Ashley M. Buckle, PhD

Structural Biology and Protein Engineering Consultant

Qualifications: BSc (Hons) (1990), PhD (1994) Cambridge University (UK)

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Professional Summary

I have more than three decades of expertise in structural biology and protein engineering, with a focus on combining state-of-the-art protein biochemistry, biophysical, structural and computational approaches in protein engineering programs. I have published more than 140 peer-reviewed scientific papers (H-index = 44, >7000 citations) in high impact journals that include Science, PNAS (10), Nature Struct. Mol. Biol. (2), Nature Chem. Biol., Nature Communications and Nature

Immunology (2), and delivered more than 90 research seminars. I have secured in excess of AUD$13 million in research funding and am the named co-inventor on 6 patents. Further details at ORCID (https://bit.ly/2PyU9mX).

Skills and Expertise

- Structural biology
- Protein engineering and design
- Bioinformatics
- Molecular modelling and molecular dynamics simulations

Key Achievements

- Track record in delivering projects from inception using computational design, through to laboratory implementation, including protein production, biophysical, structural, and functional characterisation.
- Co-inventor of minichaperone protein refolding technology, leading to MRC spin out *Avidis*.
- Discovered autoinactivation mechanism of GAD65, an autoantigen in type 1 diabetes and regulator of neurotransmitter homeostasis.
- Design of hyperstable non-antibody scaffolds for therapeutic and diagnostic use.
- Creation of new protease inhibitor biologics
- Design of novel multi-specific immunoglobulin-like molecules.
- Determined high resolution X-ray crystallographic structures of over 90 proteins, including several ‘firsts’ of medically important proteins; the autoantigen GAD65, Membrane Attack Complex / Perforin (MACPF)-like protein, the bacteriophage lysin PlyC, and T-Cell receptor:MHC complex.
- Multidisciplinary collaborations with 17 research groups from 8 countries.
- Created 8 Bioinformatics resources, including *REFOLD, PolyQ, KINETOCHORE* and *D2Odb*.
- Created the *Australasian Repositories for Diffraction Images (TARDIS)*, the world’s first online repository for raw X-ray data. Known now as *Store.Synchrotron*, it serves as a model implementation source of raw data archiving and dissemination within the structural biology research communities (https://bit.ly/2BJSZwH).

Employment

2020 – present

PTNG Consulting (founder). Consultancy in Protein Engineering. https://www.ptngconsulting.com

2020 – present

Adjunct Associate Professor, Dept of Biochemistry & Molecular Biology, Monash University (https://bit.ly/36ohyxl).

2007 – 2020

Head, Protein Engineering and Design Lab/Associate Professor, Dept of Biochemistry & Molecular Biology, Monash University, Australia.

2007 – 2012

NHMRC Senior Research Fellowships.

2014

Visiting Professor at the Sapienza Università di Roma, Italy.

2013

Erskine Fellowship (visiting Professor), University of Canterbury, Christchurch, NZ.

2012

Visiting Professor, Ecole Normale Supérieure de Cachan, Paris, France.

2003 – 2006

Senior Research Fellow, Dept. Biochemistry, Monash University.

1999 – 2003

Biodesigns Ltd (founder). Consultancy in bioinformatics. Clients: Cambridge University Transfusion Medicine; National Blood Service, UK.

1999 – 2003

Senior Staff Scientist (tenured), MRC Centre for Protein Engineering, Cambridge, UK.

1999 – 2001

Consultant for Avidis (now Imaxio after merger with Diagnogene). Avidis developed recombinant protein refolding technology based upon my postdoctoral work on minichaperones.

1994 – 1999

Postdoctoral Fellow, MRC Cambridge, UK, group of Sir Alan Fersht, a founder and

Postdoctoral Fellow, MRC Cambridge, UK, group of Sir Alan Fersht, a founder and

pioneer of protein engineering. Training in X-ray crystallography at the MRC Laboratory of Molecular Biology, Cambridge, the birthplace of structural biology.

1990 – 1995

Consultant for *Cambridge Antibody Technology* UK (molecular modelling). Acquired by *AstraZeneca* in 2006 for £702m.

1988 – 1989

Ciba-Geigy Pharmaceuticals (now *Novartis*), Horsham, UK. Research student in Advanced Drug Delivery Research Unit (1 year of BSc degree).

Education

1990 - 1994

PhD (Biochemistry), University of Cambridge (UK), group of Sir Alan Fersht (FRS).

1990

Medical Research Council (UK) Postgraduate Scholarship, University of Cambridge.

1990

Bachelor of Science (Honours; Chemistry), Kingston University (UK).

Peer Review and Service to Community

15 years' experience assessing funding applications: NHMRC, ARC, Wellcome Trust, European Research Council, MRC UK, Marsden Fund NZ, Human Frontiers, Cure Cancer Australia, Austrian START, Prostate cancer foundation, Health Research Foundation of NZ, and Worldwide Cancer Research. NHMRC (Australia) Project grant panel (Biochemistry, 2015-2017) and Monash strategic grants panel (2015-2018).

Select Publications

Complete list at Google Scholar (https://bit.ly/2oj9zAe) & PubMed (https://bit.ly/31Md0gA).

- Fodor, Stones, Brand and Buckle (2020) Intrinsic limitations in mainstream methods of identifying network motifs in biology. *BMC Bioinformatics*, 21(1):165. [PDF]
- Zammit et al. (2019) Denisovan, modern human, and mouse TNFAIP3 alleles tune A20 phosphorylation and immunity. *Nature Immunology*, 20(10):1299-1310. [PDF]
- Li et al. (2018) Structural Capacitance in Protein Evolution and Human Diseases. *J Mol Biol.*, 430; 3200. [PDF]
- Porebski et al. (2016) Circumventing the stability-function trade-off in an engineered FN3 domain. *Protein Engineering, Design and Selection*, 29, 11, 541-550. [PDF]
- Porebski et al. (2016) Smoothing a rugged protein folding landscape by sequence-based redesign. *Scientific Reports*, 6 33958. [PDF]
- Kass et al. (2014) Cofactor-dependent conformational heterogeneity of GAD65 and its role in autoimmunity and neurotransmitter homeostasis. *PNAS*, 111(25): E2524. [PDF]
- Reboul et al. (2012) Epitope Flexibility and Dynamic Footprint Revealed by Molecular Dynamics of a pMHC-TCR Complex. *PLoS Computational Biology*, 8, 3, e1002404. [PDF]
- Rosado et al. (2007) A common fold mediates vertebrate defense and bacterial attack. *Science*, 317, 1548. [PDF]
- Fenalti et al. (2007) GABA production by glutamic acid decarboxylase is regulated by a dynamic catalytic loop. *Nature Structure & Molecular Biology*, 14, 280-6. [PDF]
- Tynan et al. (2005). T cell receptor recognition of a 'super-bulged' major histocompatibility complex class I-bound peptide. *Nature Immunology*, 11, 1114-22. [PDF]
- Buckle et al. (1997) A structural model for GroEL-polypeptide recognition. *PNAS*, 94, 3571-3575. [PDF]

Recent Reviews

- Chandler & Buckle (2020) Development and Differentiation in Monobodies Based on the Fibronectin Type 3 Domain. *Cells*, 4;9(3). [PDF]
- Chandler et al. (2020) Strategies for Increasing Protein Stability. *Methods in Molecular Biology*, 2073:163-181. [PDF]

- Wilding et al. (2019) Protein Engineering: The Potential of Remote Mutations. *Biochemical Society Transactions*. pii: BST20180614. [PDF]
- Buckle & Borg (2018) Integrating experiment and theory to understand TCR-pMHC dynamics. *Frontiers in Immunology*, 9:2898. [PDF]
- Broendum et al. (2018) Catalytic diversity and cell wall binding repeats in the phage encoded endolysins. *Mol. Microbiology*, 110(6):879-896. [PDF]
- Williams et al. (2018) Thyroid peroxidase as an autoantigen in Hashimoto's disease - structure, function, antigenicity. *Hormone and Metabolic Research*, 50(12):908-921. [PDF]
- Campbell et al. (2018) Laboratory evolution of protein conformational dynamics. *Curr Opin Struct Biol*, 50 49-57. [PDF]

Select Media

- Creating order from disorder: uncovering the origins of protein evolution (2019) Monash Lens
- The spark that created life (2018) Science Daily
- 'Jekyll and Hyde' protein linked to type 1 diabetes (2014) Science Daily
- Monash scientists score breakthrough on non-antibiotic bug killer (2012) The Age
- The magic of the movies - molecules in 4D (2012) Phys.org

Select Bioinformatic Resources

D2Odb

A database of predicted structural transitions for mutations in human proteins (https://d2odb.org/).

REFOLDdb

Tool for the optimization of protein refolding (https://bit.ly/32G57eE).

PolyQ

Sequence and domain context of polyglutamine repeats in proteins (https://bit.ly/2NfpWq0).

KINETOCHORE

Database for kinetochore proteins (https://bit.ly/36c9qin)

Database for kinetochore proteins (https://bit.ly/36c9qjp).

Select Patents

- Ashley Buckle; Benjamin Porebski: PCT/AU2015/050795: UNITED STATES OF AMERICA, 2017. Highly stable polypeptide scaffolds.
- Nelson, Fischetti, Whisstock, Buckle, McGowan: 12/166,602: UNITED STATES OF AMERICA, 2009. Expired. Octameric protein for use in bio-nanotechnology applications.
- Whisstock, Law, Buckle, Fenalti, Rowley: PCT/AU2007/001362: AUSTRALIA, 2007. Crystal structures of both isoforms of human glutamic acid decarboxylase. Development of activators of GAD65 as therapeutic agents in anxiety disorders, post traumatic stress and movement disorders.
- Buckle, A.M. and Fersht, A. R.: PCT/GB00/02019: UNITED KINGDOM, 1994: GroEL Mutants with Improved Stability.