NEW CONCEPTS OF ANTI-INFECTIVE THERAPY

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NEW CONCEPTS OF ANTIMICROBIAL THERAPY

- Novel potentiators of current agents
- Combinations / Hybrid drugs
- Novel membrane-active agents / Nanotechnology
- Inhibitors of virulence and pathogenesis
- New targets
- Anti-sense nucleotides
- Bacteriophage

DEVELOPMENT OF POTENTIATORS OF KNOWN ANTIMICROBIALS

1. Beta-lactamase inhibitors with activity against Class I \(\beta\)-lactamases
2. Inhibitors of Tet protein (tetracycline efflux system)
3. Inhibitors of MDR-like efflux pumps in \(S.\ auresus\) or \(P.\ aeruginosa\)
4. Inhibitors of 2-component regulatory systems
5. Inhibitors of \(van\ H,\ van\ A,\ van\ B,\ or\ van\ X\)
6. Inhibitors of \(fem\) and/or other genes necessary for expression of methicillin resistance in staphylococci

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NOVEL HYBRID ANTIMICROBIALS

<table>
<thead>
<tr>
<th>Chemical entity</th>
<th>Target</th>
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<tbody>
<tr>
<td>Quinolactams</td>
<td>DNA gyrase/cell wall synthesis</td>
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<tr>
<td>Catechol cephalosporins</td>
<td>tna (\beta)-transport/cell wall synthesis</td>
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<tr>
<td>Rifampicin/fluoroquinolone hybrids</td>
<td>RNA polymerase/DNA gyrase</td>
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<tr>
<td>Aminosucinolide/fluoroquinolone hybrids</td>
<td>pol III e/DNA gyrase</td>
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<tr>
<td>Ozaonidinone/macrolide hybrids</td>
<td>23S rRNA (dual ribosomal binding sites)</td>
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<tr>
<td>Double conjugated MoAbs</td>
<td>Human RBC complement receptor/ (S.\ auresus) or (P.\ aeruginosa) capsular polysaccharide</td>
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<tr>
<td>Selectively targeted antimicrobial peptides (STAMPS) – antimicrobial peptide conjugated with terminal amino acid sequence of pheromone</td>
<td>Cell membrane damage via binding to pheromone receptor site ((S.\ strep) (mutans), (P.\ species))</td>
</tr>
</tbody>
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STAMPS (SELECTIVELY TARGETED ANTIMICROBIAL PEPTIDES)

- Constructed molecule made up of antimicrobial peptide fused with polypeptide domain from \(S.\ mutans\) pheromone (CSP - competence stimulating peptide)
- Shows high specificity for \(S.\ mutans\)
- Highly effective as an antimicrobial for possible use to prevent dental caries
- Used similar approach to develop antipseudomonal peptide

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ANTIMICROBIAL PEPTIDES
- Lytic enzymes (e.g., lysostaphin)
- Antibiotic peptides
- Magainins
- Defensins
- Cecrophins
- Bacteriocins (e.g., ambicins, lanthocins (nisin, etc.))
- BPI (bactericidal / permeability increasing protein)
- Squalamine mimics

ANTIMICROBIAL AGENTS MAY MODULATE VIRULENCE
- Natural quinolone modulates quorum sensing in Ps. aeruginosa and subinhibitory concentrations of fluoroquinolones may alter expression of virulence genes
- Fluoroquinolones increase release of Shiga toxin from E. coli 0157:H7
- Rifaximin does not induce or release Shiga toxin in E. coli
- Macrolides decrease production of toxins in S. pyogenes
- Oxazolidinones, clindamycin decrease production of toxins (including PVL) in MRSA
- Subinhibitory concentrations of fluoroquinolones increase expression of fibronecitin-binding proteins and may contribute to emergence and maintenance of FQ-R S. aureus in clinical settings

NANOTECHNOLOGY
- Self-assembling nanotubes
- Surfactant nanoemulsions

APPLICATIONS OF SURFACTANT NANOEMULSIONS
- Topical treatment of HSV-1
- Onycomycosis
- Topical treatment of MRSA, etc.
- Influenza and other vaccines

McKnight SL et al.  J Bact 182:2702, 2000
Bisognano C et al.  AAC 44:1428, 2000
Ochoa TJ et al.  AAC 51:2837, 2007
Moellering
QUORUM SENSING
- Bacterial cell-cell communication mechanism
- Utilizes interaction of a diffusible signal molecule ("pheromone" or "autoinducer") with a sensor or transcriptional activator
- Couples gene expression with cell population density

QUORUM SENSING AS A POTENTIAL ANTIMICROBIAL TARGET
- QS systems present in many bacterial species, but specificity of inducing peptides/pheromones creates potential problems for broad spectrum
- Inhibition of QS could render organisms avirulent
- Biofilm production controlled by QS – potential target to prevent/treat device-related infections
- Possibility to inhibit systems which allow bacterial survival in non-log phase growth

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NEW TARGETS FOR ANTIBACTERIAL AGENTS - 2007
- Fatty acid biosynthesis: GSK/Affinium; Genome Therapeutics/ArQule; Bayer
- tRNA synthesis inhibitors: Bayer; Replidyne
- Inhibitors of pro-mutagenesis proteins: Achaogen
- ATPase domain of DNA gyrase B (+ parE): Qu rever –+PFizer; Vertex
- Cell membrane: Adaptive Therapeutics, PepTx, NanoBio
- Degr proteinase (highly conserved proteinase) essential for virulence & pathogenicity in GNB & GPB: PharmAthene
- Bacterial translation elongation factors: Johnson & Johnson Pharmaceutical Research; Novartis
- Peptide deformylase inhibitors: Novartis/Versico
- Efflux systems for fluoroquinolones, tetracyclines, etc: Daiichi, Parexel, MPex
- Riboswitches: BioRelix

API-1252 (Affinium)
Fab I inhibitor
Highly active against staphylococci but not other bacteria

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<tr>
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<th>MIC₉₀</th>
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<tr>
<td>MSSA</td>
<td>0.016</td>
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<tr>
<td>MRSA</td>
<td>0.008-0.016</td>
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Phase 1 trials to begin 3Q 2007

DUAL TARGETING OF GyrB AND ParE BY NOVEL AMINOBENZIMIDAZOLE ANTIBACTERIALS
- Used structure-guided drug design to optimize series of aminobenzimidazoles that inhibit essential ATPase activity of GyrB and ParE
- Because compounds target both, mutational resistance frequency is low (<5.2 x 10⁻¹⁰)
- VRT-752586 shows excellent activity (MIC<0.5) against S aureus, S pneumoniae, E faecalis

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