Neurological Gene Ontology (GO) annotation initiative: curation of amyloid-ß species and their binding partners

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Project Overview and Objectives

This six-month Gene Ontology (GO, geneontology.org) annotation project, supported by a grant from Alzheimer's Research UK (ARUK), is based on a recent review (PMID: 26719327): Jarosz-Griffiths HH, Noble E, Rushworth JV, Hooper NM. **Amyloid-β Receptors: The Good, the Bad, and the Prion Protein**. *J Biol Chem* 2016;291(7):3174-3183.

The main goal of this project was to use GO to annotate biological roles of amyloid-ß (Aß) species and their cell surface and soluble protein receptors (Figure 1). GO annotations comprise a major resource used for analyses of findings from high-throughput experiments, such as transcriptomic, proteomic and genome wide association (GWA) studies. As annotations of Aß species and their receptors were previously underrepresented in GO, this posed a significant limitation to interpretation of high-throughput datasets in the field of dementia research, hence our aim to bridge this knowledge gap.

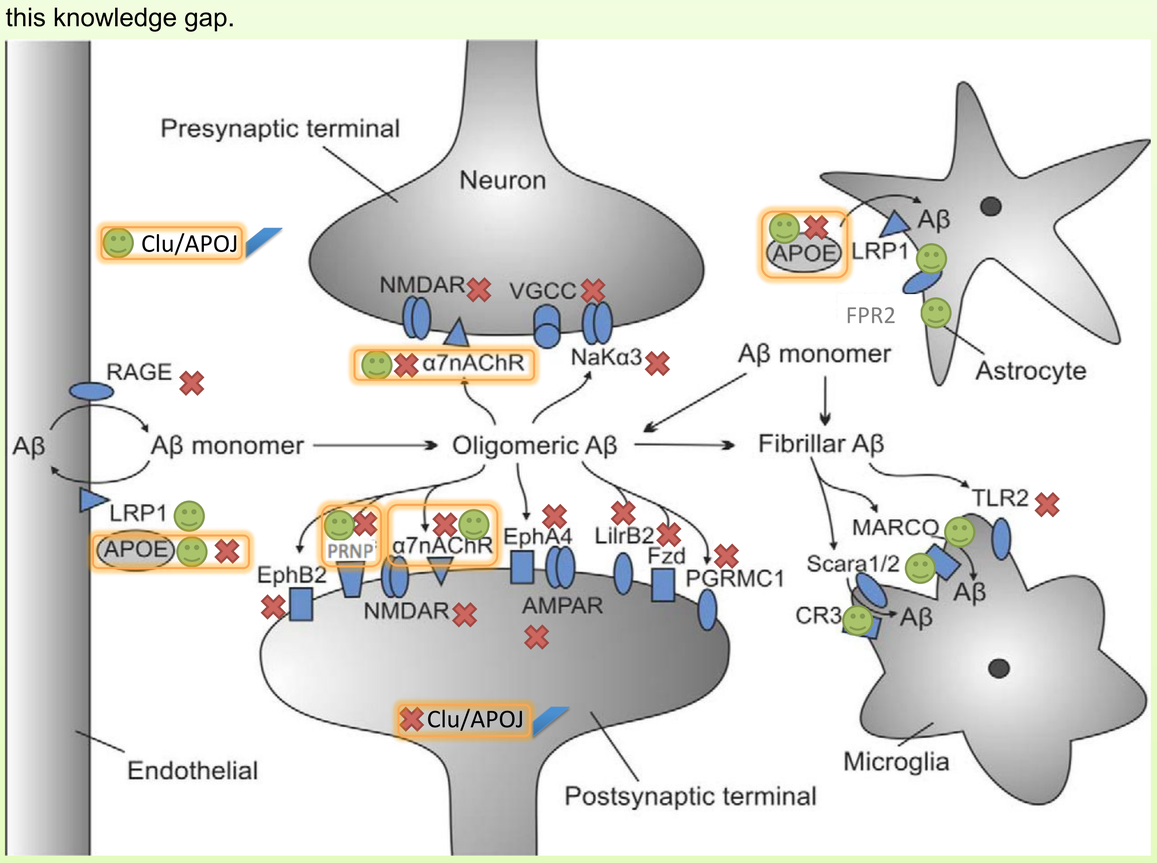
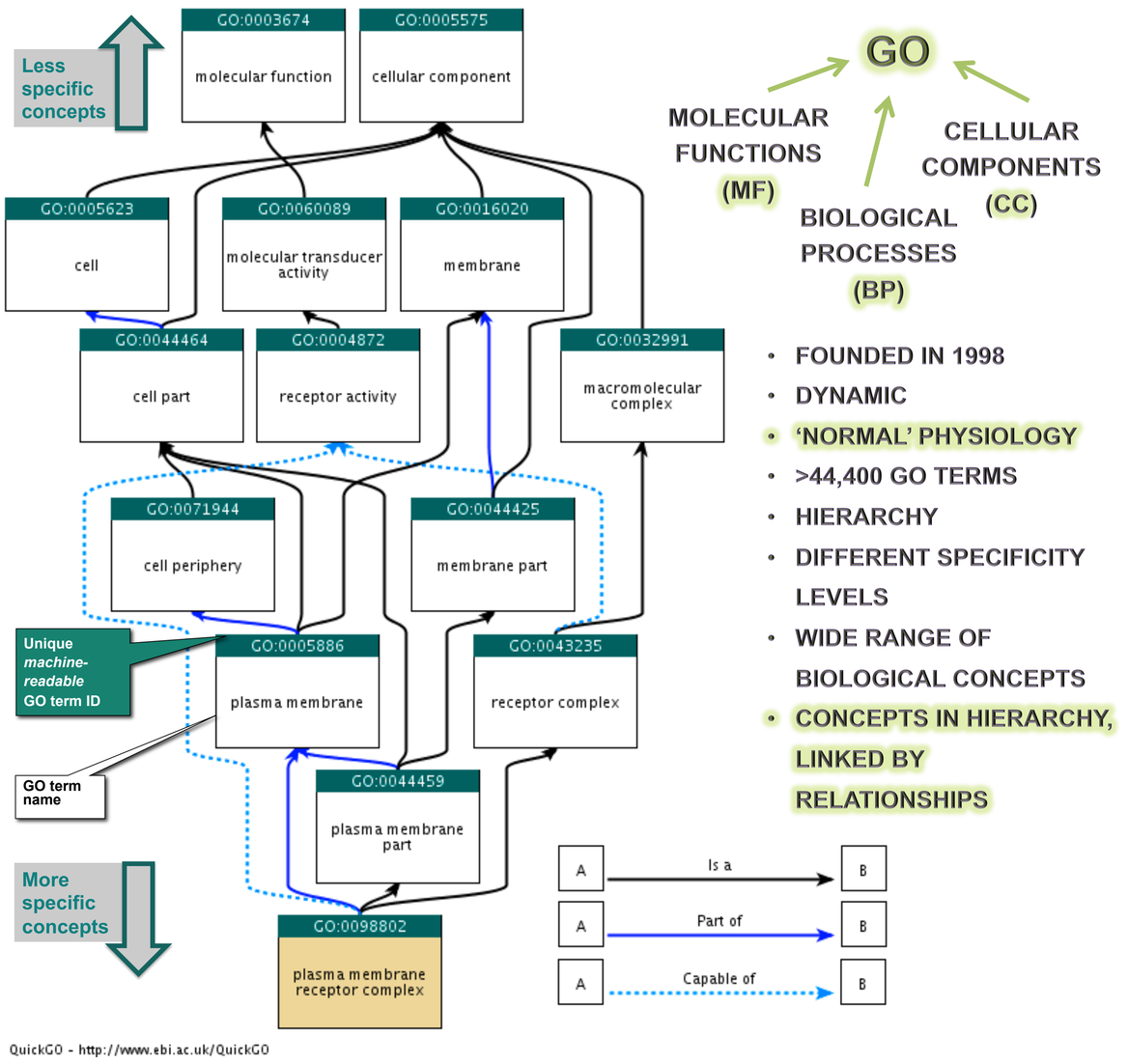


Figure 1. Aβ receptors, their cellular localisation, and the nature of their effects on cellular physiology upon interaction with Aβ. Binding of Aß to the 'bad' receptors marked with diagonal crosses ✖ typically results in impairment of normal physiological processes. The 'good' receptors marked with smiley face icons ☺ have either been shown to mediate positive effects of Aß, or (more often) are involved in Aß clearance. Some receptors have been shown to convey both: positive and negative effects of Aß binding, depending on genetic variant (APOE), localisation (Clu/APOJ), or other biological context (PrPc, α7nAChR). Not all receptors due to be annotated as a part of this project are shown (modified from Jarosz-Griffiths *et al.*, 2016, *JBC*).

Gene Ontology: a dictionary for biology

Gene Ontology (GO): a collaborative effort to provide freely-available, standardised, consistent descriptions of gene products' roles across all biological fields and species.



- FOUNDED IN 1998
- DYNAMIC
- 'NORMAL' PHYSIOLOGY
- >44,400 GO TERMS
- HIERARCHY
- DIFFERENT SPECIFICITY LEVELS
- WIDE RANGE OF BIOLOGICAL CONCEPTS
- CONCEPTS IN HIERARCHY, LINKED BY RELATIONSHIPS

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

GO curators search literature for experimental data and capture BP, MF and CC information using the universal GO terms. The resulting GO annotations are periodically submitted to GO databases (QuickGO and AmiGO 2), and they are next exported to other biological databases, such as UniProt, Ensembl, or NCBI Gene. Annotations shown in Tables 2-4 are examples of BP annotations only.

Amyloid-ß (Aß) Complexes

A major objective, identified during our curation efforts, was to distinguish between the roles of different Aß species, such as monomers, dimers, or oligomers. In GO annotations human Aß monomers are represented by UniProt identifiers P05067:PRO_0000000092 (Aß1-42) and P05067:PRO_0000000093 (Aß1-40), corresponding to processing products of amyloid precursor protein (APP, P05067). However, scientific findings have demonstrated that when the monomeric Aß peptides form dimers, or larger complexes, their properties and thus effects on cellular processes change (Aß oligomerisation results in gain of functions that Aß monomers do not have). Therefore, to be able to capture knowledge specific to either Aß dimers, or oligomers, new protein Complex Portal (CP) entries www.ebi.ac.uk/complexportal were firstly generated through manual curation of scientific literature (Table 1). The resulting Aß CP identifiers have been used for capturing some of the published roles of higher order Aß species, given that they fell within the scope of GO, i.e. represented 'normal' physiology (examples for EBI-14348029, Table 2).

Table 1. Human amyloid-β Complex Portal Entries, resulting from this project. Corresponding entries for rodent orthologues have also been created (data not shown).

Amyloid-β (Aß) Complex Type	Complex Portal identifiers
Amyloid-β 1-42 Homodimer	EBI-13943368
Amyloid-β 1-40 Homodimer	EBI-13943327
Amyloid-β 1-40 / 1-42 Heterodimer	EBI-13942506
Amyloid-β 1-42 Homooligomer	EBI-14348029
Amyloid-β 1-40 / 1-42 Heteroligomer	EBI-14032574

Table 2. Human amyloid-β 1-42 (Aß1-42) Oligomer (Complex Portal ID: EBI-14348029) – ARUK Project Annotation Examples. Key: IDA, Inferred from Direct Assay; IGI, Inferred from Genetic Interaction.

GO Term ID	GO Term Name	Evidence	Reference	GO Annotation Extension
GO: 0045666	positive regulation of neuron differentiation	IDA	PMID: 15190117	occurs_in UBERON:0002421 hippocampal formation
GO: 0043410	positive regulation of MAPK cascade	IDA	PMID: 15190117	occurs_in UBERON:0002421 hippocampal formation, part_of GO:0045666 positive regulation of neuron differentiation
GO: 0007611	learning or memory	IGI with P49582 (Chrna7)	PMID: 19118188	occurs_in UBERON:0002421 hippocampal formation
GO: 1900272	negative regulation of long-term synaptic potentiation ☀	IDA	PMID: 19118188	occurs_in UBERON:0003881 CA1 field of hippocampus
GO: 1900273	positive regulation of long-term synaptic potentiation ☀	IDA	PMID: 19118188	occurs_in UBERON:0003881 CA1 field of hippocampus

☀ PMID:19118188 findings demonstrate that Aß1-42 Oligomer has two opposite effects on long-term synaptic potentiation in hippocampus, depending on oligomer concentration. Concentration response curves indicated a positive effect with a peak around 200 pM, whereas a negative effect was observed above 20 nM. It is outside the scope of GO to capture the oligomer concentration details, resulting in two seemingly contradictory GO annotations; yet, both these GO annotations are correct.

GO annotations of the 'good' and 'bad' receptors

References cited in Jarosz-Griffiths *et al.* were used as the primary source of knowledge for GO annotation of Aß species and their cellular receptors. GO annotations were made based on experimental evidence for human gene products, if possible; or else for their rodent orthologues. Examples of annotations are provided in Tables 3 and 4.

Table 3. 'Good' Aß Receptors - ARUK Project Annotation Examples. Key: IMP, Inferred from Mutant Phenotype; IGI, Inferred from Genetic Interaction.

Entity	GO Term ID	GO Term Name	Evidence	Reference	GO Annotation Extension
Q13492 **PICALM**	GO: 0045056	transcytosis	IMP	PMID: 26005850	has_input P05067:PRO_ 0000000093 (Aß1-40), occurs_in CL:1001602 cerebral cortex endothelial cell
P25090 **FPR2**	GO: 0007186	G-protein coupled receptor signaling pathway	IGI with P05067:PRO_ 0000000092 (Aß1-42)	PMID: 11160457	part_of GO:1904646 cellular response to amyloid-beta, occurs_in CL:0000576 monocyte
P04925 **Prnp**	GO: 1902951	negative regulation of dendritic spine maintenance	IGI with P39688 (Fyn), Q01097 (Grin2b)	PMID: 22820466	part_of GO:1904646 cellular response to amyloid-beta, occurs_in CL:0002609 neuron of cerebral cortex

Table 4. 'Bad' Aß Receptors - ARUK Project Annotation Examples. Key: IMP, Inferred from Mutant Phenotype; IGI, Inferred from Genetic Interaction.

Entity	GO Term ID	GO Term Name	Evidence	Reference	GO Annotation Extension
P52800 **Efnb2**	GO: 0048167	regulation of synaptic plasticity	IGI (with P05067, APP)	PMID: 21113149	occurs_in UBERON: 0001885 dentate gyrus of hippocampal formation
P08101 **Fcgr2**	GO: 0016358	dendrite development	IMP	PMID: 17502348	occurs_in UBERON: 0002037 cerebellum
CD36	GO: 0051092	positive regulation of NF-kappaB transcription factor activity	IGI with O00206 (TLR4), Q9Y2C9 (TLR6)	PMID: 20037584	-

Summary and Conclusions

To date the project has provided a total of 1076 annotations for 157 gene products; among these: 725 annotations for 84 human gene products, including the Aß receptors (Jarosz-Griffiths *et al.*). These annotations have been included in open-access databases and are publicly available for analyses of high-throughput datasets. Additionally, 307 annotations made for higher order Aß complex species are currently pending public release. Future work will aim to revisit and review these Aß complex annotations to determine whether the annotated concepts form a part of the broader biological process of 'GO:0090647 modulation of age-related behavioral decline', i.e. represent 'normal' physiology; annotation of disease biology is outside of the scope of GO.

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