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Remembering the late Prof Robert B. Sim

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Published in:
 Immunobiology

DOI:
[10.1016/j.imbio.2023.152400](https://doi.org/10.1016/j.imbio.2023.152400)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
 Publisher's PDF, also known as Version of record

Publication date:
 2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Kishore, U., Daha, M. R., & Reid, K. B. M. (2023). Remembering the late Prof Robert B. Sim: Memorial Symposium and a Special issue of Immunobiology. *Immunobiology*, 228(4), Article 152400. <https://doi.org/10.1016/j.imbio.2023.152400>

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Editorial

Remembering the late Prof Robert B. Sim: Memorial Symposium and a Special issue of Immunobiology



ARTICLE INFO

Keywords

Bob Sim
Complement
Innate immunity
C3 activation
Host-pathogen interaction
Alternative pathway



Robert Braidwood Sim (4/4/1951-6/2/2021)

This Special issue of Immunobiology commemorates the legendary complementologist, Prof, Robert B. Sim, who sadly passed away in February, 2021. To celebrate his life and achievements, an RB Sim Memorial Symposium was organized on 9th and 10th April, 2022. Several participants of the symposium were invited to contribute research and review articles. This issue is a compilation of such articles.

<https://doi.org/10.1016/j.imbio.2023.152400>

Available online 1 June 2023
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1. Bob's life and career

Bob Sim was born at Pittentian, a cottage near Crieff on 4th April, 1951. His Mum and Dad (Margaret and Charles) had two older girls, Anne and Susan. When Bob was small, the family moved a lot, living on farms across the central region of Scotland. They lived at Gifford, south of Edinburgh, until he was 3, then Cobblehaugh adjacent to the Innerpeffray Library near Crieff, where Bob started school at Crieff Junior Secondary. They moved to a farm, North Ailey, near Kilcreggan on the Roseneath peninsula, and then moved to the Glenfarg area of Perthshire to a dairy farm, known as Newton of Balcanqual. They lived there for 7 years and subsequently remained in the area. There is a gravestone in Arngask "new" cemetery, close to Glenfarg in Perthshire, commemorating the entire family. Bob went to Glenfarg primary school and to Perth Academy where he excelled. He went to Edinburgh University in 1969 to study Biochemistry, again excelling academically. He also worked as a net fisherman on the Tay during every academic holiday from 1968 until 1974 and was also an avid short wave radio ham. Bob met Edith (his wife) at Edinburgh and they moved to Oxford for their doctoral studies: Bob worked in the MRC Immunochemistry Unit which was to have a central role in his life for over 40 years. The Unit was headed by Prof Rodney Porter, the Nobel prize winner for dissecting IgG structure, and Bob's immediate supervisor was Ken Reid, who has been a steadfast mentor with his wife Margery to both Bob and Edith.

Bob was an MRC Exchange Fellow from 1976 to 1978 in Grenoble in Maurice Colomb's laboratory before returning to a staff position in the MRC Immunochemistry Unit, Oxford

Bob and Edith were married in 1975 in Dundee and renewed their marriage vows on Christmas Day 2020. Their family, Grace and Francis, also contributed to the symposium and Emma with Bob's grandchildren-Charlie, Stanley, Wilfred and Josephine, and Peter with Mary and baby John joining them later. Josephine and John were born after Bob died.

Bob supervised many students in Oxford and also in Leicester and Kingston where he had academic posts latterly. He also had a very wide international circle of collaborators and colleagues and published over 300 papers and edited many books. Bob spent a lot of time acting as an Editor for many journals including as a founding editor of the journal, *Protein and Cell*. He was also an editor of *PLoS One* and *Immunobiology*.

A collection of obituaries for Bob can be found in the journal, *Viruses* (<https://www.mdpi.com/si/79155>). They clearly reveal the esteem in which he was held.

2. Memorial symposium

To celebrate the life and achievements of Bob, a memorial symposium was organized on 9th and 10th April, 2022 at the Department of Pharmacology, University of Oxford (Organising Committee: M. Daha, U. Kishore, KBM Reid and E Sim). It was attended by many of Bob's students, colleagues, collaborators and friends (Figs. 1, 2). A recording of the symposium can be found at <https://www.pharm.ox.ac.uk/bob-symposium>.

Tony Day (University of Manchester, UK), one of Bob's early doctoral students, gave a historical and personal insight into his research on factor H and moving on to tumour necrosis factor-stimulated gene-6 (TSG-6), whose ramifications go beyond being an extracellular matrix protein. He emphasized how Bob's watchful eyes during his doctoral training helped him subsequently to take on difficult projects. Simon Clark (University of Tübingen, Germany) delivered an online talk on the role of complement in ocular health and disease. Steve Perkins (University College London), a long-time collaborator and friend of Bob, provided intriguing and detailed insight into structure–function relationships involving factor H and C3 variants. Wilhelm Schwaebler (University of Cambridge) revealed his research engagement with Bob as a mentor and how he always envisioned a crosstalk between the three complement pathways.

Alvaro Diaz (University of Republic of Uruguay) described the immune evasion capability of the coat of the parasite, *Echinococcus*. Anna Ferreira (University of Republic of Uruguay) described her newly found passion about dissecting the innate immunity of sturgeons. Grace

Mackintosh Sim (Bob's daughter) delivered an animated talk on how she was busy increasing science access to budding scientists through her role at the Royal Veterinary College, London. Rajneesh Malhotra (Sitryx UK) raised important issues pertaining to immunomodulatory drug discovery. This was followed by a talk by Alexander Steinkasserer (University of Erlangen, Germany) on induction of immune tolerance via soluble CD83 in autoimmunity and transplantation. James Arnold (King's College London) presented his recent work, highlighting the importance of linking innate and adaptive immunity in cancer.

Francis Sim (an orthopedic surgeon and Bob's son) highlighted the incidence of idiopathic scoliosis in childhood hematopoietic malignancy. Tim Hickling (Roche Switzerland) talked about complement-based drug discovery and development. Krishna Gulla (National Institutes of Health, USA) delivered an on-line lecture on the intricacies and the scale of vaccine manufacturing processes. The last session of the symposium was kickstarted by an online talk by Zihe Rao (Chinese Academy of Sciences) that showcased how closely Bob was involved with him and his team via several visits to different parts of China. Rao highlighted the support he received from Bob as the founding editor of the journal, *Protein and Cell*. Vivek Malhotra (Centre for Genomic Research, Barcelona), Bob's first doctoral student, then offered a fascinating insight into the synthesis and packaging of triple-helical collagens via Golgi complex and its relevance in tissue fibrosis. Peter Garred (Copenhagen University, Denmark), a long-term collaborator and friend of Bob, gave an overview of the complement lectin pathway. The symposium ended with Reinhard Würzner (Innsbruck, Austria) giving a presentation on subtotal deficiencies of factor H, C6 and C7.

During the two days of the symposium, there was an exhibition (at Bob's home) of historic personal artefacts and scientific equipment that three generations of complementologists (Rodney Porter, Ken Reid and Bob Sim) used in their research.

3. Bob Sim Memorial Special Issue of Immunobiology

The first three papers in this special issue are authored/co-authored by Bob Sim. The first one by Sim et al., a paper of historical importance, describes a novel intrinsic activity of C3 using nucleophilic complement



Fig. 1. Some of the attendees at the Bob Sim Memorial Symposium at the Department of Pharmacology, University of Oxford.



Fig. 2. Bob Sim Memorial Symposium. A group of attendees and their spouses at a lunch on Sunday to celebrate Bob's life and love of gardening.

inhibitors. This work has been put in the context by an Introductory article by KBM Reid. The paper raises important points about using these rather affordable complement inhibitors in translational research. Laich *et al.* offer an alternative explanation for how systemic lupus erythematosus patients, who have C2 deficiency, show mild symptoms. They show that factor B, a C2 homologue of the complement alternative pathway, can compensate for the insufficiency of C2, thus allowing activation of the complement classical pathway as normal. Interestingly, they also show the existence of C4bBb (a chimeric C3 convertase representing alternative and classical pathways) that could cleave C3 *in vitro*, albeit to a low level. Mayilan *et al.* report measurement of serum L-ficolin and plasma MASP-2 levels, and the activity of L-ficolin-bound MASP-2, in their correlation with chronic schizophrenia. Since the genes of MBL-associated serine proteases (MASPs) of the complement lectin pathway are expressed in the developing cortex and required for neuronal migration, it is likely that dysregulation of L-ficolin-MASPs, like MBL-MASPs, can contribute to the pathogenesis of schizophrenia.

In view of the importance of dysregulated complement activation in COVID-19 patients, Tsiftoglou *et al.* report targeted genotyping of COVID-19 adult patients for Single Nucleotide Polymorphisms (coding SNPs) of alternative pathway component genes. The authors report key alleles of factor B and C3 that can potentially enhance C3 convertase assembly, and hence, heightened complement activation via the alternative pathway by SARS-CoV-2. Continuing with the theme of viral immunology, Varghese *et al.* present a comprehensive review of the state-of-the-art on innate and adaptive immune responses against influenza A virus (IAV), a highly contagious respiratory infection causing virus of global concern. The authors enumerate all key players of the innate and adaptive immunity that are likely to be protective. However, escape mechanisms exploited by the virus and likelihood of future pandemics/endemics continue to unsettle the vaccination outcomes and strategies.

There are two papers that send strong message about the importance of tackling tuberculosis, a deadly disease caused by *Mycobacterium tuberculosis* that has shown a disturbing rise in the drug resistance. Daniel and Bhakta make a passionate argument about repurposing already existing drugs for tackling drug resistant *M. tuberculosis*. There

are non-steroidal anti-inflammatory drugs (NSAIDs) that also seem to possess anti-microbial properties. Carprofen, for instance, has been shown to inhibit the efflux mechanism and disrupt biofilm formation in mycobacteria. However, there is a thin line of balance between anti-inflammatory and anti-microbial characteristics of these drugs if they are to be used as an adjunct therapy. In an elaborate review article, D'Souza *et al.* assess the importance of PE-PPE family (with nearly 170 members) of *M. tuberculosis*, which have become an area of intense research activity in the last few years. Understanding structure–function relationships, their importance in host–pathogen stand-off, and immune escape mechanisms via these new protein family may offer avenues for newer ways of diagnosis, especially of latent tuberculosis, and novel vaccine development strategies.

Two consecutive papers by Valand *et al.* examine innate immune evasion strategies used by *Candida tropicalis*, an opportunistic fungal pathogen that can cause invasive systemic infections. In order to disseminate, the pathogen uses a key virulence factor, Secreted aspartyl proteinase 1 (Sap 1) (similar to *C. albicans*) that can cleave human mannan-binding lectin (MBL) and collectin-11 (but not L-ficolin), and thus, preventing the activation of the complement lectin pathway. Interestingly but not surprisingly, clinical isolates seem to produce relatively higher amounts of Sapt1 compared to a reference strain. The second paper in this series, again by Valand *et al.* examines the importance of *C. tropicalis* pH-related antigen 1 (CtPra1), a surface bound and secretory protein, in immune escape and pathogenesis. A recombinant form of CtPra1 seems to bind human C3 and C3b, as well as factor H and C4b-binding protein. Thus, CtPra1 appears to inhibit all three complement pathways albeit to varying degrees.

The last paper in this special issue is a comprehensive review on nanotechnology and nanomedicine, an area of research that was close to Bob's heart in the last decade. Pondman *et al.* (Kirsten Pondman was a visiting graduate student with Bob in 2008–10) dwell on the nature and consequences of interactions between nanoparticles and immune system. In some instances, both seem to modify each other, offering opportunities to render nanoparticles biocompatible in the best possible way. A new threat to our health has emerged from nanoplastics, something that seems to be omnipresent.

Acknowledgements

We (together with the Sim family) wish to express our gratitude to all individuals who have donated to the Bob Sim Symposium fund as well as the commercial sponsors, Bio-Rad Antibodies and SVAR, who have been very generous. We thank the staff of the Department of Pharmacology, University of Oxford, who have been unstintingly helpful, especially Carolyn Thackrah, and Jimmy Martin and Bryony Oliver of the Events Office at the Wolfson College, Oxford. We also thank Professors Jon Austyn and Christina Redfield, and the President of Wolfson and the Uruguayan Ambassador for supporting the events at Wolfson College and the establishment of the Bob Sim Wolfson Uruguayan Exchange Fellowship facilitated by the Development office at the Wolfson College, Oxford. We are grateful to the journal Immunobiology and its Chief Editors past and present (Wilhelm Schwaeble and Viviana Ferreira) for dedicating this special issue to Bob's memory, and for all of those who have written their scientific articles in Bob's memory. There are other articles that have been written in association with the symposium (Díaz et al., 2023; Arnold and Mitchell, 2022; Karagianni et al., 2023). We are extremely grateful to Carolyn Thackrah and Barbara Zonta of the University of Oxford Pharmacology Department for making available the recording of the symposium. We also acknowledge the wonderful support of Profs Fran Platt and Antony Galione of the Pharmacology Department, Oxford for their support and assistance. The Symposium and dinner were financially supported by many individuals and also the company SVAR and BioRad who sell the anti-factor H monoclonal antibodies, OX23 and OX24, raised in Bob's Lab (Sim et al., 1983).

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¹ Bob Sim, Ken Reid and Uday Kishore were colleagues at the MRC Immunochemistry Unit, Oxford that formally closed in 2008. We have kept this affiliation here for historical reasons.