligomer; Aß42O, human Aß42 oligomer; IDA, Inferred from Direct Assay; IMP, Inferred from Mutant Phenotype; IPI, Inferred from Physical Interaction.

Entity	(Qualifier) GO Term	Evidence	Annotation Extension	Reference
Aß40O	positive regulation of neuron apoptotic process	IDA	occurs_in(dentate gyrus of hippocampal formation)	PMID:12610652
Aß40O	learning or memory (BP)	IDA	n/a	PMID:12610652
Aß40O	chaperone binding (MF)	IPI(with: CLU/P10909)		PMID:23106396
Aß42O	positive regulation of receptor internalization (BP)	IMP	has_regulation_target (LRP1/Q07954)	PMID:23386614
Aß42O	negative regulation of protein localization to plasma membrane (BP)	IDA	has_regulation_target (PRNP/P04156)	PMID:23386614
Aß42O	(colocalizes_with) lysosome (CC)	IDA	n/a	PMID:23386614
Aß42O	Memory (BP)	IDA	n/a	PMID:16541076

Conclusions

Gene Ontology (GO) annotation of the distinct biological processes (BP) and molecular functions (MF) relevant to Aß oligomers and monomers, as well as their localisations to specific cellular components (CC), will enhance the analyses and interpretation of Alzheimer's disease-related high-throughput datasets. This will help researchers gain insights into the functional molecular basis of this disease, as well as help to select biomarkers that could allow for development of less invasive diagnostic methods.

Future Work

Upon completion of this six-month ARUK-funded project to annotate the roles of Aß and its receptors, our team will continue to annotate Alzheimer's disease-relevant biology, specifically the processes associated with tau protein pathology and neuroinflammation, thanks to a recently awarded three-year ARUK grant. Please email us (goannotation@ucl.ac.uk) to suggest papers for annotation or to learn more. Please follow us on Twitter @UCL_gene.

This Gene Ontology Annotation project is funded by Alzheimer's Research UK (ARUK), grant ARUK-NSG2016-13. The UCL Functional Gene Annotation team is supported by the National Institute for Health Research UCL Hospitals Biomedical Research Centre. The 2017 ARUK Conference attendance was supported by a Travel Award from the ARUK Research Network.

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