Novel anti-infectives: is host defence the answer?
Pamela Hamill, Kelly Brown, Håvard Jenssen and Robert EW Hancock

Resistance to antimicrobial agents and the limited development of novel agents are threatening to worsen the burden of infections that are already a leading cause of morbidity and mortality. This has increased interest in the development of novel strategies such as selective modulation of our natural immune defences. Innate immunity is a complex, evolutionarily conserved, multi-faceted response to defeating infection that is naturally stimulated by pathogenic organisms through pattern recognition receptors on host cells. It is amplifiable and broad spectrum but if overstimulated can lead to the potential for harmful inflammatory responses. A broad variety of therapies are already available or increasingly under development, to stimulate protective innate immunity without overtly stimulating harmful inflammation or even suppressing such damaging pro-inflammatory responses.

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Introduction
Despite the enormous positive impact that the development of antibiotic, antiviral and antifungal drugs have made on human health in recent decades, infectious diseases remain a major contributor to morbidity and mortality and a considerable burden to healthcare systems globally. The current WHO global burden of disease report indicates that infectious diseases account for nearly a third of global deaths while HIV, malaria, tuberculosis and lower respiratory tract infections were among the top eight leading causes of death in 2004 [1]. The alarming increase in the prevalence of antibiotic-resistant bacteria together with the threat of new and variant pathogens, exemplified by the emergence of HIV, SARS and avian influenza, highlights the urgent need for new strategies to combat infectious diseases.

Innate immunity represents a conserved, complex and multi-pronged response to overcoming infection that is present in all complex host species of life. Natural stimulation of innate immunity by pathogens results in an amplifiable, broad spectrum and protective immune response but if this response is too vigorous or prolonged it can lead to the potential for harmful inflammatory responses. Selective modulation of innate immunity as an anti-infective strategy is an emerging concept driven by the huge advances in our understanding of this crucial host defence system. The discovery of key pathogen recognition receptors (PRRs) such as the Toll-like receptors (TLRs), and intracellular sensors of microbial components such as the Nod-like receptors (NLRs) and RIG-I-like receptors (RLRs) [2], has stimulated a rapid expansion in information regarding pathogen-sensing mechanisms and intracellular signaling pathways and effector strategies that lead to a rapid, highly effective clearance of pathogens. This has provided valuable insights into the role of host immunity in the pathogenesis of infectious diseases and revealed possible targets for therapeutic intervention. Here we discuss the potential for this new approach in developing urgently needed novel anti-infective therapies and the progress being made towards this goal. There is also considerable activity currently within the biotech community focused on development of immunomodulators as treatments for inflammatory conditions and as vaccine adjuvants (see [3–6] for recent reviews); however, here we discuss recent developments and potential for the use of immunomodulators in the direct treatment of infectious diseases.

Why target host innate immunity defence systems as an anti-infectious strategy?
Innate immunity is a highly effective defence system, considering the relative infrequency with which infectious diseases occur, despite our constant daily exposure to pathogens. Symptomatic diseases can progress either through damage caused directly by microbial factors or as a consequence of the immune response itself; some pathogens stimulate an overtly powerful pro-inflammatory response, while the response to other pathogens may be insufficient [7]. Hence immunomodulation offers the potential to tip the balance back in the favour of the host, either by boosting or inhibiting selected elements of the immune response as well as exploiting the powerful and multi-faceted effector mechanisms that have evolved specifically for the purpose of pathogen clearance. There are several advantages to modulating host innate immunity as an anti-infective strategy. Since the pathogen itself is not targeted, there is no selective pressure and hence a very small possibility of development of resistance to
treatment. Another attractive prospect is that, since host innate immunity utilizes effector mechanisms that are effective against a diverse array of pathogens, immunomodulation could form the basis for broad spectrum therapeutics to treat infections of bacterial, viral, fungal or parasitic origin. Further, since innate immunity is highly instrumental in directing subsequent adaptive responses, modulation of innate immunity could be used to initiate or reinforce immune responses or ‘skew’ them to either a Type I or Type II antigen-specific response, thereby encouraging the appropriate adaptive response for either intracellular or extracellular pathogens, respectively. However it is important to note that there are many potential disadvantages including the inappropriate dys-regulation of immunity causing, for example sepsis or what is known as the cytokine storm, possible unfavourable interactions between infectious agents and the immunomodulators in combination, the induction of aggressive and damaging activated cells such as inflammatory macrophages and neutrophils, a range of immunotoxicities including histamine release, apoptosis, complement hyperactivation, among others, and the induction of autoimmunity or chronic inflammation. A simple example of the potential perils of immunotherapy is that a side effect of immune suppressive chemicals and irradiation is that the body becomes extremely vulnerable to infections.

Existing and potential innate immune targets for development of anti-infectives

There is a wealth of potential targets for therapeutic intervention that capitalize on the complexities of the
<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Company</th>
<th>Status/Results</th>
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<tbody>
<tr>
<td><strong>Chronic HCV-directed therapies</strong></td>
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<tr>
<td>Zadaxin</td>
<td>Thymosin α1 (thymalfasin)</td>
<td>SciClone/ Sigma-Tau</td>
<td>Phase III: Synthetic peptide. Promotes MHC class I expression, IL-2 and IFN-γ secretion, proliferation and activation of CD4 Th1, CD8, and NK cells. Decreases Th2 cytokines IL-4 and IL-10 that are counter productive to viral infections.</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
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<tr>
<td>Oglufanide disodium</td>
<td>Dipeptide</td>
<td>Implicit Bioscience</td>
<td>Phase II: Intranasal synthetic formulation of a natural dipeptide of L-glutamic acid and L-tryptophan. Reverses suppression of the immune system.</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
</tr>
<tr>
<td>ANA773</td>
<td>TLR-7 agonist</td>
<td>SciClone</td>
<td>Phase I: Induced secretion of IFN-α from human PBMC, increased NK cell cytotoxicity and cytokine secretion in vitro</td>
<td>July 2008, Anadyss press release</td>
</tr>
<tr>
<td>IMO-2125</td>
<td>TLR-9 agonist</td>
<td>Idera Pharma</td>
<td>Phase I: TLR-9 agonist that induces IFN-α</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
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<tr>
<td>Locteron</td>
<td>IFN-α</td>
<td>Biolex Therapeutics Inc.</td>
<td>Phase II complete: Controlled-release drug delivery technology of IFN-α</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
</tr>
<tr>
<td>IL-29</td>
<td>IFN-λ</td>
<td>ZymoGenetics</td>
<td>Phase II complete: PEG-IFN-λ (long acting)</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
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<tr>
<td>Omega IFN</td>
<td>Omega IFN</td>
<td>Intarcia Therapeutics</td>
<td>Phase II complete: Implantable infusion pump releases Omega interferon</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
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<tr>
<td>Bavituximab (Tarvacin)</td>
<td>Monoclonal Ab against phospholipids</td>
<td>Peregrine</td>
<td>Phase I complete: Binding, for example, to phosphatidyl serine on the surface of virally infected cells will alert the immune system.</td>
<td>November 2007, Peregrine press release</td>
</tr>
<tr>
<td>Civacir</td>
<td>HCV Immune Globulin</td>
<td>NABI/Biotest AG</td>
<td>Phase II: Plasma-derived polyclonal antibody</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
</tr>
<tr>
<td>Ceplene</td>
<td>Histamine dihydrochloride</td>
<td>Maxim</td>
<td>Phase II (with PEG-IFN-α2b and Ribavirin): Histamine inhibits HCV NS3-induced oxidative stress and apoptosis in T cells, NK and NKT cells.</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
</tr>
<tr>
<td>PeviPRO™/ PeviTER™</td>
<td>Therapeutic vaccine</td>
<td>Pevion Biotech</td>
<td>Phase I: Virosome-based synthetic cocktail that targets CD8 and CD4 helper T lymphocytes</td>
<td>December 2006, Pevion press release</td>
</tr>
<tr>
<td>ChronVac-C</td>
<td>Therapeutic vaccine</td>
<td>Inovio/ Tripep AB</td>
<td>Phase I/II: DNA-based, immune boosting vaccine with unique pulse-delivery method. Activates T cells to kill HCV-infected liver cells.</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
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<tr>
<td>TG4040</td>
<td>Therapeutic vaccine</td>
<td>Transgene</td>
<td>Phase I: Attenuated strain of vaccinia virus (MVA), expressing non-structural proteins (NS3, NS4 and NS5B) of HCV</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
</tr>
<tr>
<td>GI-5005 (Tarmogen)</td>
<td>Therapeutic vaccine</td>
<td>GlobeImmune</td>
<td>Phase II: Delivered in combination with pegylated interferon and ribavirin. Targets two conserved HCV replication proteins.</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
</tr>
<tr>
<td>IC41</td>
<td>Therapeutic vaccine</td>
<td>Intercell/ Novartis</td>
<td>Phase II: Combination vaccine of five synthetic peptides with HCV, CD4 and CD8 T-cell epitopes</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
</tr>
<tr>
<td>NOV-205</td>
<td>Immune modulator</td>
<td>NovoLabs</td>
<td>Phase Ib complete: Hepatoprotective agent with immunomodulatory/ anti-inflammatory properties</td>
<td><a href="http://www.novolabs.com">www.novolabs.com</a></td>
</tr>
<tr>
<td>CTS-1027</td>
<td>MMP inhibitor</td>
<td>Conatus</td>
<td>Phase II: MMP inhibitor that reduces aminotransferase (ALT) activity and protects liver cells from damage during a viral infection</td>
<td><a href="http://www.conatuspharma.com">www.conatuspharma.com</a></td>
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<tr>
<td>LGD-4665</td>
<td>Receptor agonist</td>
<td>Ligand Pharmaceuticals</td>
<td>Phase I complete: Thrombopoietin receptor agonist. Stimulates platelet production. For use before or with other HCV treatments.</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
</tr>
<tr>
<td>Eltrombopag (Promacta)</td>
<td>Receptor agonist</td>
<td>Glaxo SmithKline</td>
<td>Phase II complete: Thrombopoietin receptor agonist. Stimulates platelet production. For use before or with other HCV treatments.</td>
<td><a href="http://www.hcvadvocate.org">www.hcvadvocate.org</a></td>
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**HIV-directed therapies**

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<tr>
<th>Drug</th>
<th>Description</th>
<th>Company</th>
<th>Status/Results</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Ampligen</td>
<td>TLR-3 Agonist</td>
<td>Hemisphera Biopharma, Inc.</td>
<td>Phase I complete: Poly IC-12U is a dsRNA agonist of TLR-3 that stimulates the immune system and inhibits HIV replication in vitro.</td>
<td><a href="http://www.hemisphera.net">www.hemisphera.net</a></td>
</tr>
<tr>
<td>Vacc-4x</td>
<td>Therapeutic Vaccine</td>
<td>Bionor Immuno AS</td>
<td>Phase II complete: Therapeutic vaccine consisting of modified HIV peptides with increased immunogenicity</td>
<td><a href="http://www.bionorimmuno.com">www.bionorimmuno.com</a></td>
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### Future prospects for development of anti-infective immunomodulators

The case for increased research and development of immunomodulators as anti-infective therapies is bolstered by the success of therapeutic immunomodulators already in clinical use. At present, the most viable drugs are based on pathogen signature molecules (agonists of PRRs), cytokines and antimicrobial (host defence) peptides, and include TLR agonists/antagonists and agents targeting chemokines and cytokines. Many of these are aimed, although not exclusively, at viral infections (Table 1). However their potential in bacterial infections and the associated inflammatory sequelae seems strong, especially since we are running out of novel treatment options for bacteria.

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**Table 1 (Continued)**

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<thead>
<tr>
<th>drug</th>
<th>description</th>
<th>company</th>
<th>status/results</th>
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<tbody>
<tr>
<td>Leflunomide</td>
<td>pyrimidine anti-inflammatory agent</td>
<td>sanofi-aventis</td>
<td>phase i, ii, iii; inhibitors of proliferation of activated (virally infected) T cells thereby maintaining a sufficient population of T cells for defence while limiting the number of cells in which HIV can reproduce.</td>
<td>tufts.edu/medicine/lectureseries/immunology</td>
</tr>
<tr>
<td>Soluble beta-1,3/6 glucan</td>
<td>poly saccharide</td>
<td>inimex</td>
<td>phase i: studies: For gingivitis and periodontitis and general immune modulated. Beta 1,3-D glucans are polysaccharides that activate the immune system, upregulating protective immunity while suppressing pro-inflammatory cytokine production in response to bacterial TLR agonists.</td>
<td><a href="http://www.inimexpharma.com">www.inimexpharma.com</a></td>
</tr>
<tr>
<td>IMX942 peptide</td>
<td>modeled host defence peptide</td>
<td>am-gen</td>
<td>phase i, ii: while originally developed as an antimicrobial peptide this peptide has very weak antibiotic activity and may protect via immunomodulatory activity. Trials address allogeneic bone marrow transplantation-associated infections.</td>
<td><a href="http://www.am-gen.com">www.am-gen.com</a></td>
</tr>
<tr>
<td>hLF-1-11 small peptide</td>
<td>derived from human lactoferrin</td>
<td>biotec pharmacon</td>
<td>phase i: studies: For gingivitis and periodontitis and general immune modulated. Peptide modeled from human lactoferrin, a natural antimicrobial peptide that destroys bacterial lysates, respectively, and is used as preventative and/or therapeutic treatments for respiratory tract infections.</td>
<td>biotec.no</td>
</tr>
<tr>
<td>IM8032</td>
<td>peptide modeled from 1,3-glucan</td>
<td>inntech</td>
<td>phase ii, iii: developed as an antimicrobial peptide this peptide has very weak antibiotic activity and may protect via immunomodulatory activity. Trials address allogeneic bone marrow transplantation-associated infections.</td>
<td><a href="http://www.inntech.com">www.inntech.com</a></td>
</tr>
<tr>
<td>CLS001</td>
<td>12-mer analog of antimicrobial</td>
<td>migenix</td>
<td>phase ii, iii: developed as an antimicrobial peptide this peptide has very weak antibiotic activity and may protect via immunomodulatory activity. Trials address allogeneic bone marrow transplantation-associated infections.</td>
<td><a href="http://www.migenix.com">www.migenix.com</a></td>
</tr>
<tr>
<td>hIL-11</td>
<td>small peptide derived from</td>
<td>am-gen</td>
<td>phase i: studies: For gingivitis and periodontitis and general immune modulated. Small peptide derived from human interleukin-6. Peptide modeled from human interleukin-6 with activity and is approved for the treatment of HSV, EBV and viral hepatitis. Microbes themselves are also licensed for use as immunomodulators in Europe. Products such as Bronchomunal® (Lek) and Luivac® (Daiichi Sankyo Co.) consist of lyophilized bacteria and bacterial lysates, respectively, and are used as preventative and/or therapeutic treatments for respiratory tract infections. In addition, intravenous pooled human immunoglobulin is FDA approved and used as a general immunomodulator for pediatric HIV with off-label uses for several infection-related issues including sepsis and C. difficile colitis.</td>
<td><a href="http://www.am-pharma.com">www.am-pharma.com</a></td>
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Antivirals

Although the majority of antiviral research remains focused on viral targets such as protease and polymerase enzymes, immunomodulation as an antiviral strategy is also being actively pursued. The switch to alternative approaches in antiviral development reflects the difficulties associated with successful targeting of crucial points in the virus life cycle and exploits an ever-increasing understanding of viral life cycles and immune evasion strategies. Many viruses establish chronic disease through their ability to subvert host immune responses [9,10], hence therapy based on immunomodulation to counteract viral immune evasion could be of great therapeutic value. The development of antiviral immunomodulators has been dominated to date by therapies targeting chronic viral infections such as HIV, HBV and HCV, for which there is a large unmet clinical need.

General strategies for therapeutic intervention in viral infection include boosting the host’s natural antiviral effector mechanisms by inducing release of cytokines such as IFN-α, TNF-α and IL-12, NK cell activation and strong CD8+ T cell responses, all of which are hallmarks of Th1-like immune responses that are crucial for the clearance of intracellular pathogens. The main approach to eliciting Th1-type responses is through stimulation of intracellular TLRs involved in the recognition of conserved microbial molecular signature molecules, using TLR agonists, and currently synthetic agonists directed at TLR-3 (dsRNA), TLR-7/8 (ssRNA) and TLR-9 (unmethylated CpG DNA motifs) are all in pre-clinical or clinical development Phases (Table 1).

Ampligen, a synthetic TLR-3 agonist consisting of Poly-EPolyC12U RNA, is being developed by Hemispherx (Philadelphia, USA) and is in clinical trials as an HIV therapy, having had success in earlier trials [11]. Following on from the success of imiquimod in the treatment of HPV-associated warts, other TLR-7 agonists are being developed. Takeda Pharmaceuticals (Japan) has compound R851 in Phase II clinical trials in the US also for the treatment of HPV, while Anadyr (San Diego, USA) has ANA773, an oral TLR-7 agonist produg, at a pre-clinical stage of development with current indications being Hepatitis C and cancer. Synthetic agonists of TLR-9 are currently the focus of much research and development since TLR-9 activation induces both innate and adaptive immune responses, making it an attractive target for the development of both anti-infective treatments and vaccine adjuvants. Currently, Dynavax (San Francisco, USA) has a candidate Type C TLR-9 agonist in the development for HCV therapy and similarly, Idera (Cambridge, USA) has a TLR-9 agonist, IMO-2125, as its lead candidate for the treatment of HCV in Phase I trials for patients not responding to standard interferon/ribavirin dual therapy [12].

One potential caution with such strategies is that the combination of a virus manipulating innate immunity and a TLR agonist doing the same could potentially yield surprising results, with an exacerbation of pro-inflammatory responses being the most concerning. Another issue is that TLRs have been found to be required not only for antiviral defence but also for viral infectivity that further adds to the complexity of such treatments [13,14]. TLR stimulation boosts antiviral defences by stimulating natural induction of IFN and other cytokines required to initiate a Th1 type response, but there are also ongoing efforts into developing improved IFNs for exogenous administration through increasing stability, strategies for oral delivery and increasing binding affinities for IFN receptors (Table 1).

Alternative approaches to stimulating Th1-type responses to treat viral infections are also in development. The concept of therapeutic vaccines is a growing trend in developing treatments for chronic viral infections such as HCV and HIV. Like prophylactic vaccines they contain pathogen-specific epitopes to elicit an immune response; however they are administered post-infection and frequently have additional components to encourage the appropriate Th1 responses necessary for effective clearance of intracellular pathogens. Pevion Biotech (Bern, Switzerland) is developing a therapeutic vaccine that incorporates HCV antigen peptides encapsulated in proprietary ‘virosomes’, a carrier system designed to induce specific CTL and T helper cell responses in patients with chronic HCV infection [15,16]. Bionor AS (Skien, Norway) has HIV therapeutic vaccines in clinical trials that are based on novel peptide fragments with modified sequences to enhance immunogenicity.

In addition to strategies aimed at boosting general antiviral defence mechanisms, the possibility to develop custom immunomodulators tailored to treat specific viruses also exists, provided there is suitably detailed knowledge of the virus life cycle and pathogenesis.

Host defence peptides

Other classes of immunomodulatory agents with the potential for development as anti-infectives include the host defence peptides (HDPs). HDPs are important innate immune effector molecules that are conserved in virtually all life forms [17]. While some possess direct antimicrobial activity (the ability to lyse or destabilize bacterial membranes or viral envelopes; often weak in natural peptides), others, such as the endogenous human HDP LL-37, exert potent and pleiotropic immunomodulatory effects (Figure 2) [18–20]. Synthetic peptides that retain many of the immunomodulatory properties of naturally occurring HDPs are currently being explored for their therapeutic potential [21] owing to their unique ability to promote protective innate immunity while suppressing potentially harmful inflammatory responses.
Innate Defence Regulator-1 (IDR-1), an anti-infective peptide that selectively modulates the innate immune response, represents the first proof of principle that synthetic immunomodulatory peptides offer therapeutic potential [22**]. Despite possessing no direct antimicrobial activity, IDR-1 confers protection against multiple bacterial pathogens, including multiply antibiotic resistant strains (meticillin resistant *S. aureus*, vancomycin resistant *Enterococcus*), in mouse infection models. Mechanism of action studies have shown that IDR-1 stimulates the production of monocyte chemokines, dampens pro-inflammatory cytokine responses and activates monocyte-macrophage cells, without inducing toxic side effects. A 5 amino acid immunomodulatory peptide, IMX942, is in pre-clinical development by Inimex Pharmaceuticals (Vancouver, Canada) with likely indications for future clinical trials being hospital-treated pneumonia, surgical site infections and chemotherapy-induced neutropenia. Intriguingly the peptide Omeganan, developed by Migenix Inc. (Vancouver, Canada) as an antimicrobial peptide, has demonstrated efficacy as an anti-inflammatory in suppressing the effects of acute acne and rosacea in Phase II clinical trials. The development of immunomodulatory HDPs is particularly attractive owing to their ability to resolve infections by antibiotic resistant bacteria and their ability to stimulate natural host defence effector mechanisms without inducing potentially harmful excessive pro-inflammatory responses. Since they also exhibit multi-faceted immunomodulatory capabilities, they may also circumvent the problems associated with stimulation...
or inhibition of one individual process that could affect TLR-targeted agonists/antagonists.

Other immunomodulatory peptides in development for infectious disease include SCV-07 (gamma-D-glutamyl-L-tryptophan), a synthetic peptide with proven immune stimulating properties, which is already licensed in Russia for the treatment of tuberculosis. SciClone (California, USA) has introduced this compound into Phase II trials for HCV treatment [23]. Implicit Biosciences (Brisbane, Australia) is developing IM862 (oglufanide disodium), a dipeptide of L-glutamyl-L-tryptophan with known anti-angiogenic and immunomodulatory properties initially isolated from the thymus [24], for HCV therapy, and has recently embarked on a Phase II trial in the USA.

**Challenges in the development of immunomodulatory anti-infectives**

The development of immunomodulatory therapeutics is subject to unique difficulties arising due to interspecies and intraspecies variation and redundancy within the innate immune system. The potential lack of correlation between outcomes observed in animal models and human subjects can occur owing to fundamental interspecies differences in innate immunity (e.g., between human and mouse chemokine systems [25]) and is a problem that necessitates greater thought in establishing appropriate animal models as well as improved orthology predictions for innate immune-related genes. Genetic variation between individuals is another important yet unpredictable feature that can impact upon the effectiveness of therapies and has particular relevance for the development of immune-targeted therapies, since genes encoding immune-related proteins are among the fastest evolving within mammalian genomes. Given its hugely important role, it makes sense that redundancy is a feature of the innate immune system. The duplication of crucial features creates an important safety net, but also potentially undermines the effectiveness of therapies that target a single immune component, such as chemokines or their receptors. Despite their enormous potential, many new immunomodulator candidates have not progressed through clinical trials. This can be attributed partly to our incomplete understanding of the complex nature of the immune system and interindividual variability [26]. Certainly, continued interrogation of innate immunity using functional genomic and proteomic approaches at the systems biology level together with sophisticated bioinformatics analysis is necessary for the progression of novel immunomodulatory candidates into clinical use.

**Knowledge and technology advances that will accelerate the development of novel anti-infective immunomodulators**

The application of new systems biology approaches and techniques such as siRNA gene silencing and transcriptional network profiling to study innate immunity is already underway and will undoubtedly improve our understanding of innate immune responses and host-pathogen interactions and thus hopefully expedite the development of novel immunomodulators [27–29]. New bioinformatics resources have recently become available with the launches of Innate DB ([www.innatedb.com](http://www.innatedb.com)) [30*] and IIIDB ([http://db.systemsbiology.net/IIDB](http://db.systemsbiology.net/IIDB)) [31], which are innate immunity-specific databases that include data analysis resources to facilitate the functional analysis of innate immune responses, as well as the IIPGA program ([www.innateimmunity.net](http://www.innateimmunity.net)), which is a collaborative effort to analyze polymorphisms in human innate immunity genes.

It is noteworthy that the majority of existing and prospective immunomodulators are proteins, peptides or nucleic acids, which renders them more prone to difficulties in drug stability and delivery than conventional small molecule drugs. The development of pegylated forms of IFN, that display greatly enhanced stability, demonstrates how technological advances can improve the clinical usefulness of biologic therapies. Idera Pharmaceuticals (Cambridge, MA, USA) has recently generated chemically modified RNA compounds with increased resistance to nuclease activity that stimulate TLR-7 and TLR-8 in *in vitro* and *in vivo* [32] as part of its development of nucleic acid-based TLR agonists. Advances in delivery systems for cytokines have also been made, such as the use of biodegradable microparticles constructed from poly-(lactide-co-glycolide) (PLGA), designed for *ex vivo* T-cell expansion, that permit the sustained release of IL-2 [33]. Such advances in formulation and delivery systems will also help expedite the progression of immunomodulators into clinical use [34].

**Conclusion**

In recent years it has become evident that we are entering a ‘post-antibiotic era’ in which many previously successful drug regimes are becoming ineffective and it is only a matter of time before others follow suit. Pathogen-directed treatments will always be subject to the risk of the emergence of resistance; consequently the time has come to vigorously pursue alternative potential treatment approaches to infectious diseases. The targeting of innate immunity represents an intuitive new approach, and one that should be explored since there are few practical options available. Since disease is a manifestation of the pathogen’s ability to overcome or subvert host immune responses, we argue that the development of novel anti-infectives that target the host immune system should warrant high priority. While this approach is not without its risks, as with conventional, pathogen-directed drug therapies, the therapeutic targeting of innate immunity is a concept in its infancy and hence the risks associated may be mitigated by more extensive research into the field, which is already underway, together with the implementation of new technology platforms and...
methodologies. Greater understanding of the processes and regulation of innate responses will intuitively lead to improved strategies and solutions to overcome the problems that accompany the development of any new treatment.

So far, the concept of harnessing innate immunity to treat infectious diseases has been adopted primarily by the biotech community to target viral infections, despite the urgent clinical need also for treatments of antibiotic resistant bacterial strains. This perhaps reflects the recent emergence of viral diseases of global concern such as SARS and avian influenza, but also the fact that since the generation of pathogen targeting antiviral therapies has traditionally been more challenging, the prospect of alternate approaches to treating viral disease has been received with greater enthusiasm.

In addition, because antibiotics have been so successful for many decades, most ongoing anti-infective development has remained focused on pathogen-directed therapies. It is well documented that the extent of anti-bacterial research is woefully mismatched to the need for new treatments and this is also due to financial obstacles in the development of new treatments, since anti-infectives tend to be less profitable then ventures targeting other types of diseases and are therefore less attractive to large pharmaceutical companies [35,36].

The existence of immunomodulators already in clinical use highlights that intelligent targeting of components of innate immunity is an achievable and efficacious route, and one that offers great potential for the future since it circumvents the problems of resistance that blight current treatments for infectious diseases. Immunomodulators may also be useful as adjunct therapies in conjunction with current anti-infectives, such that the treatment regime might consist of dual or multiple drugs that conjointly target the microbe itself in addition to providing an immunomodulator that boosts, suppresses or subtly adapts the immune response in such a way as to enhance host defences.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:• of special interest•• of outstanding interest


This paper describes innovations in the development of immunopotentiating influenza virosomes, which increase stability while inducing potent antigen delivery system to induce cellular and humoral immune responses. This work describes advances in the development of immunopotentiating influenza virosomes, which increase stability while inducing potent.


This paper presents the first proof of principle study showing that a synthetic immunomodulatory peptide can confer protection against infection with multiple bacterial pathogens, including multiple antibiotic resistant strains, without toxicity and while suppressing harmful pro-inflammatory responses.


This is an elegant study of the application of siRNA knockdown methods and comparative genomics to identify novel genes involved in the regulation of innate immunity, in both C. elegans and murine systems, which may also represent novel therapeutic targets.


Introduces a novel, highly detailed, and manually curated, database of genes and cellular pathways involved in innate immunity in human and murine systems together with new analysis and visualization tools to facilitate innate immunity research.


