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Alternative therapeutic strategies to fight bacterial infections

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Introduction

In spite of the large arsenal of antibiotherapies that have help humanities fighting bacterial infections, we are still facing diseases, hospitalization, and death caused by pathogenic agents [1-8]. The advent of the first sulfa drugs in the mid-thirties has launched almost a century of race toward the discoveries of new therapeutic agents by the pharmaceutical industries. The development of the Gram +ve linezolid in 2000 as the first family members of oxazolidinones as well as the Gram-negative lipopeptide antibiotic daptomycin, first discovered by Eli Lilly in 1980 but commercialized in the US in 2003 (23 years gap) have successfully lifted the long innovation gap in the medicinal chemistry era (Figure 1). Ceftaroline, a member of the fifth-generation cephalosporins discovered in 2010 is known to be particularly active against methicillin resistant Staphylococcus aureus (SARM), thus marking the beginning of alternative weapons against this particularly resilient infectious agent.

The advent of medicinal chemistry has allowed the relatively fast discoveries of diverse families of antibiotics working under a wide range of bactericidal or bacteriostatic mechanisms. Unfortunately, bacteria have similarly developed a plethora of defense mechanisms that include: (a) active efflux and sequestration of antibiotics by protein binding; (b) deactivation by enzymatic modification; (c) modification of antibiotic receptors; (d) metabolic bypass of the inhibited reaction; (e) overproduction of the antibiotic targets [9,10].

Since the discoveries of a plethora of therapeutics antibacterial agents, working on more or less similar mechanisms, scientists developed several additional strategies encompassing alternative mechanisms (Table 1). They ranged from cell wall destructions through polycationic entities such as polypeptides and nanoparticles [11,12]; bacterial starving by blocking nutrients input [13]; blocking genes and proteins expressions through siRNA [14]; triggering immune responses by vaccines directed against cell wall components such as capsular polysaccharides, etc. [15,16]. This last approach has been particularly successful in eradicating bacterial infections caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenza* type b and so on [17-19].

Of particular interest was the discovery that numerous bacteria express carbohydrate-binding proteins called lectins as virulence factors [31]. In these cases, the bacterial infection is initiated by a carbohydrate-protein recognition process (adhesion) from which the lectins bind to glycoconjugate receptors (glycoproteins, glycolipids) on the host cells (Figure 2). The ensuing steps include the release of deadly toxins and biofilm formation. Amongst these, *Pseudomonas aeruginosa*, uropathogenic *E. coli*, several *Shigella* species, and *Burkholderia cenocepacia* are representative examples. The case of uropathogenic *E. coli* infections (UPECs) is particularly well documented because the lectins responsible for the host cell adhesion are known and their structures fully characterized by X-ray crystallography [32]. The *E.*

Table 1. List of alternative therapies against bacterial infections and their mechanism of action

Strategy	Therapeutic agent	Action mechanism	References
1	Nanoparticles	Blocking biofilm formation	12
2	Quoring sensing	Blocking bacterial communication and biofilms	20
3	Siderophore	Enzyme co-factors	21
4	Polycationic peptides	Membrane disruption	11
5	Polycationic NPs	Membrane disruption	20
6	Phytochemicals	Varied	22
7	Repurposing anticancer drugs	Varied	23
8	Vaccines	Antibody-directed bacterial antigens	15-19
9	Antisense oligonucleotides	Inhibition of gene expression	14
10	Peptide Nucleic Acids (PNA)	Inhibition of gene expression	24
11	Transition metals (ex. Silver cations)	Inner membrane disruption	13,25
12	Innate immunity	Macrophage stimulation through TLRs	26
13	Adaptive immunity	Antibody-antibiotic conjugates	27
14	Phage display	Bacterial membrane lysis	28
15	Carbohydrate analogs	Inhibition of carbohydrate processing enzymes	29
16	Carbohydrates	Inhibition of adhesion	30
17	Pilicides	Inhibition of pili formation	38

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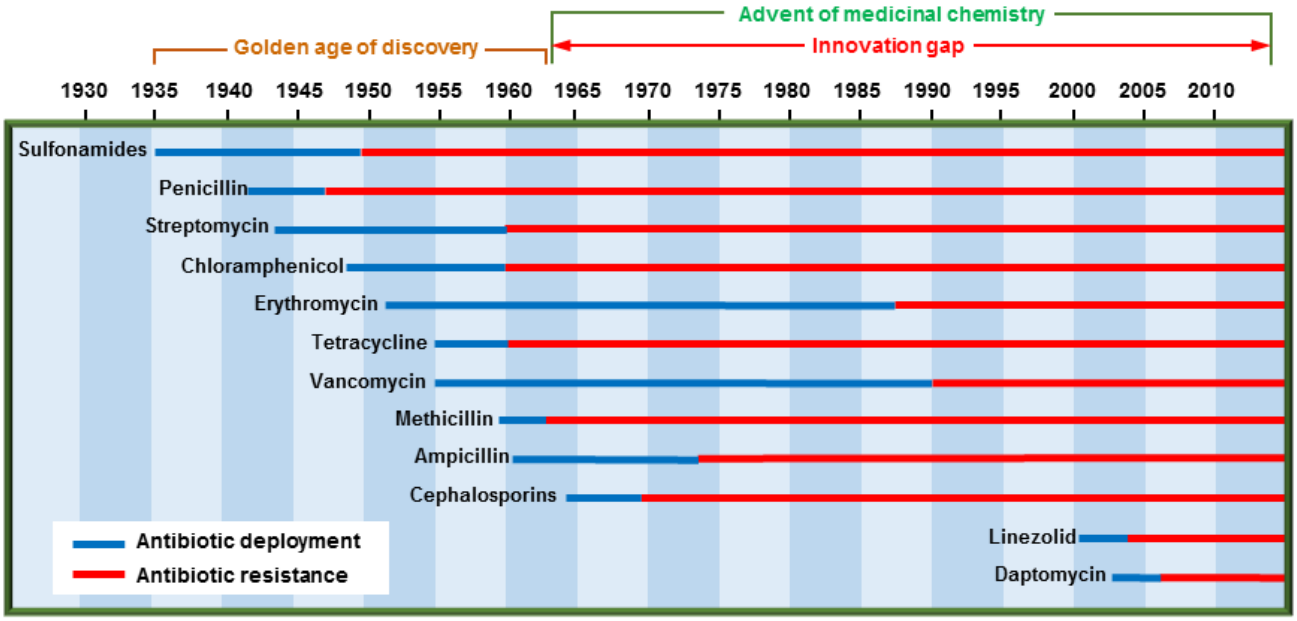

Figure 1. Development and bacterial resistance pattern of current antibiotics [9]

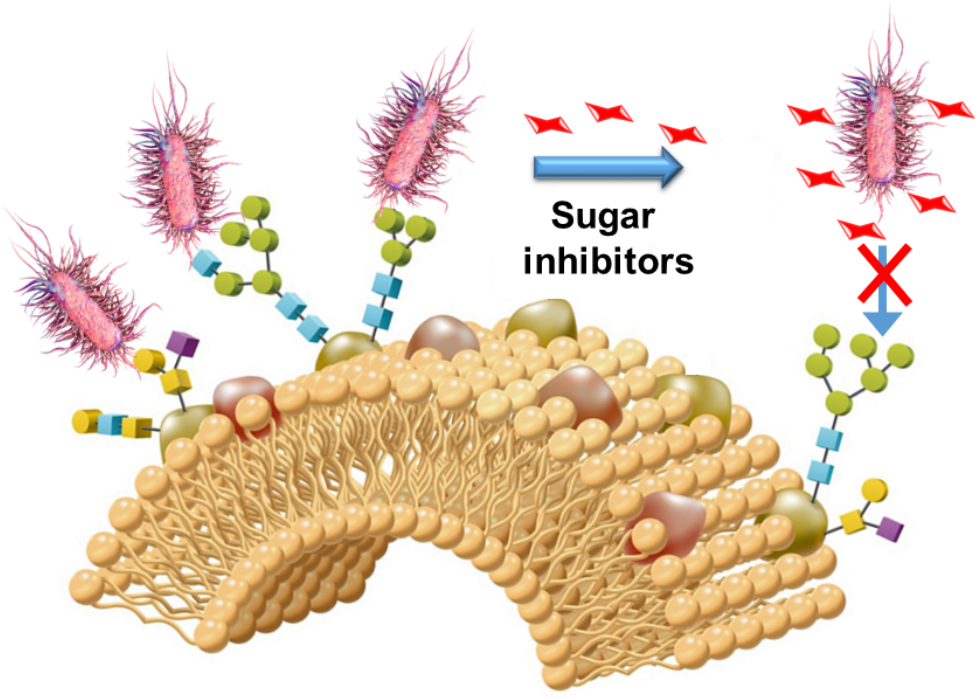

Figure 2. Blocking bacterial adhesion by carbohydrate anti-adhesives [33a]

coli FimH lectin has led to intensive medicinal chemistry efforts that ultimately allowed the discovery of small molecule inhibitors that recently successfully passed clinical Phase 1 [33,34].

Actually, the proof of principle that clearly demonstrated the first examples of inhibition of bacterial adhesion by carbohydrates was obtained through the pioneering activities of Sharon *et al.* [35]. For instance, recent investigations showed the direct consequences of exposing carbohydrate ligands such as carbohydrate additives and α-D-mannopyranoside antagonists between uropathogenic *E. coli* CFT073 bound to human 5637 bladder epithelial cells *in vitro* (Figure 3) [36-38]. The binding of green fluorescent protein-labelled *E. coli* strain (CFT073-GFP) could be efficiently inhibited in the presence of low concentration of the sugar as shown by fluorescence microscopy. In addition, there are growing demonstrations that the effect of mannopyranoside antagonists can alter the binding of various uropathogenic *E. coli* strains in microarray settings including human tissues. Hence, the therapeutic value of identifying potent sugar antagonists against adherent invasive *E. coli* strains represents an important goal in our arsenal of new drug development.

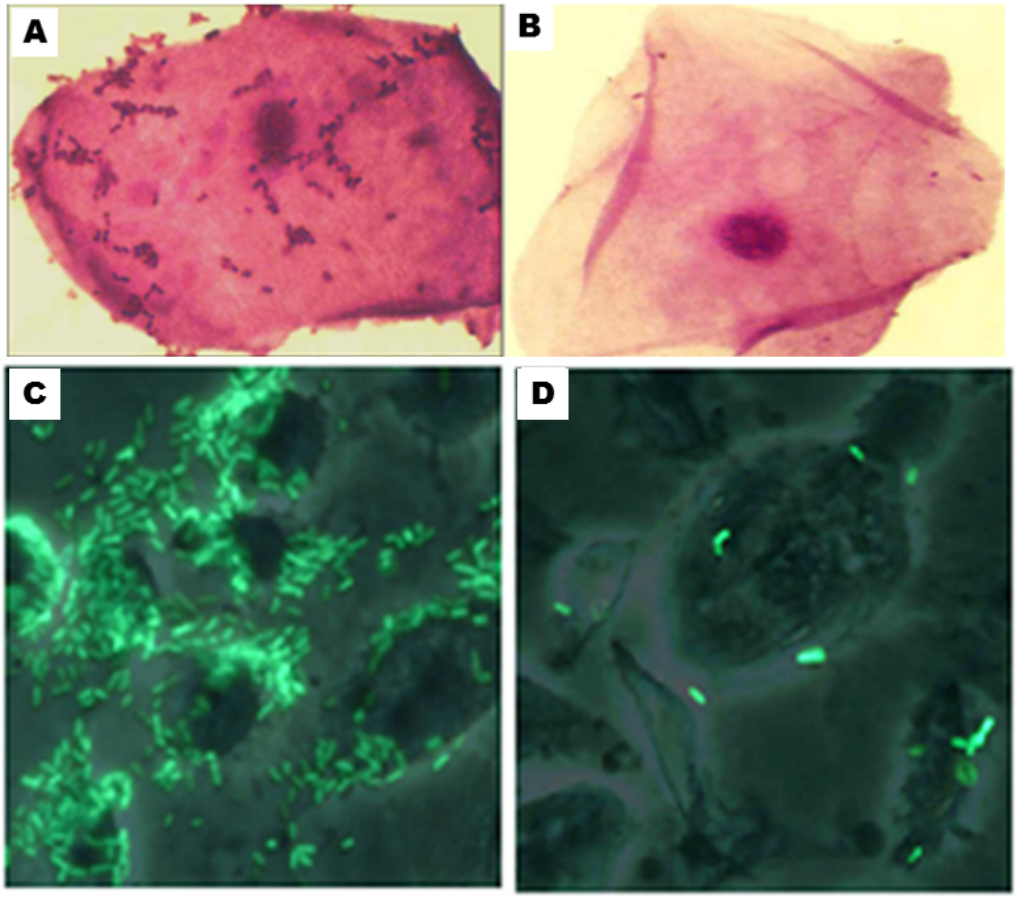

Figure 3. (Top panel): Adherence of *E. coli* to epithelial cells in the presence of sucrose (**A**) and mannose (**B**); adapted [36] (Bottom panel): Effect of type 1 fimbriae on adherence of uropathogenic *E. coli* to human bladder epithelial cells *in vitro* (**C**) and inhibition of binding in the presence of methyl α-D-mannopyranoside using fluorescence microscopy (**D**) adapted [37]

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