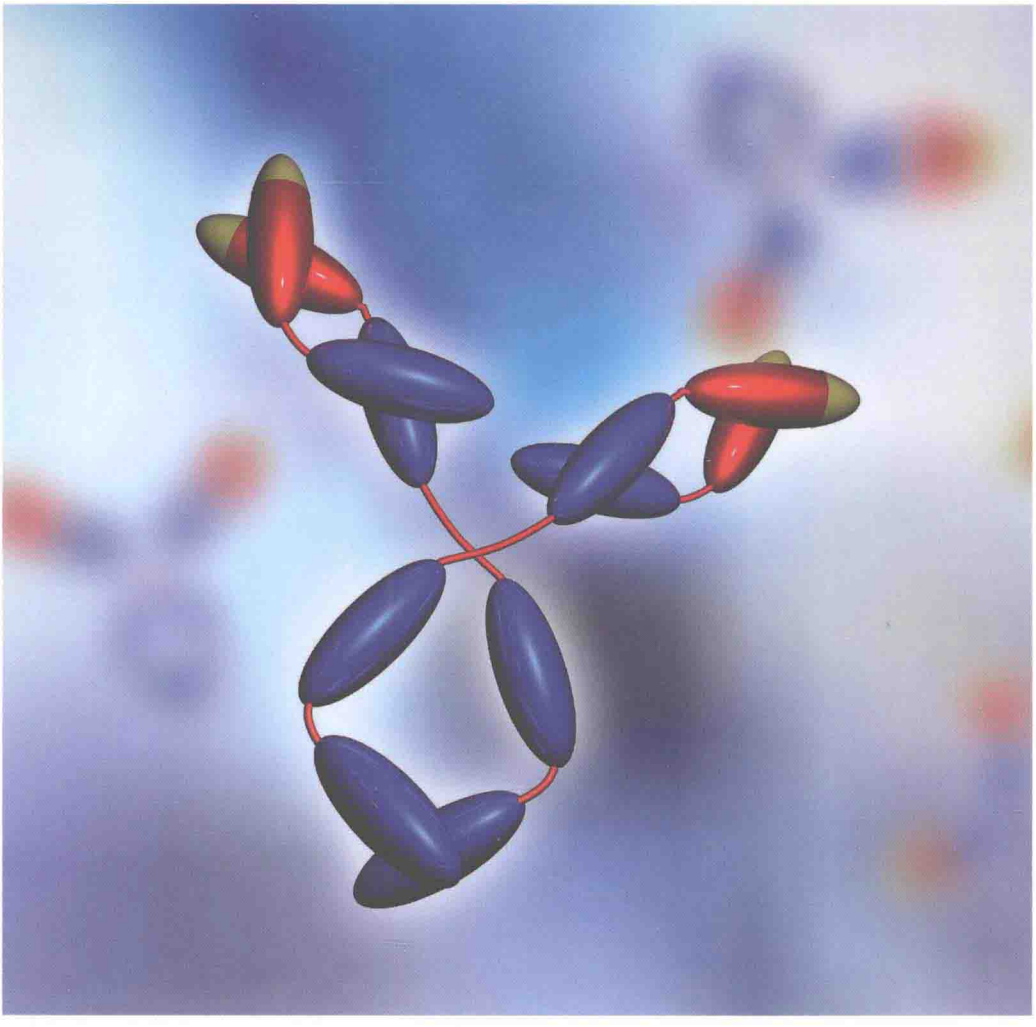
RSC Drug Discovery

Edited by Lyn H Jones and Andrew J McKnight

# Biotherapeutics

## Recent Developments using Chemical and Molecular Biology



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# *Biotherapeutics*
## *Recent Developments using Chemical and Molecular Biology*

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RSC Publishing

RSC Drug Discovery Series No. 36

ISBN: 978-1-84973-601-5
ISSN: 2041-3203

A catalogue record for this book is available from the British Library



Published by The Royal Society of Chemistry,
Thomas Graham House, Science Park, Milton Road,
Cambridge CB4 0WF, UK

Registered Charity Number 207890

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# *Preface*

Biotherapeutic modalities are often considered beyond the reach of the medicinal chemist. The language and terminology can differ significantly between small and large molecule drug discovery, and yet the aims are essentially the same. We believe chemistry has an essential role in the future success of this exciting area, and this book was conceived as an attempt to illustrate the successful partnership of chemical and molecular biology to enable and advance biotherapeutics (so-called 'chemologics').

The design–synthesis–screen–design cycle, an engine for successful small molecule drug discovery, is not usually a component of biotherapeutic discovery, yet our challenge to this community is that that need not be the case – a deeper molecular understanding should be brought to bear in the biotherapeutics field, such that the empiricism that currently persists can be addressed. The challenge will be to generate knowledge and apply those learnings prospectively to avoid making the same mistakes and accelerate our decision making – the delineation of structure–function or structure–toxicology relationships will find increasing value in the biotherapeutic space. Small molecule drug discovery has already evolved past the period of 'make lots of stuff, screen lots of stuff, and see what pops out!' It is neither inspiring nor cost effective – design strategies are now far more sophisticated, augmented significantly by advances in biophysical techniques, computational sciences and the accuracy of predictive *in silico* tools. Our belief is that these methods will be harnessed to a greater extent in the advancement of biotherapeutic discovery and optimization approaches in the future.

This book approaches the huge area of biotherapeutics from the perspective of improved *molecular design*, which draws from the synergies between chemical biology, medicinal chemistry and molecular biology in particular. Recent developments in these disciplines that have delivered drugs, clinical candidates or significantly advanced biotherapeutic discovery and design will

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Published by the Royal Society of Chemistry, www.rsc.org

be described. A broad range of modalities are highlighted that will appeal to those working in a number of biomolecular areas (oligonucleotides, sugars, proteins and peptides). The chapters, written by an impressive list of world experts in their respective fields, detail a number of diverse therapeutic opportunities, including immunopharmacotherapy, optimized fully human or humanized antibodies, bicyclic peptide phage libraries, synthetic proteins and vaccines, micro-RNA, bacterial toxins, stabilized cyclotides, antibody–drug conjugates, peptide epitope mimicry and synthetic immunology.

Additionally, we believe this book will serve as inspiration for the medicinal chemistry community, particularly when presented with examples of how their expertise can make considerable impact in the biotherapeutics arena. Much has been made of the need to chose the 'best target' in drug discovery, but as much emphasis should then be placed on choosing the 'best modality', really, our approach should be 'modality agnostic'.

Our vision is that all biopharmaceutical chemists, whether in industry or academia, are equipped with capabilities both in small and large molecule drug discovery (and as a minimum can speak the language of, and engage in, 'biotherapies') and we hope this book will help towards that goal. In some ways, this book is a call to the traditional small molecule medicinal chemistry community to ask broader questions of their projects and therapeutic programmes. At the earliest stage of interest in a biological target we should be asking 'what therapeutic modalities shall we apply?' and both chemists and biologists are fundamental to the success of those strategic discussions, as well as the successful prosecution of the programme.

We are extremely grateful to the authors of the chapters in this book. They have not only described their areas of interest and expertise with great skill, but they have also shared compelling insights into the future opportunities for biotherapeutics. We also thank Rosalind Searle and Cara Sutton, RSC Publishing, for their editorial support and encouragement.

*Lyn H. Jones and Andrew J. McKnight*

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Published by the Royal Society of Chemistry, www.rsc.org

CHAPTER 1

# *Synthetic Immunology*

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## 1.1 Introduction and Scope

The field of immunology has become increasingly lucid at the level of atoms and molecules. Owing also to advances in synthetic chemistry, the rational design and construction of synthetic systems that perform complex immunological functions – an area termed synthetic immunology – has come within reach. Here we will highlight one facet of synthetic immunology concerned with the development of low-molecular weight ("small"), synthetic molecules that are capable of functionally mimicking biological molecules. It is important to note at the outset that this article does not aim to be comprehensive in scope. At the expense of being all-inclusive, we focus on several specific contributions, which highlight how advances in immunology and chemistry have proven mutually complementary. We have divided this chapter into four subsections: (1) synthetic ligands for pattern recognition receptors, including toll-like receptors (TLRs), NOD-like receptors (NLRs), nuclear family receptors and C-type lectins, (2) synthetic molecules that modulate the complement system,

[†]These authors contributed equally to this work.

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(3) synthetic systems for controlling cell–cell communication, including chemokine/cytokine mimetics, and (4) synthetic ligands for modulating adaptive immune processes, including T-cell and B-cell functions.

We regret not being able to cover all of the exciting developments that might be classified into the area of Synthetic Immunology. Such areas include: synthetic vaccine development, as this topic is covered elsewhere in this book;[1] synthetic modulators of cellular signaling processes, as the functions of such molecules extend beyond the immune system;[2–5] protein-based and cellular immunotherapies, including therapeutic monoclonal antibodies;[6–9] immunomodulator strategies involving nanoparticles or virus-like particles;[10–13] DNA- and RNA-based therapeutics;[14–16] and strategies for controlling cellular differentiation.[17–20] Lead references to each of these areas are provided for interested readers.

It is our hope that this chapter will serve as a broad-based introduction for biomedical scientists, including chemists interested in extending their activities into the immunological realm, as well as immunologists looking to learn about how modern synthetic chemistry can enhance fundamental biological understanding. Ultimately, we believe that the intellectual perspective residing at the interface between synthetic chemistry and immunology will enable scientific advances that were never before thought possible, thus proving critical to the furtherance of basic biomedical research and patient care.

## 1.2 Synthetic Ligands for Pattern Recognition Receptors (PRRs)

Pattern recognition receptors (PRRs) are a diverse class of proteins that function canonically as part of the innate immune response. These receptors recognize pathogen-associated molecular patterns (PAMPs), which are widely conserved, repeating motifs found within pathogens and not within hosts, as well as damage-associated molecular patterns (DAMPs), which are host-derived molecules that arise from tissue damage.[21,22] Improper activation of these receptors has been shown to cause hyper-inflammatory disease states, and extensive research efforts have focused on identifying PRR antagonists. Such developments have been reviewed elsewhere.[23–33] In this section we discuss a few select examples of molecules that functionally mimic the natural ligands of PRRs.

### 1.2.1 Synthetic Mimics of TLR Ligands

Toll-like receptors (TLRs) were originally discovered as important receptors for *Drosophila melanogaster* embryonic development,[34] and were later found to play a critical role in innate immunity in humans.[35] Extensive research during the past two decades has revealed the TLR superfamily to contain more than ten different family members (TLRs 1–13).[22]