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A Case Analysis in Site Attachment Inhibition

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Abstract

The concern with respect to antimicrobial resistance and the associated health threat has gained increasing attention and there has been difficulty in gaining traction globally. Given the lack of success by the two pathways established to date which have focused on: 1) "replication of infective agent" and, 2) "immune system enhancement," the current researcher has conceptualized and developed the new, or third, mode of action pathway represented by *"site attachment inhibition (or, negation of cellular attachment by infective agents)."* This mode of action pathway is presented in the manuscript that follows. This publication extends on the previous literature by the current researcher (author) through presentation of the Case Example namely that of Clostridium Difficile.

Keywords

Antimicrobial; Bacteria; Glycoprotein; Infective Agent; Protease; Virus

Background

The concern with respect to antimicrobial resistance and the associated health threat has gained increasing attention and there has been difficulty in gaining traction globally [1]. Given the lack of success by the two pathways established to date which have focused on: 1) "replication of infective agent" and, 2) "immune system enhancement," the current researcher has conceptualized and developed the new, or third, mode of action pathway represented by *"site attachment inhibition (or, negation of cellular attachment by infective agents)."* The current author anticipates site attachment inhibition therapeutics to include drug (medication) based therapies, stem cell based treatment (including prenatal and earlier spanning back to spermatogenesis and oogenesis) incorporating new generation immunization methods, and waveform (E.g. electromagnetic radiation) based treatment. With respect to viruses, support for the likely success of the new mode of action pathway: A) the known CCR5-Δ32 mutation achieves resistance (immunity) against HIV through negation of cellular attachment; B) other areas of medicine use analogous receptor antagonism (E.g. beta blocker therapy); C) advanced IT uses analogous site attachment inhibition to remove viruses. With respect to bacteria, support for the likely success of the new mode of action pathway: A) advanced IT uses analogous site attachment inhibition to remove IT infections; B) glycoproteins are key proteins/receptors for attachment and, analogous to glycoprotein IIb/IIIa medications which inhibit (negate) platelet aggregation and thrombus formation, it seems reasonable to pursue antagonism or blockade of other glycoprotein receptors in order to prevent bacterial attachment to human cells (note: this is also relevant to viral infections); C) the human immune system perhaps coats infective agents in an attempt to negate cellular attachment, therefore this mode of action represented by site attachment inhibition makes scientific sense [2].

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This publication extends on the previous literature by the current researcher (author) through presentation of the Case Example namely that of Clostridium Difficile.

Case Example: Clostridium Difficile

The Case Example to be used in this publication is Clostridium Difficile. In a previous publication, HIV was used as a Case Example. In brief, with regards to HIV, for treatment of established infection, glycoprotein antagonism/inhibition (similar to above) may be a pathway of interest. For new generation immunization, mutagenesis (or, knockout) of genes related to CCR5, CXCR4 and CD4 was discussed [3]. That being said, attention must be directed toward correctly identifying the target receptors and appreciating the difference between association and causation. Looking at mutations noticed in the human population and connecting this to the innate resistance they possess to certain infections is not enough as this may simply represent association as opposed to causation. Even the known CCR5-Δ32 mutation has not been completely confirmed as direct/causative of the inhibition of attachment to (and transfer / entry into) human cellular biology by the given pathogen.

Clostridium Difficile

Clostridium Difficile attaches to (and, enters by way of) human cellular epithelium lining the gastrointestinal tract. Specifically, the relevant epithelium contains surface proteins/receptors (in the gastrointestinal tract, which clostridium difficile attaches to) including: (1) peptidases (a form of protease); (2) esterases; (3) glycoproteins. Depending on the text, peptidase can be used synonymously with protease or alternatively distinguished by way of the the polypeptides commonly cleaved.

There are protease inhibitors with respect to Mode of Action Pathway (1) replication of infective agent. With respect to *site attachment inhibition* (Mode of Action Pathway 3) protease inhibition (or, inhibition of peptidases) would be the target and this would be by way of measures including selective targeting of receptor mediated endocytosis (RME; clathrin mediated endocytosis) moderated by proteases in the plasma membrane of the human cells (gastrointestinal tract and elsewhere). This means that instead of 'replication of infective agent' being inhibited it is site attachment inhibition (or, inhibition of receptor mediated endocytosis) [4]. Note, however, there is overlap between the two methodologies.

Glycoprotein inhibition has been discussed previously. An example where selective inhibition of glycoproteins has occurred previously is with respect to glycoprotein IIb/IIIa medications which inhibit (negate) platelet aggregation and thrombus formation.

Esterases will be discussed in subsequent publications.

With regards to new generation immunization, as discussed in previous publications, relevant issues include the following:

• Selective mutagenesis or knockout of genes (including prenatal or earlier, spanning back to spermatogenesis and oogenesis) that govern relevant attachment transfer of the infective agent into the human cellular biology. New generation immunisation programs, based on site attachment inhibition, have been discussed in previous publications by the current author. There has been an increasing interest in prenatal genetic therapy. Adult genetic therapy remains of interest but poses particular difficulties.

• Analysis of innate genetic variations for guidance. For instance: CCR5-Δ32 is associated with innate immunity to HIV with the homozygous and, perhaps heterozygous variation not having been linked to any serious adverse health states; heterozygous sickle cell gene variation (AS) protects against Malaria, although homozygous variation in that regard causes sickle cell anaemia (disease state).

• Attention must be directed toward correctly identifying the target receptors and appreciating the difference between association and causation. Looking at mutations noticed in the human population and connecting this to the innate resistance they possess to certain infections is not enough as this may simply represent association as opposed to causation. Even the known CCR5-Δ32 mutation has not been completely confirmed as direct/causative of the inhibition of attachment observed in research analyses. Note: Site attachment inhibition is also able to be termed transfer inhibition.

• Ethics committee and community consideration remains important with biological and medical treatments, as outlined in previous publications. Respect for biology

should remain at the highest level as it involves; as with other entities, potential life forms [5].

Future Research

The use of site attachment inhibition to treat cancer including by way of antagonism of transmembrane glycoproteins called cell adhesion molecules, with examples of these glycoproteins including selectins, integrins, syndecans, and cadherins. Other areas relevant to cancer have been detailed in previous publications [1-6].

USA has been assisting with HIV in Africa for prehaps over fifty years, yet to date it has not had any widely accepted cases of curative success. This is the same with other countries. USA reportedly has temporarily delegated or transferred some of its program to countries including Russia but it is not clear whether this includes any of the assistance regarding Africa. Given the length of the time period USA has had without major success regarding Africa and HIV it may be that the goals set by United Nations need to be lengthened. With that said, it should remain important that Africans not be victims blamed for the time period length being taken to assist with their issues.

An important note is that the issues regarding antimicrobial resistance and metaphorical superbugs span widely and are not just focused on Africa or HIV.

Conclusion

In conclusion, this paper presents the new, or third, mode of action pathway in antimicrobial therapy represented by *site attachment inhibition therapeutics*. Site attachment inhibition therapeutics consists of: 1. Treatment of established infections (E.g. medication based); 2. New generation immunization programs (preventative treatment) utilizing stem cell based therapy. New content presented in this manuscript revolves around the Case Example of Clostridium Difficile. Future publications are planned to discuss CRISPR, including CRISPR-Cas9, and related technologies as solutions with regards to association and causation issues.

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