fections in humans who were in contact with the pigs (Dawood et al., 2009; Shinde et al., 2009; Trifonov et al., 2009). However, the widespread and effective transmission to humans did not start until May 2009.

A looming influenza pandemic has always been feared prior to the H1N1 "swine flu". Previously, subtypes H5N1, H7N3, H7N7 and H9N2 of avian origin were feared as potential human pandemic strains since they were all endemic in birds. (Cauthen et al., 2000; Fouchier et al., 2004; Hirst et al., 2004; Lin et al., 2000) The H9N2 strain was considered to be low pathogenic in birds, but has sporadically been transmitted to humans, (Cameron et al., 2000; Hossain et al., 2008) resulting in disease development and influenza-like symptoms, though no deaths have been reported (Uyeki et al., 2002). The H7N7 and H5N1 strains differ from H9N2 in that they are highly pathogenic in birds (Horimoto and Kawaoka, 2005). In humans, H7 avian influenza A commonly manifests as conjunctivitis and/or respiratory symptoms (Belser et al., 2009). In contrast, H5N1 can produce respiratory symptoms, encephalopathy and/or diarrhea, and in severe cases, multi-organ failure (Beigel et al., 2005; Cheung et al., 2002). There have been multiple reported cases of bird to human transmission of H5N1 and H7N7 in recent years and human to human transmission has been suggested in some households (Beigel et al., 2005; Horimoto and Kawaoka, 2005). Fortunately, these viruses have not attained the efficiency of human to human transmission that the "swine flu" has attained. Although it is feared that eventual mutations could lead to improved transmission of these viruses between humans, thus leading to a pandemic strain.

Host Antiviral Response to Influenza Infections

Typically, influenza infects the epithelial cells of the upper respiratory tract, but it is also capable of infecting monocytes/macrophages and other leukocytes, though immune cell infections are less productive for the virus, as only a few viruses are produced prior to the virus-induced apoptosis of these cells (Julkunen et al., 2000; Julkunen et al., 2001; Kaufmann et al., 2001). Humans are equipped with the necessary mechanisms for clearance of the virus during influenza infections. Primarily, the innate immune system participates in this process by providing a strong T_h1 response induced by type 1 interferons (Fernandez-Sesma et al., 2006). This response would require activation of at least nuclear factor kappa B, interferon regulatory factor and signal transducers and activators of transcription pathways (Julkunen et al., 2000; Julkunen et al., 2001). The following pathways would then allow the affected cells to produce the chemokines and cytokines involved in the desired antiviral immune response. Influenza A virus infected macrophages/monocytes secrete macrophage inflammatory protein-1α/β and -3α, chemokine C-C motif ligand 5, monocyte chemotactic protein-1/3, interferon-inducible protein-10, interferon-α/β, interleukin-1 and -6, and tumor necrosis factor-α while epithelial cells infected with influenza secrete chemokine C-C motif ligand 5, monocyte chemotactic protein-1, interleukin-8 and interferon-α/β (Julkunen et al., 2000; Julkunen et al., 2001). In addition to this proinflammatory response, the human body also expresses numerous host defence peptides, both constitutively and in response to stimuli.

Host defence peptides have been demonstrated to be key players in bridging the complex interplay between innate (germline encoded) and adaptive (antigen specific) immunity. These signature molecules of host defence are present in virtually all species of life and carry a broad spectrum of activities, i.e. direct antibacterial, antifungal, antiviral and antiparasitic activities (Jenssen et al., 2006b) as well as modulation of host cell immune responses (Hancock and Sahl, 2006; Oppenheim and Yang, 2005; Hancock, 2001; Zasloff, 2002). They are generally short (12 to 50 residues), with a net positive charge (+ 2 to 9) due to an excess of basic arginine/lysine residues, and contain up to 50% hydrophobic amino acids. Structurally they are sorted into four classes based on their amphiphilic conformations (i.e., β-structures with two to four β-strands, amphipathic α-helices, loop and extended structures). Consequently, due to their broad spectrum of activities, several of the novel drug candidates that are currently passing through clinical trials are tailored around host defence peptides.

Influenza Virus Evasion of the Immune System

Despite the measures taken by the body to fight off an influenza infection, the virus has its own mechanism for subverting the host immune system. Three different studies of clinical patients infected with influenza A H5N1 observed that infected patients had higher serum levels of proinflammatory cytokines and chemokines in their plasma compared to healthy controls (Beigel et al., 2005; Horimoto and Kawaoka, 2005; Seo et al., 2002). This has also been observed in vitro when macrophages from healthy blood donors were infected with H5N1. In comparison to the cells infected with influenza H3N2 or H1N1, it was found that H5N1 infected cells had greater up-regulation of proinflammatory cytokines and chemokines in response to the infection (Cheung et al., 2002). Hypercytokinemia and the subsequent reactive hemophagocytic syndrome have also been implicated as the cause of death of many H5N1 infected patients as it results in the observed sepsis syndrome, acute respiratory distress syndrome and multi-organ failure (Beigel et al., 2005; Cheung et al., 2002). Therefore, the exaggerated immune response is suspected of causing the severity that is observed in these infections (Cheung et al., 2002). Despite the surge of proinflammatory cytokines, H5N1 is able to avoid clearance as its non-structural protein 1 is able to interfere with maturation of the immune response by inhibiting dendritic cell maturation and interferon-α/β production in myeloid dendritic cells (Fernandez-Sesma et al., 2006).

Similarly, in some cases of H1N1 "swine flu" infected individuals, the symptoms, unlike seasonal influenza, are similar to those found in H5N1 infected patients (Peiris et al., 2009). The specific inflammatory responses to the virus have yet to be determined but hypercytokinemia and reactive hemophagocytic syndrome may also be suspected as the cause of death in these individuals. This outlines the crucial role the immune system plays in the pathogenesis of influenza and thus, must be addressed to be able to alleviate the symptoms or eliminate infections.

Influenza Vaccination

The technique of vaccination dates back more than two hundred years to when Edward Jenner successfully vaccinated his patients against smallpox virus through exposure to cowpox virus. Vaccination has since proven a very effective public health

initiative, preventing the severity and magnitude of several infectious diseases. In principle vaccination is done through administration of an attenuated micro-organism or important components of a micro-organism (e.g. surface proteins) able to trigger an immune reaction in the host. The efficacy of a vaccine relies completely on the T_h cell regulated development of high affinity B cell memory and the consolidation of the response through antigen re-challenge. Resultant B cell memory is the key feature yielding immunity after vaccination. Influenza vaccines have been available since the 1940s and are without doubt the most important strategy to prevent influenza virus epidemics. Since the circulating influenza strains are constantly changing U.S. Food and Drug Administration annually recommend two of the influenza A strains (currently a wild type of H3N2 and H1N1) and one B strain most responsible for human infections to be included in the following seasons vaccine. There are several licensed manufacturers world wide, and all of them produce their vaccines in eggs, either formulated as a trivalent inactivated influenza vaccine for intramuscular injection or as a live attenuated influenza vaccine administered as an intranasal spray. Comparative studies of the two vaccine types have indicated that the live attenuated influenza vaccines offers a significantly better protections against both well matched influenza strains and against strains that have undergone antigenic drift (Belshe et al., 2007). This broad spectrum protection provided by the live attenuated influenza vaccine has later been confirmed to also apply to vaccine batches from other seasons (Piedra et al., 2007). The achieved vaccine protection is on average between 70-90% and is predominantly affected by the age and immune competence of the immunized individual. Lower protection can be expected in years with a suboptimal match between the vaccine strain and the circulating viral strains. However this does not always hold true, since the vaccine in general will reduce disease symptoms even though it initially fails to protect against the primary infection (Herrera et al., 2007; Nichol et al., 2007). This illustrates that one important focal point both for improved epidemic vaccine manufacturing and for increased pandemic preparedness would be to better understand the mechanism behind vaccine cross-protection (Boon and Webby, 2009). For a comprehensive overview of the current trends on seasonal influenza vaccination the readers are refereed to Fiore et al. (2009); Chen and Subbarao (2009).

There are also strategies in place for prepandemic vaccine production, using an eight plasmid system (i.e. plasmid-based reverse genetics or reassrotment) (Hoffmann et al., 2002a; Hoffmann et al., 2002b) with six plasmids carrying attenuating internal protein genes from a stable master donor virus, and two plasmids with hemagglutinin and neuraminidase from the potential pandemic strain (for review see Chen and Subbarao, 2009; O'Neill and Donis, 2009). Though the initial prepandemic vaccine trials demonstrated rather disappointing immunogenicity, formulation and use of new adjuvant strategies has lately produced vaccine alternatives giving a more satisfactory protection (Leroux-Roels et al., 2008; Leroux-Roels et al., 2007; Treanor et al., 2006). Despite this success and great potential of the prepandemic vaccines program there is an ethical aspect that should also be mentioned. Vaccines are expensive and many nations will not have the economic means to stockpile these prepandemic vaccines types, given that there is no guarantee that the pandemic strain will match the strain the vaccine is tailored around. To illustrate this; in 1996 the first devastating reports came on the highly pathogenic avian flu (H5N1), and variants of this have since circulated in domestic and wild birds resulting in an imminent threat of a pandemic onset (de Jong et al., 1997; Yen and Webster, 2009). Despite several reported cases of avian to human transmission, the influenza strain has so far not been able to adopted the ability to efficiently spread amongst humans, and has not per definition caused a pandemic. However, in this same time period, investors and granting agencies have enabled initiation of more than 60 prepandemic clinical vaccine trials against the strain. Then, almost out of the blue came reports on an influenza strain (H1N1) from porcine origin that started to cause severe influenza-like respiratory illnesses in Mexico in Fraser et al., (2009) and by early May 2009 the World Health Organization classified this as an influenza pandemic (Neumann et al., 2009).

Although there is no doubt that vaccination has proven extremely efficient in the control of influenza, the protection is never a hundred percent, hence supporting the need for good influenza drugs both for prophylactic and therapeutic use. Drug development could also be encouraged as an international preparation strategy for the next influenza pandemic, as these pandemics are caused by novel strains of influenza where human immunity is lacking and the protection from a prepandemic vaccines may be somewhat limited.

Influenza Drugs for Prophylactic and Therapeutic Use

Adamantane derivatives have long been in use as treatment alternatives against influenza virus infection. Amantadine was the first of these compounds that demonstrated the ability to inhibit replication of influenza (Figure 1) (Davies et al., 1964), possibly through blocking of the interior channel within the tetrameric helical bundle of the viral matrix 2 protein (Sansom and Kerr, 1993), thus inhibiting the influx of H+ ions into the virion, a process crucial for triggering the uncoating stage (Horimoto and Kawaoka, 2005). Another derivative in this drug family of matrix 2 protein ion-channel blockers is rimantadine (Figure 1). Both compounds have long been available for both prophylactic and therapeutic treatment of influenza A virus infections. However, their current usefulness is limited as many influenza strains easily develop resistance or have already developed resistance against this group of drugs (Englund et al., 1998; Hayden, 2006). Amongst the reported strains that have attained this resistance is the 2004 H5N1 strain (Beigel et al., 2005). Thus, the use of adamantane derivatives may not be sufficient in handling future influenza threats.

Neuraminidase inhibitors are a more successful class of drugs that have been approved for influenza prophylaxis and treatment. The viral neuraminidase mediates spread of influenza progeny after successful replication, by cleaving of N-acetylneuraminic acid from the cell surface glycoprotein. Thus, by inhibiting this cleavage, release of newly formed viral particles is prevented (Moscona, 2005a). Due to the important and highly conserved role of neuraminidase in the infection cycle of influenza, this enzyme is a prime target for anti-influenza therapeutics. Amongst the influenza drugs that inhibit this pathway are the commonly recommended oseltamivir (Kim et al., 1997) (Tamiflu; Roche) and zanamivir (von Itzstein et al., 1993) (Relenza; GlaxoSmithKline) (Figure 1). Both drugs prevent vi-

ral spread by mimicking the substrate of neuraminidase, and by binding to its active site, it inhibits the enzymatic role of the protein (Moscona, 2005b). However, oseltamivir requires a rearrangement in the neuraminidase active site to be effective. Thus, a mutation that prevents the structural rearrangement from occurring would render the drug ineffective. Not surprisingly, several influenza strains have already acquired such resistance against oseltamivir including several isolated cases of H5N1 (Beigel et al., 2005; Horimoto and Kawaoka, 2005; Moscona, 2005b). In contrast, zanamivir acts on neuraminidase without the conformational change oseltamivir requires to be effective (Moscona, 2005a; Moscona, 2005b). Zanamivir-resistant H3N2 influenza strains have been found to have poor viability as mutations that permit zanamivir resistance commonly reduces the neuraminidase activity (Zurcher et al., 2006). Thus, although resistance is emerging against oseltamivir, zanamivir is still a viable alternative for influenza treatment.

Novel Influenza Intervention Strategies and Drugs in Clinical Trial

There are several different drugs in clinical development for influenza treatment (i.e. peramivir, ribavirin, taribavirin, T-705, Fludase®), and common for all of them is that they are classified as small molecule drugs (Figure 1). Small molecules have been the drug class of choice from a pharmaceutical point of view for decades for several reasons, one being the low cost of synthesizing these drug molecules. In addition to the rather inexpensive final product, chemical modification and library generation is also fairly easy and inexpensive, enabling biologists to screen thousands of small molecule derivatives in their chase for a lead candidate. If that is not enough, computational solutions and in silico prediction models (e.g. Monte Carlo, molecular dynamics simulation, ligand docking, etc.) with small molecules are also relatively easy and accurate, as the molecular flexibility and variation is highly restrained by the size of the molecule (Christmann-Franck et al., 2004; Mizutani and Itai, 2004; Steindl and Langer, 2004). However, a big drawback with these types of small molecule drugs is that they are primarily designed to target and interfere with the viral entry, replication and release cycle. Hence, resistance development occurs rather easily over time, as has been illustrated throughout the history and evolution of antibiotic against influenza (Englund et al., 1998; Hayden, 2006; Beigel et al., 2005) and against other pathogens.

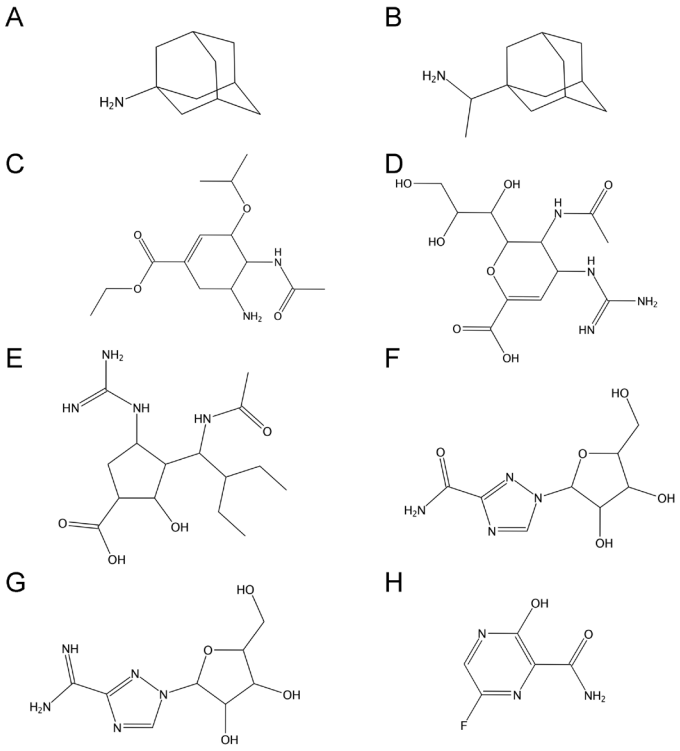

Figure 1: Structural small molecules approved or in clinical trails; (A) Amantadine, **(B)** Rimantadine, **(C)** Oseltamivir, **(D)** Zanamvir, **(E)** Peramivir, **(F)** Ribavirin, **(G)** Taribavirin and **(H)** T-705.

Peramivir (RWJ-270201) is the next generation cyclopentane derivatives of a neuraminidase inhibitor (Figure 1). It is currently undergoing Phase III clinical testing as a result of the collaborative effort of the U.S. Department of Health & Human Services and BioCryst Pharmaceuticals (http://www.biocryst.com/peramivir.htm). Studies comparing peramivir to traditional neuraminidase inhibitors has demonstrated a similar or greater inhibitory effects against influenza in both in vitro and in vivo models (Bantia et al., 2006; Bantia et al., 2001; Chand et al., 2005; Govorkova et al., 2001). Even more intriguing, comparative studies of peramivir with oseltamivir and zanamivir have also demonstrated that strains resistant to the latter two compounds, still were susceptible to peramivir (Mishin et al., 2005). However, in vivo protection with peramivir is highly dependent on the route of administration due to the low oral bioavailability (Barroso et al., 2005) and thus, new formulations are currently being made and tested by BioCryst Pharmaceuticals.

Ribavirin has long been recognized as a broad spectrum antiviral drug, with the potential for treating respiratory syncytial virus, hepatitis, influenza and herpes (Figure 1) (Eggleston, 1987). It targets inosine 5'-monophosphate dehydrogenase, which plays a role in GTP biosynthesis and viral RNA synthesis. Thus, as it targets a key enzyme for virus replication, there have been no reported cases of ribavirin-resistant influenza. Although ribavirin seems to be a highly effective drug against influenza in vitro and in vivo, it does not perform well in clinical trials and has been implicated as having potential teratogenicity and the ability to cause hemolytic anemia (Cohen et al., 1976; Rodriguez et al., 1994; Smith et al., 1980). Therefore, in the guidelines for H5N1 management of infected individuals, the World Health Organization strongly advises against the use of ribavirin.

Taribavirin (Viramidine) is a carboxamidine analog of ribavirin, which has been proven to have significant antiviral effects on influenza A and B infections in vitro and in vivo (Figure 1) (Sidwell et al., 2005). The drug has just finished Phase IIb testing (Valeant Pharmaceuticals Int.; http://www.valeant.com/) as an oral drug candidate for treatment of hepatitis C virus infections, demonstrating comparable activity as ribavirin with significantly lower toxic effects. Based on the non-toxic nature and oral bioavailability of taribavirin, it has been accredited with market potential for treatment of influenza virus infections (Sidwell et al., 2005).

T-705 (favipiravir) is a RNA polymerase inhibitor developed

by Toyama Chemical Co., Ltd., (http://www.toyama-chemical.co.jp/en/index.html) which is currently being tested in Phase II clinical trials (Figure 1). A series of pyrazinecarboxamide derivatives including T-705, have demonstrated very broad spectrum antiviral activity against a range of various RNA viruses, including influenza virus, arenaviruses, West Nile virus and yellow fever virus (Furuta et al., 2009). In particular, T-705 has demonstrated a potent and selective inhibitory activity against a panel of different influenza strains both in vitro and in vivo (Furuta et al., 2002). Though the efficacy was less than that exerted by oseltamivir and zanamivir, it demonstrated a remarkably better protection than ribavirin (Sidwell et al., 2007). In time of addition studies, it has been established that T-705 targets the early- to middle-stages of the viral replication cycle and that the compound neither has an effect on viral adsorption nor on viral release (Furuta et al., 2005). However, even in single dose treatment experiments where a 100% lethal dose of influenza A virus was administered to the mice, protection could be observed when T-705 was administered up to 60 hours after viral infection (Sidwell et al., 2007).

Fludase® (DAS181) is a recombinant sialidase fusion protein that is being developed by NexBio (http://www.nexbio.com). It works through cleavage of sialic acid residues on the host cells (Belser et al., 2007; Malakhov et al., 2006). Sialic acid is the entry receptor for influenza and is consequently crucial for the infection to occur. The typical receptor for avian and equine influenza viruses is α(2,3)-linked sialic acid while human influenza viruses traditionally use an α(2,6)-linked sialic acid (Ito, 2000). Both receptor types are found on human respiratory epithelial cells, though the majority are α(2,6)-linked sialic acids (Hassid et al., 1999; Matrosovich et al., 2004). Fludase® is capable of cleaving both types of sialic acids, as well as ?(2,8)-linked sialic acid, an entry receptor used by some laboratory-generated influenza strains (Malakhov et al., 2006). Due to the variety of sialic acids that can be cleaved by Fludase®, this drug candidate has the potential of being effective against all circulating strains of influenza. Also, since it targets host cell components instead of the virus directly, drug resistance is hardly likely to occur (Malakhov et al., 2006). The drug is still in clinical Phase I trials, but has demonstrated very promising results both from a prophylactic and a therapeutic treatment point of view.

The drugs that have been discussed above are all effective or interesting drug candidates for influenza intervention and therapy. However, they all target different parts of the influenza infection cycle, rendering them susceptible for resistance development. This together with the constant threat of influenza epidemics and pandemics of various origins underscores the need for drugs that would be persistently effective against influenza in the future. A novel approach for treating influenza may be the use of innate defence regulators that can swing the host immune response towards a greater proinflammatory or anti-inflammatory route since the immune system plays a large role in an influenza infection. The benefit of using immunomodulators for antiviral intervention, overcomes the problem of resistance as these types of drugs target the host cells instead of the rapidly mutating viruses. Thus, it might be advantageous to explore the possibility of using host defence peptides or derivatives thereof in the prophylaxis and treatment of influenza.

Though the majority of the initial peptide drug candidates either failed approval by U.S. Food and Drug Administration or got terminated due to lack of efficacy, there is a growing body of evidence supporting their potential as therapeutic drugs targeting a variety of microbial- and immune-related disorders. However, there are still several strongest arguments against drug development around a peptide scaffold, one being the high cost of goods. By moving from traditional solid-phase synthesis to solution-phase- and hybrid methodologies, the cost of goods can easily be reduced, thereby alleviating the problem to some extent. Roche and Trimeris joint success in producing Enfuvirtide (Fuzeon, T-20), a 36 amino acid peptide that interacts with the HIV glycoprotein gp41 to block viral entry into CD4+ T-cells, is a great example that even large peptides can succeed in the clinic. Enfuvirtide is currently being produced by solid- and solution-phase hybrid synthesis at a level of 3.7 metric tons annually (in 2005) and is used as the drug of last resort for treatment of drug resistant HIV (Andersson et al., 2000; Schneider et al., 2005). From a drug development point of view there was (a decade ago) some truth in the high expense and complexity of generating peptide libraries, compared to small molecule libraries, but development of new synthesis strategies have revolutionized the way scientists look at peptide libraries, making them affordable even for small-size academic labs (Hilpert et al., 2005; Winkler et al., 2009).

Computer hardware has gone through an even more rapid evolution over the past decades, increasing the computing power of a standard machine significantly, thus making chemoinformatics and computer-aided drug design more mainstream. Computational simulations and prediction models make use of chemical descriptors describing the biochemical and physical characteristics of a molecule. These models were originally restrained to small molecules, but through the development of new descriptors and the assistance of stellar processing capacity, robust and precise prediction models can now also be constructed for peptide molecules (Cherkasov et al., 2009; Fjell et al., 2009; Jenssen et al., 2008; Jenssen et al., 2006a; Jenssen et al., 2007). Peptides, as drugs, have also been faced with scepticism regarding their poor pharmacokinetic properties, short half-life and lack of oral bioavailability (Chatterjee et al., 2008). However formulation technologies and/or chemical modification (e.g. N-methylation) may significantly improve the peptides' pharmacokinetic profile. Multiple N-methylations has been demonstrated to significantly improve the oral bioavailability, metabolic stability and intestinal permeability of peptides (e.g. Veber-Hirschmann- and α-IIb-β3 intergrin-analogues) (Biron et al., 2008; Chatterjee et al., 2008). Pegylation of interferon-α for chronic hepatitis C virus treatment has prolonged the retention time of the drug in the body and so demonstrates that it is possible to improve circulation half-life of peptide drugs (Barnard, 2001). Advances in formulation and delivery systems, e.g. implantable scaffolds, hydrogels and micro- or nano- particle systems will also help expedite the progression of peptide drugs into clinical use (Kobsa and Saltzman, 2008).

An advantage for peptide drugs are their tolerability and relatively low toxic potential as a result of their susceptibility for proteolytic degradation. One may argue that this, in general, is a negative feature of peptide drugs. However, results indicate that the responses they trigger are so rapid that sufficient protection

can be initiated prior to protease cleavage. A good example is the innate defence regulator-1 (IDR-1), an anti-infective peptide that selectively modulates the innate immune response (Figure 2) (Scott et al., 2007). The peptide, by itself, has no direct antibacterial activity in vitro. However, it demonstrates significant protection in an invasive murine S. aureus model even when administered 24 hours prior to bacterial challenge, indicating that it triggers a long lasting immunity (Scott et al., 2007). A 5-mer derivative of IDR-1 (IMX942) has been developed by Inimex Pharmaceuticals (http://www.inimexpharma.com/) and is showing promising results in the current Phase I safety testing in healthy volunteers. This success also demonstrates that although peptide drugs (Figure 2) originally were viewed as much larger chemical structures than the small molecule drugs (Figure 1), the current size difference is less obvious.

In a typical influenza infection, the non-structural protein 1 is able to interfere with the host immune system by preventing efficient type I interferon production (Fernandez-Sesma et al., 2006). Thus, the immune responses are suppressed and the proinflammatory response must be boosted in order to facilitate clearance of the virus. The idea of boosting the immune system has been visited previously with attempts at administering interferon intranasally for prophylaxis of influenza A infections, but this was not very effective (Isomura et al., 1982; Phillpotts et al., 1984). The recent success of pegylated interferon-α with ribavirin treatment for hepatitis C virus infections (Palumbo, 2009) has revitalized the possibility of using immunomodulation as a form of influenza therapy and it has even been suggested that the combined ribavirin and pegylated interferon-α therapy has a possible applicability in influenza infections. There are also many other hepatitis C virus drugs in clinical trials that exert immunomodulatory effects that could possibly be used against influenza such as a di-peptide, IM862 (Implicit Bioscience; www.implicitbioscience.com), isolated from the calf thymic peptide complex Thymalin (Anisimov et al., 2000) and a synthetic derivative of IM862, SCV-07 (SciClone;). Both drugs are currently in Phase II clinical trials and have demonstrated the ability to stimulate the production of immune cells and trigger a T_h1 response assisting in resolving the hepatitis C virus infections (Figure 2) (Orellana, 2002; Tulpule et al., 2000). SCV-07 has also demonstrated significant reduction of recurrent lesions when administered orally in a guinea pig model of recurrent genital herpes simplex virus 2 (Rose et al., 2008), indicating the broad spectrum activity and immune modulation potential of these peptide drugs.

Due to the effectiveness of HIV and Mycobacterium tuberculosis combination therapies, there have been studies examining different combinations of antiviral drugs that could potentially be used in influenza infection. For example, in a study combining rimantadine and different neuraminidase inhibitors, synergistic and additive effects were observed at specific concentrations and combinations of the drugs (Govorkova et al., 2004). Immunomodulators could also potentially be used in combination with the conventional influenza antivirals as a supplement that would not only facilitate more efficient elimination of the virus, but also decrease the severity of the symptoms that manifest in infected patients. Further study is obviously warranted to determine whether such combined therapy truly is applicable for influenza infections. This approach may also be valuable in a pandemic situation where several of the conventional influenza drugs can experience reduced efficacy.

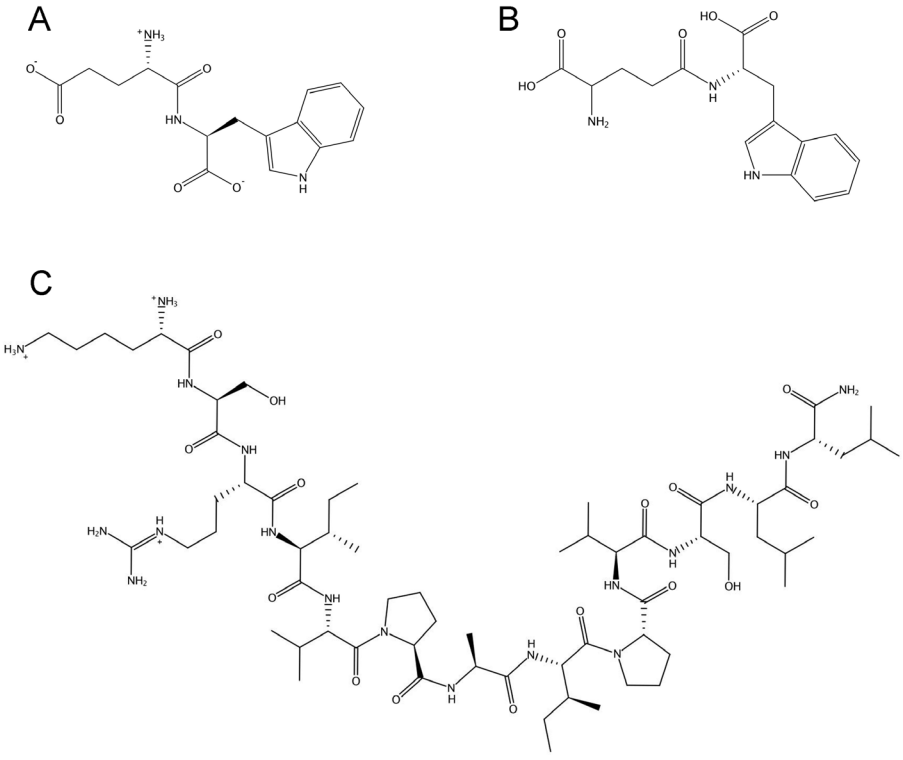

Figure 2: Selected peptides in clinical trails; (A) IM862, **(B)** SCV-07 and **(C)** IDR-1.

Conclusion

Influenza research has been a hot topic for the past decade, fuelled by the imminent public fear of a pandemic. We are starting to see the fruits of this focused research; novel drug candidates are being pursued and more detailed understandings of the immunological responses to influenza are being drawn up. However, fear as a motivator is dangerous in itself, as the general public rapidly will adapt and over time show decreasing interest to the problem at hand. Let us hope some of the enthusiasm in this field can progress and outlive the focused attention from the public media on this topic, thus leading to a diverse mix of influenza treatment strategies. Development of small molecules and peptide drugs targeting viral infections are now, more than ever, an innovative and very interesting strategy that if pursued with research and adaptation of new technology platforms, may one day bear significant fruits.

References

1. Andersson L, Blomberg L, Flegel M, Lepsa L, Nilsson B, et al. (2000) Large-scale synthesis of peptides. Biopolymers 55: 227-250. » CrossRef » PubMed » Google Scholar

2. Anisimov VN, Khavinson VK, Morozov VG (2000) Immunomodulatory synthetic dipeptide L-Glu-L-Trp slows down aging and inhibits spontaneous carcinogenesis in rats. Biogerontology 1: 55-59. » CrossRef » PubMed » Google Scholar

3. Bantia S, Arnold CS, Parker CD, Upshaw R, Chand P (2006) Anti-influenza virus activity of peramivir in mice with single intramuscular injection. Antiviral Res 69: 39-45. » CrossRef » PubMed » Google Scholar

4. Bantia S, Parker CD, Ananth SL, Horn LL, Andries K, et al. (2001) Comparison of the anti-influenza virus activity of RWJ-270201 with those of oseltamivir and zanamivir. Antimicrob Agents Chemother 45: 1162-1167. » CrossRef » PubMed » Google Scholar

5. Barnard DL (2001) Pegasys (Hoffmann-La Roche). Curr Opin Investig Drugs 2: 1530-1538. » PubMed » Google Scholar

6. Barroso L, Treanor J, Gubareva L, Hayden FG (2005) Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. Antivir Ther 10: 901-910. » CrossRef » PubMed » Google Scholar

7. Beigel JH, Farrar J, Han AM, Hayden FG, Hyer R, et al. (2005) Avian influenza A (H5N1) infection in humans. N Engl J Med 353: 1374-1385. » CrossRef » PubMed » Google Scholar

8. Belser JA, Bridges CB, Katz JM, Tumpey TM (2009) Past, present, and possible future human infection with influenza virus A subtype H7. Emerg Infect Dis 15: 859-865. » CrossRef » PubMed » Google Scholar

9. Belser JA, Lu X, Szretter KJ, Jin X, Aschenbrenner LM, et al. (2007) DAS181, a novel sialidase fusion protein, protects mice from lethal avian influenza H5N1 virus infection. J Infect Dis 196: 1493-1499. » CrossRef » PubMed » Google Scholar

10. Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, et al. (2007) Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med 356: 685-696. » CrossRef » PubMed » Google Scholar

11. Biron E, Chatterjee J, Ovadia O, Langenegger D, Brueggen J, et al. (2008) Improving oral bioavailability of peptides by multiple N-methylation: somatostatin analogues. Angew Chem Int Ed Eng l47: 2595-2599. » CrossRef » PubMed » Google Scholar

12. Boon AC, Webby RJ (2009) Antigenic cross-reactivity among H5N1 viruses. Curr Top Microbiol Immunol 333: 25-40. » CrossRef » PubMed » Google Scholar

13. Cameron KR, Gregory V, Banks J, Brown IH, Alexander DJ, et al. (2000) H9N2 subtype influenza A viruses in poultry in pakistan are closely related to the H9N2 viruses responsible for human infection in Hong Kong. Virology 278: 36-41. » CrossRef » PubMed » Google Scholar

14. Cauthen AN, Swayne DE, Schultz-Cherry S, Perdue ML, Suarez DL (2000) Continued circulation in China of highly pathogenic avian influenza viruses encoding the hemagglutinin gene associated with the 1997 H5N1 outbreak in poultry and humans. J Viro l74: 6592-6599. » CrossRef » PubMed » Google Scholar

15. Chand P, Bantia S, Kotian PL, El-Kattan Y, Lin TH, et al. (2005) Comparison of the anti-influenza virus activity of cyclopentane derivatives with oseltamivir and zanamivir in vivo. Bioorg Med Chem 13: 4071-4077. » CrossRef » PubMed » Google Scholar

16. Chatterjee J, Gilon C, Hoffman A, Kessler H (2008) N-methylation of peptides: a new perspective in medicinal chemistry. Acc Chem Res 41: 1331-1342. » CrossRef » PubMed » Google Scholar

17. Chen GL, Subbarao K (2009) Live attenuated vaccines for pandemic influenza. Curr Top Microbiol Immunol 333: 109-132. » CrossRef » PubMed » Google Scholar

18. Cherkasov A, Hilpert K, Jenssen H, Fjell CD, Waldbrook M, et al. (2009) Use of artificial intelligence in the design of small peptide antibiotics effective against a broad spectrum of highly antibiotic-resistant superbugs. ACS Chem Biol 4: 65-74. » CrossRef » PubMed » Google Scholar

19. Cheung CY, Poon LL, Lau AS, Luk W, Lau YL, et al. (2002) Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease. Lancet 360: 1831-1837. » CrossRef » PubMed » Google Scholar

20. Christmann-Franck S, Bertrand HO, Goupil-Lamy A, der Garabedian PA, Mauffret O, et al. (2004) Structure-based virtual screening: an application to human topoisomerase II alpha. J Med Chem 47: 6840-6853. » CrossRef » PubMed » Google Scholar

21. Cohen A, Togo Y, Khakoo R, Waldman R, Sigel M (1976) Comparative clinical and laboratory evaluation of the prophylactic capacity of ribavirin, amantadine hydrochloride, and placebo in induced human influenza type A. J Infect Dis 133: A114-120. » CrossRef » PubMed » Google Scholar

22. Davies WL, Grunert RR, Haff RF, McGahen JW, Neumayer EM, et al. (1964) Antiviral Activity Of 1-Adamantanamine (Amantadine). Science 144: 862-863. » CrossRef » PubMed » Google Scholar

23. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, et al. (2009) Emergence of a novel swine-origin influenza A

(H1N1) virus in humans. N Engl J Med 360: 2605-2615. » CrossRef » PubMed

24. de Boer GF, Back W, Osterhaus AD (1990) An ELISA for detection of antibodies against influenza A nucleoprotein in humans and various animal species. Arch Virol 115: 47-61. » CrossRef » PubMed » Google Scholar
25. de Jong JC, Claas EC, Osterhaus AD, Webster RG, Lim WL (1997) A pandemic warning. Nature 389: 554. » CrossRef » PubMed » Google Scholar
26. Eggleston M (1987) Clinical review of ribavirin. Infect Control 8: 215-218. » CrossRef » PubMed » Google Scholar
27. Englund JA, Champlin RE, Wyde PR, Kantarjian H, Atmar RL, et al. (1998) Common emergence of amantadine- and rimantadine-resistant influenza A viruses in symptomatic immunocompromised adults. Clin Infect Dis 26: 1418-1424. » CrossRef » PubMed » Google Scholar
28. Fernandez-Sesma A, Marukian S, Ebersole BJ, Kaminski D, Park MS, et al. (2006) Influenza virus evades innate and adaptive immunity via the NS1 protein. J Virol 80: 6295-6304. » CrossRef » PubMed » Google Scholar
29. Fiore AE, Bridges CB, Cox NJ (2009) Seasonal influenza vaccines. Curr Top Microbiol Immunol 333: 43-82. » CrossRef » PubMed » Google Scholar
30. Fjell CD, Jenssen H, Hilpert K, Cheung WA, Pante N, et al. (2009) Identification of novel antibacterial peptides by chemoinformatics and machine learning. J Med Chem 52: 2006-2015. » CrossRef » PubMed » Google Scholar
31. Fouchier RA, Munster V, Wallensten A, Bestebroer TM, Herfst S, et al. (2005) Characterization of a novel influenza A virus hemagglutinin subtype (H16) obtained from black-headed gulls. J Virol 79: 2814-2822. » CrossRef » PubMed » Google Scholar
32. Fouchier RA, Osterhaus AD, Brown IH (2003) Animal influenza virus surveillance. Vaccine 21: 1754-1757. » CrossRef » PubMed » Google Scholar
33. Fouchier RA, Schneeberger PM, Rozendaal FW, Broekman JM, Kemink SA, et al. (2004) Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. Proc Natl Acad Sci USA 101: 1356-1361. » CrossRef » PubMed » Google Scholar
34. Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van Kerkhove MD, et al. (2009) Pandemic potential of a strain of influenza A (H1N1): early findings. Science 324: 1557-1561. » CrossRef » PubMed » Google Scholar
35. Furuta Y, Takahashi K, Fukuda Y, Kuno M, Kamiyama T, et al. (2002) In vitro and in vivo activities of anti-influenza virus compound T-705. Antimicrob Agents Chemother 46: 977-981. » CrossRef » PubMed » Google Scholar
36. Furuta Y, Takahashi K, Kuno-Maekawa M, Sangawa H, Uehara S, et al. (2005) Mechanism of action of T-705 against influenza virus. Antimicrob Agents Chemother 49: 981-986. » CrossRef » PubMed » Google Scholar
37. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, et al. (2009) T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections. Antiviral Res 82: 95-102. » CrossRef » PubMed » Google Scholar
38. Govorkova EA, Fang HB, Tan M, Webster RG (2004) Neuraminidase inhibitor-rimantadine combinations exert additive and synergistic anti-influenza virus effects in MDCK cells. Antimicrob Agents Chemother 48: 4855-4863. » CrossRef » PubMed » Google Scholar
39. Govorkova EA, Leneva IA, Goloubeva OG, Bush K, Webster RG (2001) Comparison of efficacies of RWJ-270201, zanamivir, and oseltamivir against H5N1, H9N2, and other avian influenza viruses. Antimicrob Agents Chemother 45: 2723-2732. » CrossRef » PubMed » Google Scholar
40. Hamill P, Brown K, Jenssen H, Hancock RE (2008) Novel anti-infectives: is host defence the answer. Curr Opin Biotechnol 19: 628-636. » CrossRef » PubMed » Google Scholar
41. Hancock RE (2001) Cationic peptides: effectors in innate immunity and novel antimicrobials. Lancet Infect Dis 1: 156-164. » CrossRef » PubMed » Google Scholar
42. Hancock RE, Sahl HG (2006) Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat Biotechnol 24: 1551-1557. » CrossRef » PubMed » Google Scholar
43. Hassid S, Choufani G, Nagy N, Kaltner H, Danguy A, et al. (1999) Quantitative glycohistochemical characterization of normal nasal mucosa, and of single as opposed to massive nasal polyps. Ann Otol Rhinol Laryngol 108: 797-805. » CrossRef » PubMed » Google Scholar
44. Hayden FG (2006) Antiviral resistance in influenza viruses—implications for management and pandemic response. N Engl J Med 354: 785-788. » CrossRef » PubMed » Google Scholar
45. Herrera GA, Iwane MK, Cortese M, Brown C, Gershman K, et al. (2007) Influenza vaccine effectiveness among 50-64-year-old persons during a season of poor antigenic match between vaccine and circulating influenza virus strains: Colorado, United States, 2003-2004. Vaccine 25: 154-160. » CrossRef » PubMed » Google Scholar
46. Hilpert K, Volkmer-Engert R, Walter T, Hancock RE (2005) High-throughput generation of small antibacterial peptides with improved activity. Nat Biotechnol 23: 1008-1012. » CrossRef » PubMed » Google Scholar
47. Hirst M, Astell CR, Griffith M, Coughlin SM, Moksa M, et al. (2004) Novel avian influenza H7N3 strain outbreak, British Columbia. Emerg Infect Dis 10: 2192-2195. » CrossRef » PubMed » Google Scholar
48. Hoffmann E, Krauss S, Perez D, Webby R, Webster RG (2002a) Eight-plasmid system for rapid generation of influenza virus vaccines. Vaccine 20: 3165-3170. » CrossRef » PubMed » Google Scholar
49. Hoffmann E, Mahmood K, Yang CF, Webster RG, Greenberg HB, et al. (2002b) Rescue of influenza B virus from eight plasmids. Proc Natl Acad Sci USA 99: 11411-11416. » CrossRef » Google Scholar
50. Horimoto T, Kawaoka Y (2005) Influenza: lessons from past pandemics, warnings from current incidents. Nat Rev Microbiol 3: 591-600. » CrossRef » PubMed » Google Scholar
51. Hossain MJ, Hickman D, Perez DR (2008) Evidence of expanded host range and mammalian-associated genetic changes in a duck H9N2 influenza virus following adaptation in quail and chickens. PLoS One 3: e3170. » CrossRef » PubMed » Google Scholar
52. Isomura S, Ichikawa T, Miyazu M, Naruse H, Shibata M, et al. (1982) The preventive effect of human interferon-alpha

on influenza infection; modification of clinical manifestations of influenza in children in a closed community. Biken J 25: 131-137. » PubMed » Google Scholar

53. Ito T (2000) Interspecies transmission and receptor recognition of influenza A viruses. Microbiol Immunol 44: 423-430. » CrossRef » PubMed » Google Scholar

54. Jenssen H, Fjell CD, Cherkasov A, Hancock RE (2008) QSAR modeling and computer-aided design of antimicrobial peptides. J Pept Sci 14: 110-114. » CrossRef » PubMed » Google Scholar

55. Jenssen H, Gutteberg TJ, Rekdal O, Lejon T (2006a) Prediction of activity, synthesis and biological testing of anti-HSV active peptides. Chem Biol Drug Des 68: 58-66. » CrossRef » PubMed » Google Scholar

56. Jenssen H, Hamill P, Hancock RE (2006b) Peptide antimicrobial agents. Clin Microbiol Rev 19: 491-511. » CrossRef » PubMed » Google Scholar

57. Jenssen H, Lejon T, Hilpert K, Fjell CD, Cherkasov A, et al. (2007) Evaluating different descriptors for model design of antimicrobial peptides with enhanced activity toward P. aeruginosa. Chem Biol Drug Des 70: 134-142. » CrossRef » PubMed » Google Scholar

58. Julkunen I, Melen K, Nyqvist M, Pirhonen J, Sareneva T, et al. (2000) Inflammatory responses in influenza A virus infection. Vaccine 19: S32-37. » CrossRef » PubMed » Google Scholar

59. Julkunen I, Sareneva T, Pirhonen J, Ronni T, Melen K, et al. (2001) Molecular pathogenesis of influenza A virus infection and virus-induced regulation of cytokine gene expression. Cytokine Growth Factor Rev 12: 171-180. » CrossRef » PubMed » Google Scholar

60. Kanzler H, Barrat FJ, Hessel EM, Coffman RL (2007) Therapeutic targeting of innate immunity with Toll-like receptor agonists and antagonists. Nat Med 13: 552-559. » CrossRef » PubMed » Google Scholar

61. Kaufmann A, Salentin R, Meyer RG, Bussfeld D, Pauligk C, et al. (2001) Defense against influenza A virus infection: essential role of the chemokine system. Immunobiology 204: 603-613. » CrossRef » PubMed » Google Scholar

62. Khiabanian H, Trifonov V, Rabadan R (2009) Reassortment patterns in Swine influenza viruses. PLoS One 4: e7366. » CrossRef » PubMed

63. Kim CU, Lew W, Williams MA, Liu H, Zhang L, et al. (1997) Influenza neuraminidase inhibitors possessing a novel hydrophobic interaction in the enzyme active site: design, synthesis, and structural analysis of carbocyclic sialic acid analogues with potent anti-influenza activity. J Am Chem Soc 119: 681-690. » CrossRef » PubMed » Google Scholar

64. Kobsa S, Saltzman WM (2008) Bioengineering approaches to controlled protein delivery. Pediatr Res 63: 513-519. » CrossRef » PubMed » Google Scholar

65. Lai Y, Gallo RL (2008) Toll-like receptors in skin infections and inflammatory diseases. Infect Disord Drug Targets 8: 144-155. » PubMed » Google Scholar

66. Leroux-Roels I, Bernhard R, Gerard P, Drame M, Hanon E, et al. (2008) Broad Clade 2 cross-reactive immunity induced by an adjuvanted clade 1 rH5N1 pandemic influenza vaccine. PLoS One 3: e1665. » CrossRef » PubMed » Google Scholar

67. Leroux-Roels I, Borkowski A, Vanwolleghem T, Drame M, Clement F, et al. (2007) Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. Lancet 370: 580-589. » CrossRef » PubMed » Google Scholar

68. Lin YP, Shaw M, Gregory V, Cameron K, Lim W, et al. (2000) Avian-to-human transmission of H9N2 subtype influenza A viruses: relationship between H9N2 and H5N1 human isolates. Proc Natl Acad Sci USA 97: 9654-9658. » PubMed » Google Scholar

69. Malakhov MP, Aschenbrenner LM, Smee DF, Wandersee MK, Sidwell RW, et al. (2006) Sialidase fusion protein as a novel broad-spectrum inhibitor of influenza virus infection. Antimicrob Agents Chemother 50: 1470-1479. » PubMed » Google Scholar

70. Matrosovich MN, Matrosovich TY, Gray T, Roberts NA, Klenk HD (2004) Human and avian influenza viruses target different cell types in cultures of human airway epithelium. Proc Natl Acad Sci USA 101: 4620-4624. » CrossRef » PubMed » Google Scholar

71. Mishin VP, Hayden FG, Gubareva LV (2005) Susceptibilities of antiviral-resistant influenza viruses to novel neuraminidase inhibitors. Antimicrob Agents Chemother 49: 4515-4520. » CrossRef » PubMed » Google Scholar

72. Mizutani MY, Itai A (2004) Efficient method for high-throughput virtual screening based on flexible docking: discovery of novel acetylcholinesterase inhibitors. J Med Chem 47: 4818-4828. » CrossRef » PubMed » Google Scholar

73. Moscona A (2005a) Neuraminidase inhibitors for influenza. N Engl J Med 353: 1363-1373. » CrossRef » PubMed » Google Scholar

74. Moscona A (2005b) Oseltamivir resistance—disabling our influenza defenses. N Engl J Med 353: 2633-2636. » CrossRef » PubMed » Google Scholar

75. Neumann G, Noda T, Kawaoka Y (2009) Emergence and pandemic potential of swine-origin H1N1 influenza virus. Nature 459: 931-939. » CrossRef » PubMed » Google Scholar

76. Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E (2007) Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med 357: 1373-1381. » CrossRef » PubMed » Google Scholar

77. O'Neill E, Donis RO (2009) Generation and characterization of candidate vaccine viruses for prepandemic influenza vaccines. Curr Top Microbiol Immunol 333: 83-108. » CrossRef » PubMed » Google Scholar

78. O'Neill LA (2006) Targeting signal transduction as a strategy to treat inflammatory diseases. Nat Rev Drug Discov 5: 549-563. » CrossRef » PubMed » Google Scholar

79. Oppenheim JJ, Yang D (2005) Alarmins: chemotactic activators of immune responses. Curr Opin Immunol 17: 359-365. » CrossRef » PubMed » Google Scholar

80. Orellana C (2002) Immune system stimulator shows promise against tuberculosis. Lancet Infect Dis 2: 711. » CrossRef » PubMed » Google Scholar

81. Palumbo E (2009) Peg-Interferon in Acute and Chronic Hepatitis C: A Review. Am J Ther. » CrossRef » PubMed » Google Scholar

82. Peiris JS, Poon LL, Guan Y (2009) Emergence of a novel

swine-origin influenza A virus (S-OIV) H1N1 virus in humans. J Clin Virol 45: 169-173. » CrossRef » PubMed » Google Scholar

83. Phillpotts RJ, Higgins PG, Willman JS, Tyrrell DA, Freestone DS, et al. (1984) Intranasal lymphoblastoid interferon ("Wellferon") prophylaxis against rhinovirus and influenza virus in volunteers. J Interferon Res 4: 535-541. » CrossRef » PubMed » Google Scholar

84. Piedra PA, Gaglani MJ, Kozinetz CA, Herschler GB, Fewlass C, et al. (2007) Trivalent live attenuated intranasal influenza vaccine administered during the 2003-2004 influenza type A (H3N2) outbreak provided immediate, direct, and indirect protection in children. Pediatrics 120: e553-564. » CrossRef » PubMed » Google Scholar

85. Reid AH, Fanning TG, Janczewski TA, Lourens RM, Taubenberger JK (2004) Novel origin of the 1918 pandemic influenza virus nucleoprotein gene. J Virol 78: 12462-12470. » CrossRef » PubMed » Google Scholar

86. Rodriguez WJ, Hall CB, Welliver R, Simoes EA, Ryan ME, et al. (1994) Efficacy and safety of aerosolized ribavirin in young children hospitalized with influenza: a double-blind, multicenter, placebo-controlled trial. J Pediatr 125: 129-135. » CrossRef » PubMed » Google Scholar

87. Romagne F (2007) Current and future drugs targeting one class of innate immunity receptors: the Toll-like receptors. Drug Discov Today 12: 80-87. » CrossRef » PubMed » Google Scholar

88. Rose WA 2nd, Tuthill C, Pyles RB (2008) An immunomodulating dipeptide, SCV-07, is a potential therapeutic for recurrent genital herpes simplex virus type 2 (HSV-2). Int J Antimicrob Agents 32: 262-266. » CrossRef » PubMed » Google Scholar

89. Sansom MS, Kerr ID (1993) Influenza virus M2 protein: a molecular modelling study of the ion channel. Protein Eng 6: 65-74. » CrossRef » PubMed » Google Scholar

90. Schneider SE, Bray BL, Mader CJ, Friedrich PE, Anderson MW, et al. (2005) Development of HIV fusion inhibitors. J Pept Sci 11: 744-753. » CrossRef » PubMed » Google Scholar

91. Schnitzler SU, Schnitzler P (2009) An update on swine-origin influenza virus A/H1N1: a review. Virus Genes. » CrossRef » PubMed » Google Scholar

92. Scott MG, Dullaghan E, Mookherjee N, Glavas N, Waldbrook M, et al. (2007) An anti-infective peptide that selectively modulates the innate immune response. Nat Biotechnol 25: 465-472. » CrossRef » PubMed » Google Scholar

93. Seo SH, Hoffmann E, Webster RG (2002) Lethal H5N1 influenza viruses escape host anti-viral cytokine responses. Nat Med 8: 950-954. » CrossRef » PubMed » Google Scholar

94. Shinde V, Bridges CB, Uyeki TM, Shu B, Balish A, et al. (2009) Triple-reassortant swine influenza A (H1) in humans in the United States, 2005-2009. N Engl J Med 360: 2616-2625. » CrossRef » PubMed » Google Scholar

95. Sidwell RW, Bailey KW, Wong MH, Barnard DL, Smee DF (2005) In vitro and in vivo influenza virus-inhibitory effects of viramidine. Antiviral Res 68: 10-17. » CrossRef » PubMed » Google Scholar

96. Sidwell RW, Barnard DL, Day CW, Smee DF, Bailey KW, et al. (2007) Efficacy of orally administered T-705 on lethal avian influenza A (H5N1) virus infections in mice. Antimicrob Agents Chemother 51: 845-851. » CrossRef » PubMed » Google Scholar

97. Smith CB, Charette RP, Fox JP, Cooney MK, Hall CE (1980) Lack of effect of oral ribavirin in naturally occurring influenza A virus (H1N1) infection. J Infect Dis 141: 548-554. » CrossRef » PubMed » Google Scholar

98. Steindl T, Langer T (2004) Influenza virus neuraminidase inhibitors: generation and comparison of structure-based and common feature pharmacophore hypotheses and their application in virtual screening. J Chem Inf Comput Sci 44: 1849-1856. » CrossRef » PubMed » Google Scholar

99. Suzuki Y (2005) Sialobiology of influenza: molecular mechanism of host range variation of influenza viruses. Biol Pharm Bull 28: 399-408. » CrossRef » PubMed » Google Scholar

100. Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wolff M (2006) Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. N Engl J Med 354: 1343-1351. » CrossRef » PubMed » Google Scholar

101. Trifonov V, Khiabanian H, Greenbaum B, Rabadan R (2009) The origin of the recent swine influenza A(H1N1) virus infecting humans. Euro Surveill 14. » CrossRef » PubMed » Google Scholar

102. Tulpule A, Scadden DT, Espina BM, Cabriales S, Howard W, et al. (2000) Results of a randomized study of IM862 nasal solution in the treatment of AIDS-related Kaposi's sarcoma. J Clin Oncol 18: 716-723. » CrossRef » PubMed » Google Scholar

103. Uyeki TM, Chong YH, Katz JM, Lim W, Ho YY, et al. (2002) Lack of evidence for human-to-human transmission of avian influenza A (H9N2) viruses in Hong Kong, China 1999. Emerg Infect Dis 8: 154-159. » CrossRef » PubMed » Google Scholar

104. von Itzstein M, Wu WY, Kok GB, Pegg MS, Dyason JC, et al. (1993) Rational design of potent sialidase-based inhibitors of influenza virus replication. Nature 363: 418-423. » CrossRef » PubMed » Google Scholar

105. Wales J, Andreakos E, Feldmann M, Foxwell B (2007) Targeting intracellular mediators of pattern-recognition receptor signalling to adjuvant vaccination. Biochem Soc Trans 35: 1501-1503. » CrossRef » PubMed » Google Scholar

106. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y (1992) Evolution and ecology of influenza A viruses. Microbiol Rev 56: 152-179. » CrossRef » PubMed » Google Scholar

107. Winkler DF, Hilpert K, Brandt O, Hancock RE (2009) Synthesis of Peptide Arrays Using SPOT-Technology and the CelluSpots-Method. Methods Mol Biol 570: 157-174. » CrossRef » PubMed » Google Scholar

108. Yen HL, Webster RG (2009) Pandemic influenza as a current threat. Curr Top Microbiol Immunol 333: 3-24. » CrossRef » PubMed » Google Scholar

109. Zasloff M (2002) Antimicrobial peptides of multicellular organisms. Nature 415: 389-395. » CrossRef » PubMed » Google Scholar

110. Zurcher T, Yates PJ, Daly J, Sahasrabudhe A, Walters M, et al. (2006) Mutations conferring zanamivir resistance in human influenza virus N2 neuraminidases compromise virus fitness and are not stably maintained in vitro. J Antimicrob Chemother 58: 723-732. » CrossRef » PubMed » Google Scholar