Towards an Ontological Representation of Resistance: The Case of MRSa

Albert Goldfain[1], Lindsay G. Cowell [2], Barry Smith[3]

[1]Blue Highway, Syracuse, New York

[2] Duke University Medical Center, Durham, North Carolina

[3] University at Buffalo, Buffalo, New York

agoldfain@blue-highway.com, lgcowell@duke.edu, phismith@buffalo.edu

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Aims

- This work is funded by the National Institutes of Health through Grant R01 AI 77706-01
  - Immune System Biological Networks: A Case Study in Improved Data Integration & Analysis

- **Aim 1: Create an ontology-based representation of host-pathogen interactions, focusing on Staphylococcus aureus bacteremia.**
- Aim 2: Empirically test the ability of the ontology-based representation created in Aim 1 to improve the analysis and interpretation of clinical data.
- Aim 3. Empirically test the impact of the ontology-based representation created in Aim 1 on understanding Staphylococcus aureus pathogenesis, on identifying novel therapeutic targets, and on improving patient management.

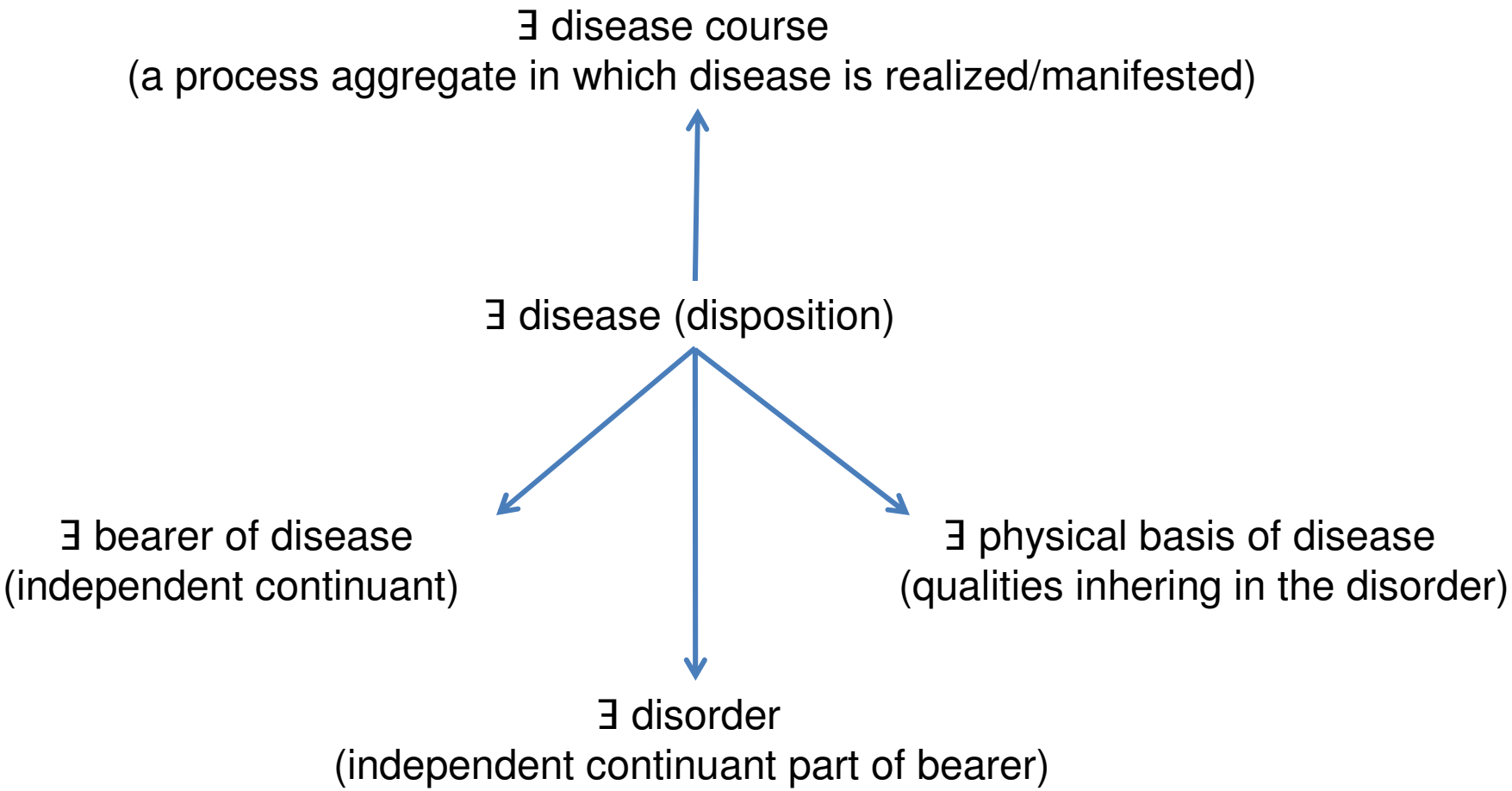
Outline

I. Introduction to IDO
II. Resistance phenomena and their ontological representation
III. Case Study: The antibiotic resistance of MRSa
IV. Formalization into triples
V. A definition for protective resistance
VI. Conclusion

Infectious Disease Ontology (IDO)

- An domain ontology extending BFO
- An interoperable part of the OBO foundry.
- Top-level IDO: A core upper ontology for the entire infectious disease domain
  - At different biological scales
  - From different disciplinary perspectives
  - ~200 terms
- IDO-extensions: A family of reference ontologies for specific diseases and pathogens (e.g., Staph aureus, Malaria, Influenza…)
- See http://www.infectiousdiseaseontology.org and IDO consortium invitation

Dispositional view of disease



Resistance Phenomena

- Examples:
  - Resistance of an individual to a disease
  - Resistance of a tumor to a treatment
  - Resistance of a pathogen to a drug
  - Herd immunity of an organism population to a
  - Immunity of an individual to an infectious organism
  - Resistance of certain bacteria to UV!
    http://edition.cnn.com/2009/TECH/science/03/17/india.bacteria/
- Resistance as a disposition
  - Different types of bearers at different biological scales
- Several ontologies/terminologies include resistance terms.

Resistance in existing terminologies

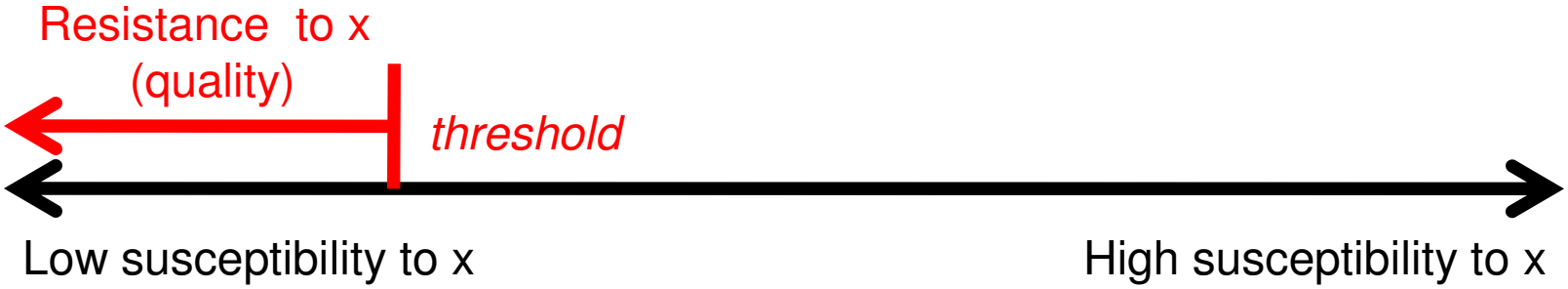
- *[NCI Thesaurus: C19391]* ***Resistance****: Natural or acquired mechanisms, functions, activities, or processes exhibited by an organism to maintain immunity to, or to resist the effects of, an antagonistic agent, e.g., pathogenic microorganism, toxin, drug.*
- Issues:
  - Circular definition: uses 'resist' in definition for resistance!
  - What is the type: mechanism? function? activity? process?
  - Restricted to organism bearer
  - Too many disjunctions to be useful

Desiderata for IDO Representation

- BFO-compatible
- Positive/active principle
  - Don't characterize resistance by what is not happening
  - Use **lacks** wherever necessary
- Non-proliferation of relations principle
  - don't propose a trivial relation **resistant_to**
  - work with OBO RO and RO-proposed relations
- Correct granularity
  - General enough to cover examples
  - Specific enough to be useful
- Pragmatic Concerns: IDO/IDO-extension terms should mirror scientific interest in resistance types.
  - Example: water-resistant walls are probably also lemonade-resistant, but we don't put 'lemonade resistance' in our ontology.

Resistance the quality vs Resistance the disposition

- Resistance disposition
  - possessed in virtue of internal physical arrangement of bearer
  - not always manifested when borne
  - realized in active processes at some physical scale
- Resistance quality
  - a sufficiently low susceptibility

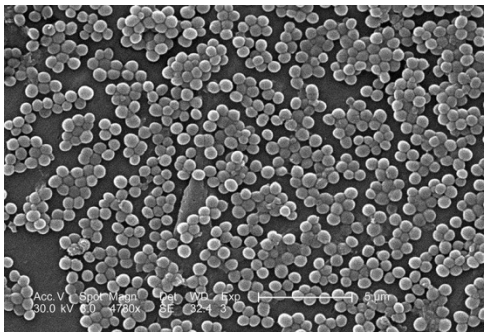


Dispositions in BFO 2.0

- BFO Disposition
  - BFO Capability: a disposition that enables its bearer to participate in certain processes.
    - BFO Function: a capability which evolved in its bearer or whose bearer was designed to have the disposition.
- Categorical Base/Ground is a BFO Quality
  - A disposition at a macroscale is usually conferred on its bearer by qualities of parts at a microscale
    - This is the utility of dispositions in reasoning
    - A chain of dispositions-in-wholes and qualities-in-parts all the way down

Case Study: MRSa

- Methicillin Resistant Staph aureus (MRSa)
  - A type of Staph aureus characterized by resistance to methicillin (and other β-lactam antibiotics).
  - As such, treatment decisions and public-health policies hinge on detecting MRSa
  - Currently: A huge problem for healthcare providers…



Source: CDC's PHIL

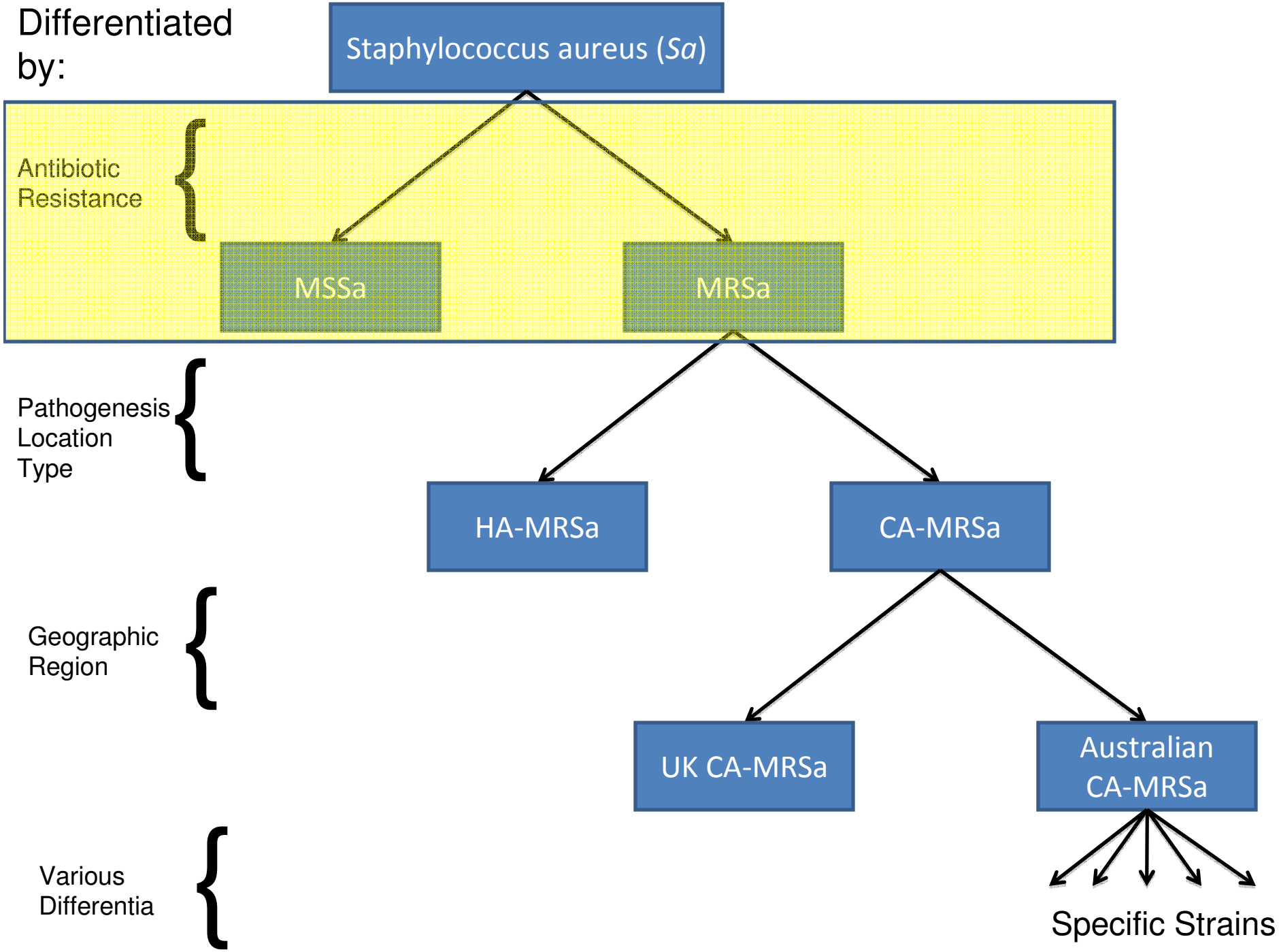
Our representation consists of:
1.A set of triples describing the entities involved in the resistance of MRSa to methicillin.
2.Logical inference rules a reasoner might use to *justify* the resistance.

Then use this formalization to inform a general definition for IDO

The Rise and Antibiotic Resistance in Sa

Year	Antibiotic Effectiveness
1943	Penicillin available
1947	First resistant strains reported
1960s	Switch to methicillin
1961	Methicillin-resistant strain found in Cairo
1980s	Methicillin resistance rising, vancomycin used as a last resort
1992	15% methicillin-resistant
1996	35% methicillin-resistant
2000	50% methicillin-resistant
2002	Vancomycin resistance reported

(from Knobler et al, 2003)



Formalizing MRSa Resistance

Domain

1. bacteria **is_a** organism
2. MRSa **is_a** bacterium
3. synthesis_of_peptidoglycan **is_a** process and **has_participant** Penicillin_Binding_Protein (PBP)
4. PBP **has_function_realized_as_process** synthesis_of_peptidoglycan
5. Bacterial_cell_wall **is_location_of** PBP
6. synthesis_of_peptidoglycan **results_in_development_of**

10. affinity_to_methicillin **disposition_of** some PBP to undergo a methicillin_PBP_binding_process that is **realized** in the presence of a methicillin.
11. methicillin_PBP_binding_process **negatively_regulates** synthesis_of_peptidoglycan.
12. PBP2a **lacks** affinity_to_methicillin
13. *mecA* **is_a** gene
14. MRSa **has_part** *mecA*
15. *mecA* **generically_specifies** PBP2a_production
16. PBP2a_production **results_in_formation_of** PBP2a

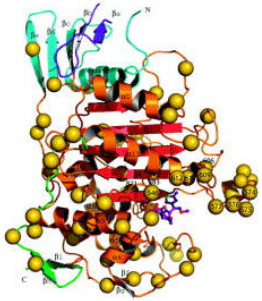
Inferences

- (IR1) *x* **is_a** *y* & *y* **is_a** *z* → *x* **is_a** *z*
- (IR2) *x* **has_part** *y* & *y* **has_part** *z* → *x* **has_part** *z*
- (D1) MRSa **is_a** organism
- (IR3) *o* **is_a** organism & *g* **is_a** gene & *o* **has_part** *g* & *g* **generically_specifies** *proc* & *proc* **results_in_formation_of** *prod* & *o* **has_part** *locp* & *locp* **is_location_of** *prod*) → *o* **has_part** *prod* **located_in** *locp*

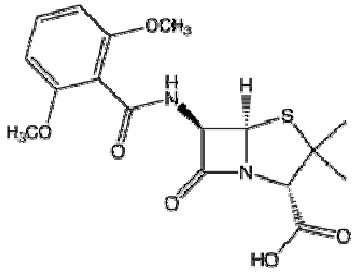
16 triples + 6 inference rules + 5 derived triples
but let's look at this in pictures…

- in situation *s*, *p* **participates_in** *proc2*
- (D3) In the presence of methicillin, PBP2a **participates_in** synthesis_of_peptidoglycan.
- (IR5) In situation *s*, *p1* **participates_in** *proc* & *p1* **located_in** *p2* & o has_part p2 → *proc* **unfolds_in** *o* in situation *s*.
- (D4) synthesis_of_peptidoglycan **unfolds_in** MRSa in the presence of methicillin.
- (IR6) In situation *s*, *proc* **unfolds_in** *o* & *proc* **results_in_development_of** *p* → *p* **part_of** *o* in situation *s*
- (D5) Canonical bacterial_cell_wall **part_of** MRSa in the presence of methicillin.

Why MSSa is Susceptible



PBP



Methicillin

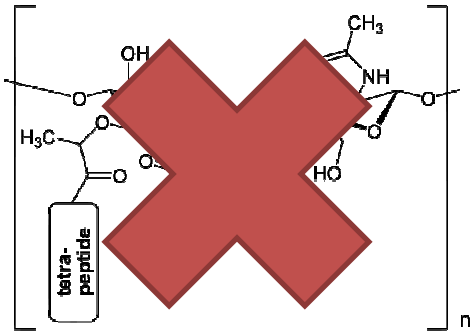
has_participants

Methicillin_PBP_Binding_Process

Bacterial_Cell_Wall

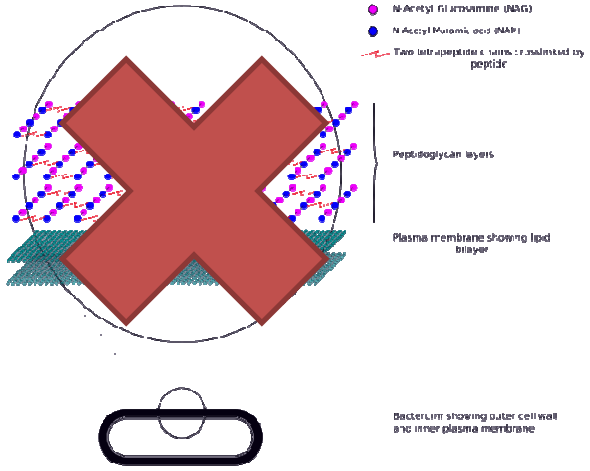
negatively_regulates

Synthesis of Peptidoglycan



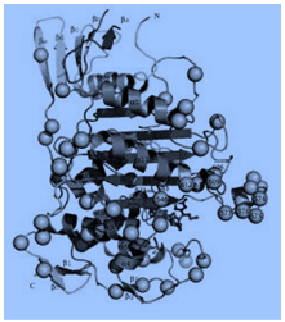
Peptidoglycan

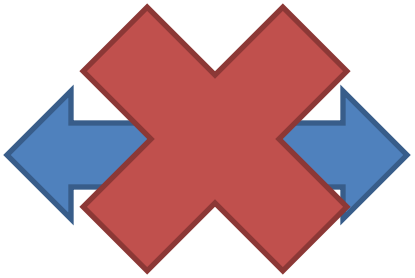
part_of

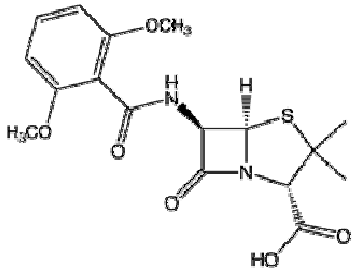


Simplified schematic of cell wall in a gram-positive bacterium
(showing plasma membrane; teichoic acids not shown)

Why MRSa is Resistant







PBP2a

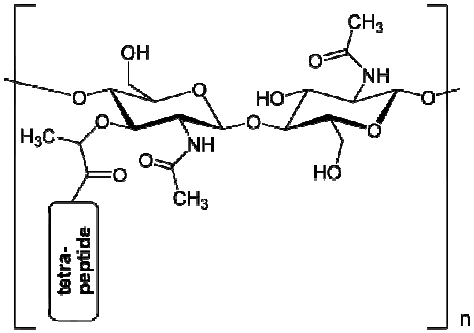
lacks

affinity_to_methicillin

Methicillin

No Methicillin_PBP_Binding_Process

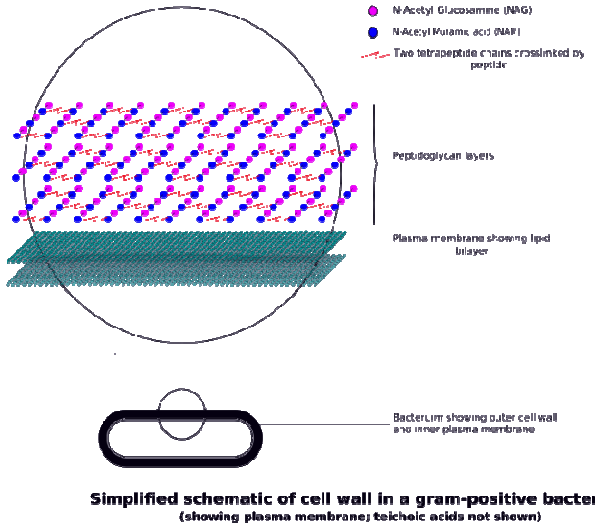
Synthesis of Peptidoglycan



Peptidoglycan

part_of

Bacterial_Cell_Wall



IDO's Protective Resistance

- IDO: *Protective resistance is a* *disposition* *that inheres in an* *material entity x* *by virtue of the fact that the entity h… a part (e.g., a gene product), whi… …position to ensure a physiologic response of … certain degree to a* *potentially dam…* *…y y, or to* *prevent the comple…on o… …cess* *caused by y … …tion or mitigati… …y.*

Allows for both organisms and tumors

Usually a function, but may be just a capability

with the ca… …lity to da…

e.g., CCR5 mutation prevents the completion of HIV invasion of host T cell

Conclusions

- Resistance is a very ***important*** biological phenomenon…
  - Guiding treatment decisions
  - Public health policy
- and a very ***general*** phenomenon…
  - Multi-scale (gene, cell, organ, organism, population)
  - Multi-discipline (clinical, biological, epidemiological)
- Whose representation in an ontology is ***non-trivial***
  - Even a particular instance of resistance requires many triples for description and inference.
  - Needs further analysis of lacking a disposition (e.g., lacking the affinity to methicillin).

Thanks!