

# Discovery-Stage Pipeline

**CUBIST**  
PHARMACEUTICALS

# Discovery Overview



- Mission:
  - Discovery of new therapies consistent with Cubist's acute care focus
- Strategy:
  - Focus on anti-bacterials
    - Innovation around existing classes
    - Pursuit of other targets with pre-clinical stage validation
  - Additional efforts in RSV and acute pain (through external collaboration)
- Tactics:
  - Small molecule approaches
  - Natural product semi-synthesis

# Discovery Strategy

Strategic Focus

## Infectious Diseases

## Non-ID

### Anti-bacterials

### Anti-virals

### Hospital-initiated therapies

Next generations:  
Modify existing  
classes

Find new classes as  
NCE starting  
substrate

**RSV**  
Others being  
considered

**Post-op pain**  
Others being  
considered

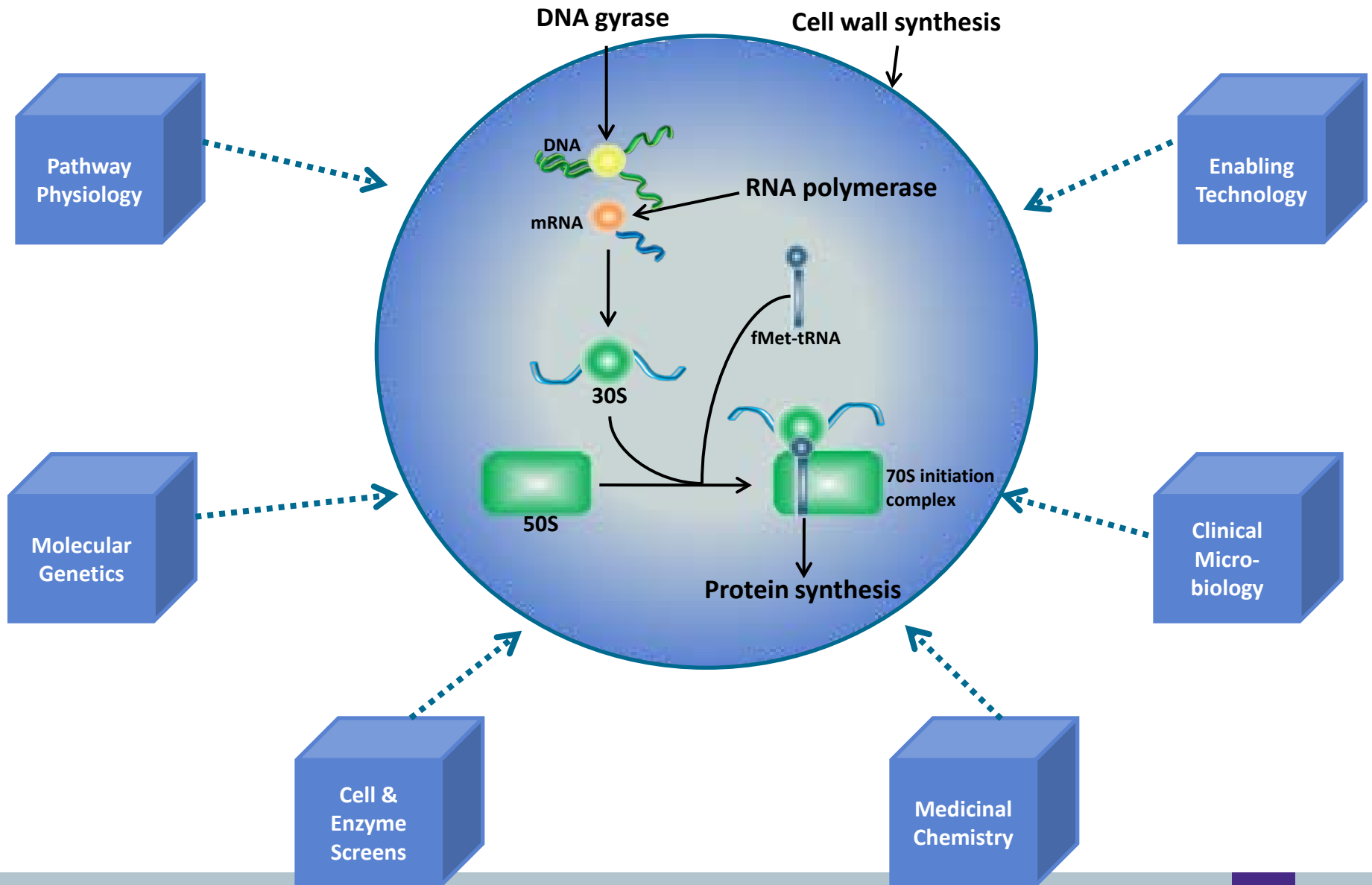
Execution

Primarily internal;  
selected strategic  
collaborations

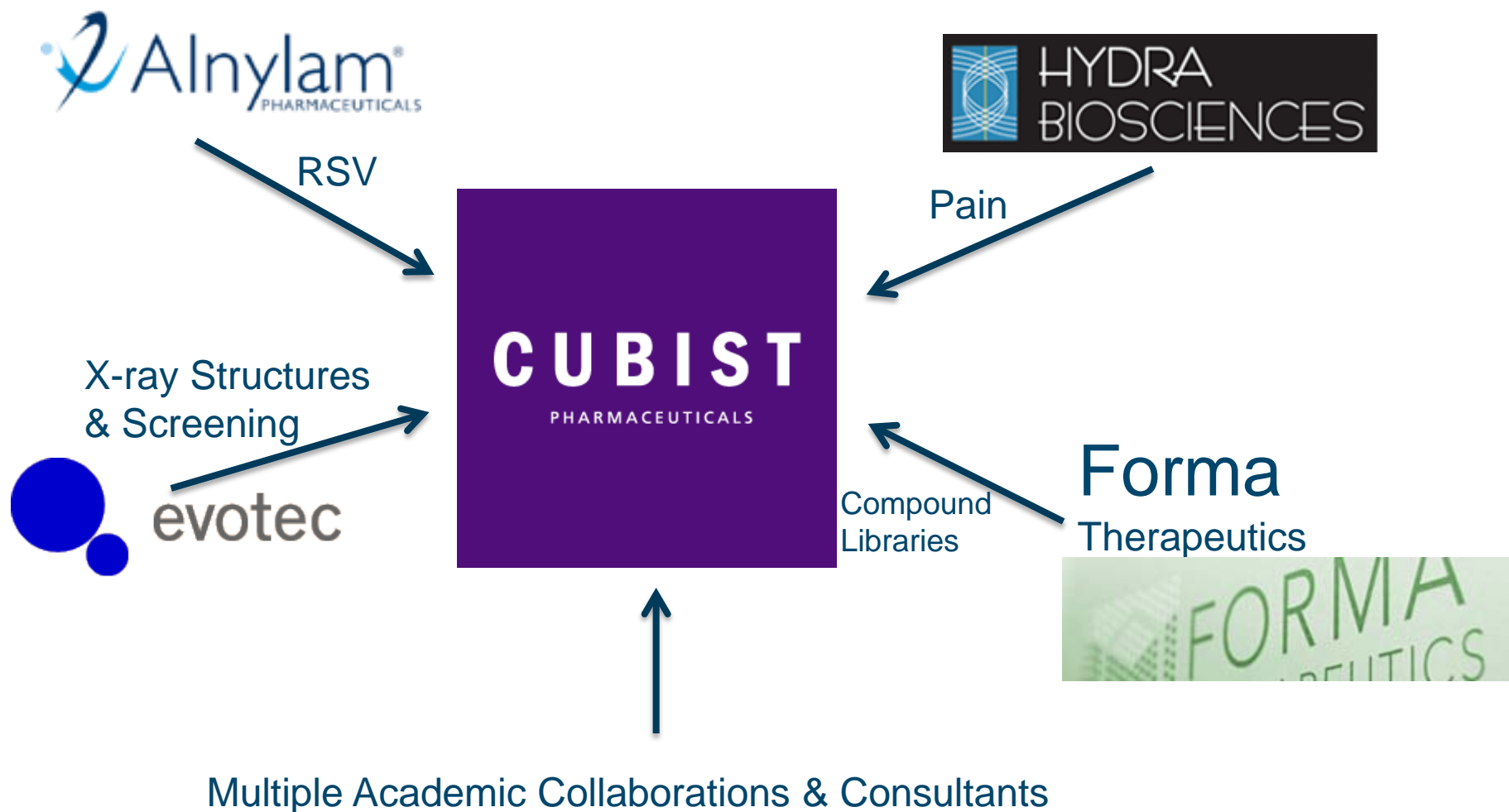
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collaborations;  
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# Integrated Antibacterial Drug Discovery Capabilities



# External Collaborations That Extend Reach of Our Internal Team



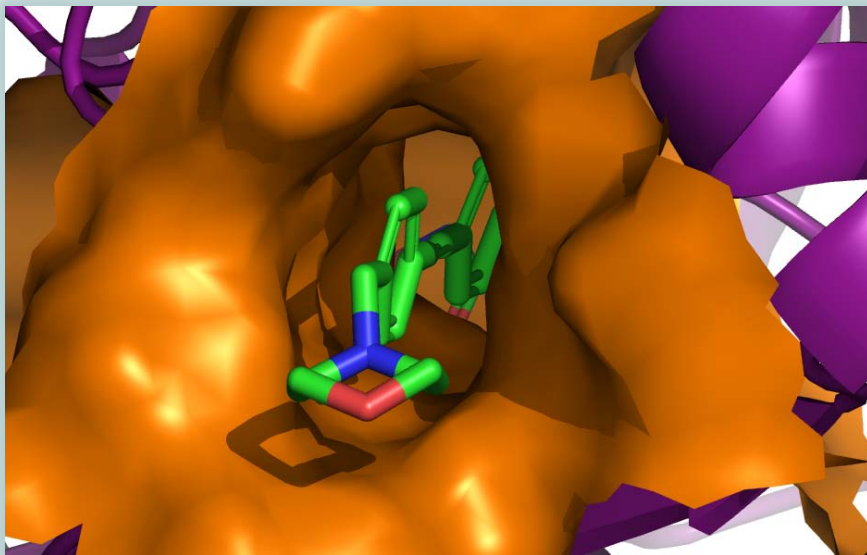
# Case Example: LpxC as a Gram-Negative Target

- Target Background
  - Inhibition is lethal
  - Absent in human genome
  - Required for formation of outer membrane in Gram negative bacteria
  - Metallo protease that requires zinc for catalytic activity
- Adopted structure-assisted discovery approach
  - X-ray/NMR structural data to address both target spectrum and potency
  - Med Chem ideas generated via docking studies in protein structural models
  - Combine empirical SAR with modeling data to drive compound optimization
  - Interactive Med Chem/Discovery Technology modeling meetings are key (3D room)



# LpxC- Progress Summary

- High resolution X-ray co-structures generated with inhibitors and LpxC enzymes from multiple bacterial pathogens
- Novel, proprietary LpxC inhibitors generated
- Potent MICs achieved across important Gram-negative species
- *In vivo* efficacy demonstrated in multiple animal models



Structure of prototype inhibitor bound to LpxC

# Cubist Drug Discovery Summary

- Significant commitment to the discovery of novel and next generation Gram-negative as well as Gram-positive antibacterial agents
- Brings together scientific insights with enabling technologies
- We have established one of the strongest antibacterial discovery teams in the industry
- Maintaining anti-infective focus and emphasis, while also expanding footprint in other therapeutic areas
  - Leverage strategic alliances, e.g. Alnylam (RSV); Hydra Biosciences (acute pain)