Combatting the Global Threat of Antimicrobial Resistance and Antiviral Deficiencies

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Abstract: This report presents the conceptualization and development of site attachment inhibition (or, negation of cellular attachment by infective agents). Site attachment inhibition therapeutics will likely involve drug (medication) based therapies in addition to stem cell based treatment. The current researcher has presented site attachment inhibition at 6th International Conference on Immunology (USA; Chicago IL 870th Congress 2016) and invitation has been received for subsequent conference and dissemination proceedings internationally (including UAE).

Keywords: Antimicrobial; Bacteria; CCR5-Δ32; Covalent Bonds; Glycoprotein; Microorganism; Resistance; Virus.

1. Introduction

The purpose of this report is to delineate the current global position in respect of combating the world threat represented by infectious disease including antimicrobial resistance, the presence of metaphorical superbugs, and deficiencies in successful antiviral therapies [1-3]. The report summarizes in an efficient manner the two traditional key mode of action pathways for combating infective agents utilized to date and, following this, the report then details the new, or third, mode of action pathway for combating infective agents conceptualized and developed by the current researcher. The report also considers delivery mechanisms for each of the antimicrobial pathways, in addition to further areas for research.

2. Mode of action pathways for antimicrobial therapies

The two traditional antimicrobial mode of action pathways established to date have focused on: 1) negating the replication of the infective agents; and, 2) immune system enhancement [1-2, 4-7]. The threat of antimicrobial resistance, metaphorical superbugs, and antiviral deficiencies is significant, with World Health Organization (WHO) having engaged directed conference proceedings with regards to the issue [3]. Given the current two pathways are failing to adequately deal with the situation, the current author has conceptualized and developed, in recent publications of IJSBAR presented at 6th International Conference on Immunology (USA; Chicago IL 870th Congress 2016), the new mode of action pathway represented by “site attachment inhibition (or, negation of cellular attachment by infective agents).”

In brief, the theory, conceptualization, development and proposed application of the new mode of action pathway represented by site attachment inhibition (or, negation of cellular attachment by infective agents) is as follows directly below, with focus commencing on viruses then moving through to bacteria.

Viral Infections: the conceptualization and development of site attachment inhibition

Report 1 IJSBAR by the current author identified the following key problematic issues: A) The lack of successful antiviral drugs (therapies) despite many years of pursuit; B) No cure for Human Immunodeficiency Virus (HIV) despite many years of exploration [1-2]. The pathways to combat HIV and other viruses to date: 1) virus replication; 2) enhancement of immune function [1-2, 4-7]. Given the lack of success achieved by these two pathways, the conceptualization and development of the new strategic pathway for antiviral therapies represented by “site attachment inhibition (or, negation of cellular attachment by viruses)” was delineated [1-2, 8]. Further to this, HIV was used in case analysis with strategic measures detailed including prenatal genetic therapy focusing on mutagenesis and knockout, targeted at genes (receptors; and, surface proteins) including CCR5 and CXCR4, as a means of achieving innate resistance (immunity) similar to the known CCR5-Δ32 mutation, in addition to treatment strategy following established infection designed to block attachment of the virus to CCR5 and CXCR4, including antagonism or blockade of the receptors (analogous to beta blockade), stem cell therapy, radiation, and targeted therapy designed to attack the mechanisms of the virus in its attachment ability to the given receptors (CCR5, CXCR4) and any other relevant. Support for site attachment inhibition strategy was further consolidated through...
consideration with respect to advanced information technology in which one key mechanism for virus removal is represented by negation of site attachment.

Further to the above, exploration of stem cell therapy potential should span right back to earlier stages including spermatogenesis and oogenesis.

The evidence in support of the scientific sense and potential success of site attachment inhibition in respect of viral infections:

1. The known innate resistance achieved by CCR5-Δ32 mutation.
2. The immune system coats infective agents as a method of attempting to negate attachment to human cells.
3. Advanced information technology utilizes negation of site attachment as one key strategy in virus removal.

Bacterial Infections: the conceptualization and development of site attachment inhibition

Report 2 IJSBAR by the current researcher delineated analogous strategic conceptualization of site attachment inhibition for bacterial infections (or, negation of cellular attachment by bacteria). A summary of the report is as follows:

At this stage, two key fundamentals regarding site receptors:

1. The attachment by bacteria to glycoprotein receptors
2. The attachment mechanism through adhesins and formation of covalent bonds

In considering the potential support for success of this strategy:

(1) Treatment of specific blood disorders, requiring negation of platelet aggregation and thrombus formation, utilize a class of drugs (medications) termed Glycoprotein IIb/IIIa inhibitors, and it seems reasonable to suggest that inhibition, blockade or antagonism of other glycoprotein receptors would be worth pursuing as a potential pathway for treatment of bacterial infections [2].

(2) The human immune system attempts to coat infective agents as a means to negate attachment by bacteria and other infective agents to human cells, and therefore it makes scientific sense to pursue this new pathway for antibacterial development [1-2, 9].

(3) Site attachment inhibition strategy is further consolidated through consideration with respect to advanced information technology as indicated above [1-2].

This pathway regarding site attachment inhibition for bacteria may not be as robust at this stage as that for viruses presented in the previous report however, given the current global context of antibiotic resistance, definitely presents as worthy of pursuit.

3. Delivery mechanisms for antimicrobial therapies

In brief, the main delivery mechanisms for antimicrobial treatments include: oral (example, medication); topical (example, ointment); and, parental (example, intravenous administration). There are other less commonly used delivery mechanisms.

A core point here is consideration of the future given the increasing threat of antibiotic resistance, metaphorical superbugs, and deficiencies in effective (curative) antiviral drugs [1-3, 8].

There has been no successful immunization therapy or curative antiviral drugs developed for Human Immunodeficiency Virus (HIV) despite many years of pursuit [1, 8]. Similarly, Ebola Virus (EBOV), which is a Filovirus, has also gained attention as a global threat. This is in addition to a range of infective agents becoming noticed with respect to antimicrobial resistance profile.

With the above in mind, it seems reasonable to accept the need to seriously consider implementing stem cell therapy based site attachment inhibition therapy (SCT based site attachment inhibition) in the prenatal period or earlier spanning back to spermatogenesis or oogenesis. The objective being achievement of innate resistance to these infective agents analogous to the more traditional (historical) strategy of immunization. The difference between SCT based site attachment inhibition and immunization is the mode of action pathway with site attachment inhibition achieving innate immunity through negation of cellular attachment by the infective agents, and immunization achieving immunity by way of immune system enhancement.

The evidence in support of the likely success of site attachment inhibition is detailed earlier in the report and appears optimistic based on observation of innate immunity achieved by the known CCR5-Δ32 mutation.
Δ32 mutation, support from advanced IT comparison, analogous examples relating to glycoprotein antagonism and beta blockade, and the scientific sense of the proposed pathway evident in the fact that the human immune system coats infective agents as a measure to negate cellular attachment by infective agents.

Whilst it is not clear with respect to whether therapeutic SCT based site attachment inhibition of HIV would require one or both CCR5 genes to be mutated (or, knocked out), there is evidence that tends to suggest that persons born with mutation of both genes, i.e. CCR5-Δ32/Δ32, achieve the resistance to HIV without any adverse health effects to come from the mutation. It is noted that innate resistance also appears to be achieved against EBOV through mutagenesis (or, knockout), for instance NPC1 mutation [10]. However, it would appear from analyses of innate NPC1 mutation and also knockout mice that if both NPC1 genes are mutated (or, knocked out) then serious disease states revolving around that of the autosomal recessive Niemann-Pick type C disease are likely to occur. There is some research, based essentially on knockout mice, that given the autosomal recessive nature of the above condition, namely Niemann-Pick type C, it may still be possible to achieve a good degree of resistance through knockout (or, mutagenesis) of one NPC1 gene. That being said, further research must be undertaken as there have been reports of some association between conditions including adult parkinsonism and heterozygous carrier status with respect to the NPC1 gene mutation, although the evidence is not that strong at this stage [11]. Of interest is that innate resistance would seem reasonably argued as theoretically able to be achieved against Malaria through heterozygous mutagenesis (or, knockout) of genes linked to the heterozygous sickle cell state without significant adverse health effects, which is of interest given the lack of successful vaccine. Risk versus benefit analysis is discussed below.

The medical profession needs to progress and head toward the future. It would not seem unreasonable to aim for SCT based site attachment inhibition to eventually become as common as other early interventions for instance chorionic villus sampling and amniocentesis.

Mutating or deleting a number of (perhaps greater than several) genes for the purposes of achieving site attachment inhibition resistance against numerous infections is not something that should provoke particular anxiety in itself. There is research to indicate that deleting (or, inactivating) a significant number of genes presents as relatively safe [12]. The process instead is to systematically work through the likely safety profile of each proposed mutagenesis or knockout and weigh up the risks and benefits of the proposed course of management for each infection decided to be of interest.

With respect to research directed at pushing forward the area regarding SCT based site attachment inhibition, practicability issues may be present, however trials in areas such as Africa where the potential benefits may well outweigh risks would seem worthy of consideration as an initial starting point. This would seem particularly so in respect of HIV utilizing CCR5-Δ32 mutation given the likely safety profile advantages. Trials for SCT based site attachment inhibition with respect to EBOV may potentially also be worthy of consideration for high-risk areas including Africa after careful consideration of risk versus benefit analysis.

The potential for risks to be associated with SCT based site attachment inhibition are acknowledged and that with NPC1 in particular are noted above. Also noteworthy is that it would appear that, with respect to Typhoid, SCT based site attachment inhibition therapy may pose risk of induced cystic fibrosis. With that said, the potential benefit of SCT based site attachment inhibition must not be overlooked and it would appear optimistic that for various infectious diseases including HIV the safety profile may be reasonable.

4. Target Receptors

Attention must be directed toward the target receptors and the difference between association and causation must be considered carefully. Looking at mutations noticed in the human population and the innate resistance they possess to certain infections is not enough as this may simply represent association as opposed to causation. The proposed receptors linked to the innate resistance must be tested and this be done in accordance with formal evidence based medicine (EBM) principles. This would need to include the administration of Randomized Controlled Trials (RCT) in respect of the given therapeutic site attachment inhibitor treatments.

Ethics committee consideration is important.

The above said, there should be provision for progressing the laboratory and clinical research with respect to all forms of site attachment
inhibition in a speedily manner and a balance achieved between: A) Achieving fast progression in the field; and, B) Ensuring research results are supported by adherence to EBM principles (including RCT protocol).

Site attachment inhibition is intended to be explored for application to all viral and bacterial infections, in addition to other infectious organisms.

5. Areas for Future Research

Report 1 IJSBAR as a side note detailed the possible low-level consciousness of infective agents, perhaps better termed an ability to sense surroundings. There is also other research to indicate sensory abilities of infective agents including through use of ion gated channel communications [13-15]. As previously detailed, the current research may explore in future the possibility of attacking the sensory abilities of infective agents and whether this would hinder their ability to strategically evade the immune system through drift/shift measures, morphogenetic alterations and other. That being said, the current researcher anticipates that it would require more than simply attacking basics such as ion gated channel communications.

In extension of the above, it should be noted that there are also serious ethical considerations with respect to the topic of attacking infective agents by way of methods revolving around the above given it contains questions of consciousness and the author is not yet of the opinion that attack from that avenue is appropriate.

Ethics committee consideration is important.

6. Contribution to medical knowledge

This report essentially contributes completely new knowledge, conceptualization, development and understanding to the existing medical literature. Specifically, the creation, conceptualization and development of site attachment inhibition therapeutics.

7. Summary

The two traditional antimicrobial mode of action pathways established to date have focused on: 1) negating the replication of the infective agents; and, 2) immune system enhancement. The threat of antimicrobial resistance, metaphorical superbugs and antiviral deficiencies is significant, with World Health Organization (WHO) having engaged directed conference proceedings with regards to the issue. Given the current two pathways are failing to adequately deal with the situation, the current author has conceptualized and developed, in recent publications of IJSBAR presented at 6th International Conference on Immunology (USA; Chicago IL 870th Congress 2016), the new mode of action pathway represented by “site attachment inhibition (or, negation of cellular attachment by infective agents).”

The evidence in support of the likely potential for success of site attachment inhibition (or, negation of cellular attachment by infective agents):

1. The known innate immunityagainst HIV achieved by CCR5-Δ32 mutation.
2. The immune system coats infective agents as a method of attempting to negate attachment to human cells.
3. Advanced information technology utilizes negation of site attachment as one key strategy in virus removal.
4. Treatment of specific blood disorders, requiring negation of platelet aggregation and thrombus formation, utilize a class of drugs (medications) termed Glycoprotein IIb/IIIa inhibitors, and it seems reasonable to suggest that inhibition, blockade or antagonism of other glycoprotein receptors would be worth pursuing as a potential pathway for treatment of bacterial infections.
5. Other areas of medicine utilize analogous methods, for instance beta blockers which negate attachment of epinephrine and norepinephrine from attaching to beta receptors.

Delivery mechanisms would likely include drug (medication) and SCT based treatments at a minimum.

SCT site attachment inhibition is discussed in this report mainly in the context of prenatal therapy, with analogy drawn with immunization. It is planned that adult SCT site attachment inhibition will be discussed in a subsequent report.

Any clearance rate differences between site attachment inhibitor treatments (example, virus versus bacteria therapies) will be analyzed in future research.

7. Conclusion

This report presents the conceptualization and development of site attachment inhibition (or, negation of cellular attachment by infective
agents). Prior to this, there were two traditional antimicrobial mode of action pathways established: 1) negating the replication of the infective agents; and, 2) immune system enhancement. Site attachment inhibition therefore represents a new, third, mode of action pathway in respect of antimicrobial therapeutics. The current researcher has presented site attachment inhibition at 6th International Conference on Immunology (USA; Chicago IL 870th Congress 2016) and invitation has been received for subsequent conference and dissemination proceedings, including UAE.

References


McGraw-Hill: NY USA.


Biographical Data

The author (researcher) of the current report, Dr Simon Raymond MPH, is a consultant (specializing in medical and scientific research) and an Alumnus of Melbourne University (Rank of Number 1 in Australia and Number 33 in the World). The above stated researcher has acted as a reviewer for the respected Medical Journal of Australia, has received invitations internationally to review from prestigious medical journals including JAMA (Journal of American Medical Association) Network, received award in recognition of his research by Royal Australasian College of Surgeons (PSC, 2006) and invited to conferences internationally as an official delegate and researcher, including that in USA and China. Dr Simon Raymond has acted as the principle researcher in the highest powered form of medical trial—Randomized Controlled Trial (RCT). The above stated researcher is also a member of the Golden Key International Society for honoured and outstanding academics and has been cited as a notable global leader.