



## Cubist Pharmaceuticals

The Shape of Cures to Come™

# **Digging for Gold in the BAARN: The Future of Natural Products in Drug Discovery**

Victoria Knight-Connoni  
2013 BAARN Symposium



**1** Introduction

**2** Barriers to Success

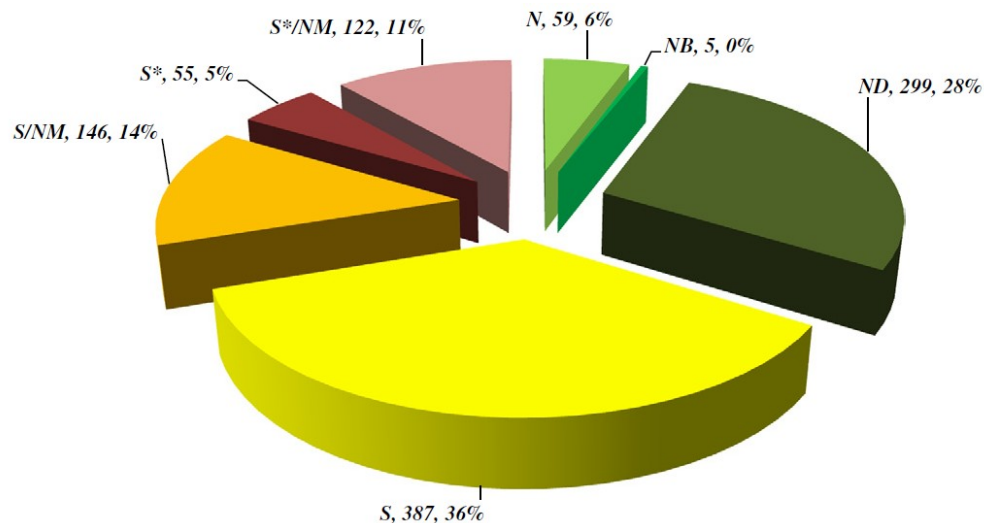
**3** Cubist's Approach

**4** Future Directions and Summary



# Introduction: Why Natural Products ?

- 64% of all new small molecule chemical entities (1073) approved drugs from 1981-2010 are or are inspired by natural products



Key	
Unmodified natural product	
Botanical	
Modified natural product	
Synthetic	
Synthetic -Natural product pharmacophore	
Synthetic -Competitive inhibitor of NP	

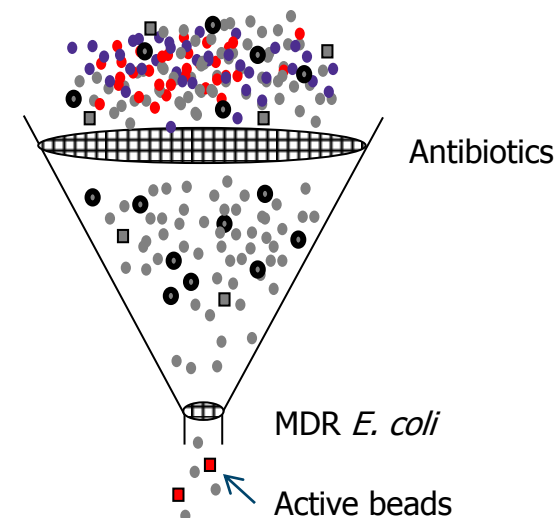
- Over this same period, 77% of approved antibacterials, 75% of cancer treatments were derived directly from natural products
- Provide unique complexity, structural diversity, inherent bioactivity (receptor binding activity) and different chemical space than small molecule libraries

- Timeline for natural products is longer than small molecule approaches
  - Does not fit in with small molecule HTS paradigms
  - Dereplication remains a bottleneck
- Jackpot nature of natural products
  - Resupply can be difficult
  - Semi-synthetic modification challenging
- Rediscovery rate limits new scaffolds
  - Need to dig deep for novel compounds
- Many secondary metabolites are cryptic
  - Produced under limited conditions at low titer or not at all

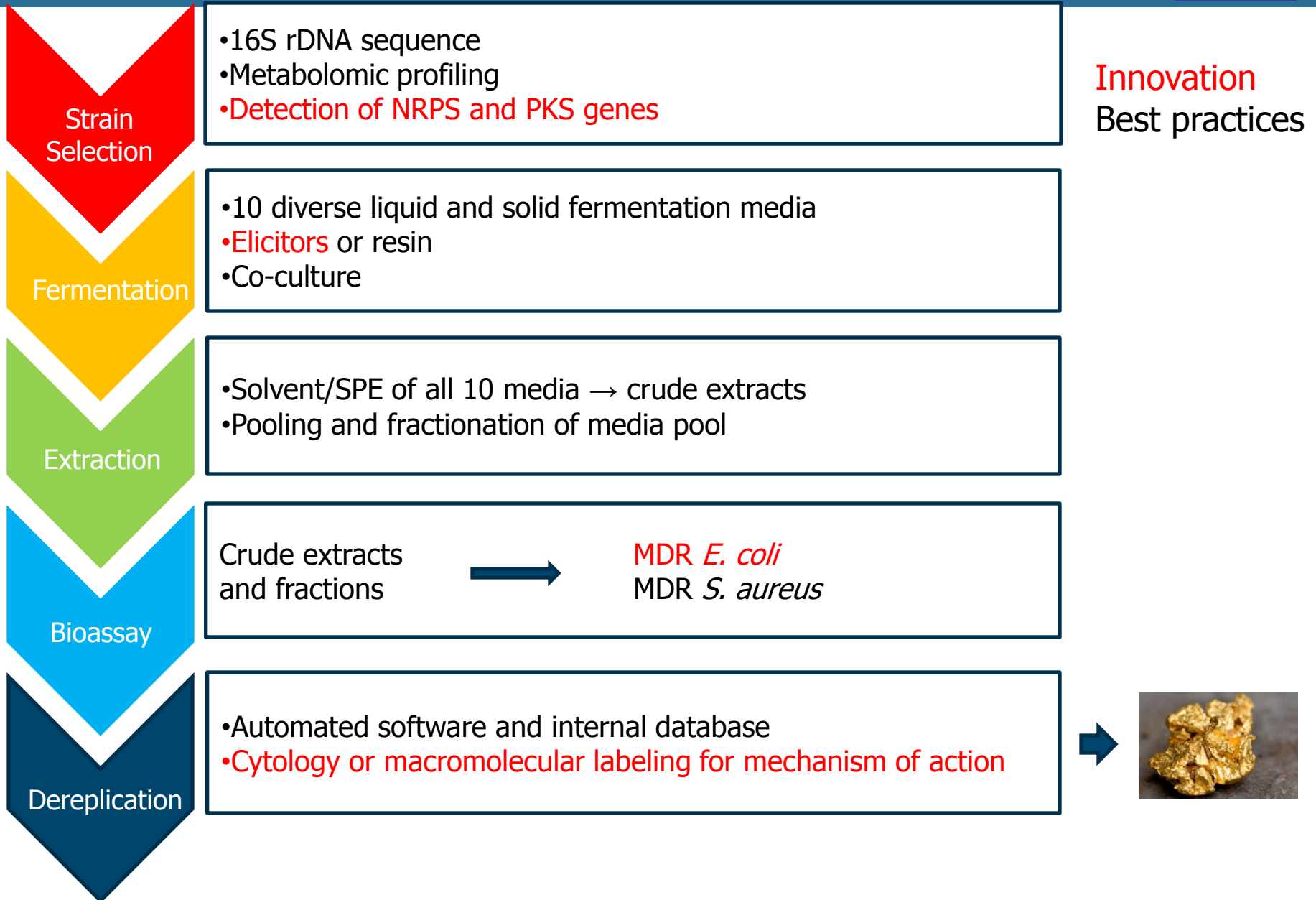


# History of Natural Products at Cubist

- Previous natural products screening effort at Cubist was terminated in 2008
  - Focus was on Cubist's novel macrodroplet technology combined with engineered MDR *E. coli*
  - Provided a source of innovation but low confirmation rate
  - Rediscovery of nuisance compounds frequent
  
- Cubist identified best practices plus innovative approaches to re-engage in natural product drug discovery in 2012
  - Emphasis on increasing diversity of strains entering fermentation
  - Still aspects of "grind and find" approach
  - Use of innovation to find gold



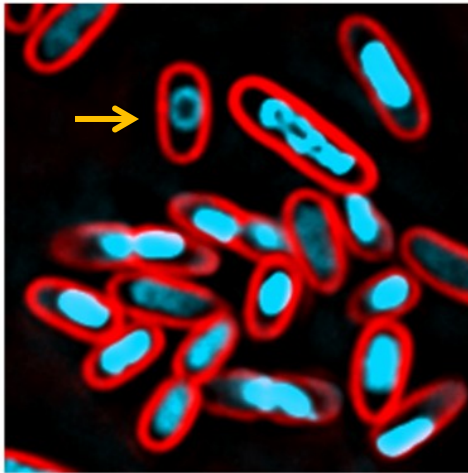
# Cubist's Approach



# Mechanism of Action Studies in Crude Extracts

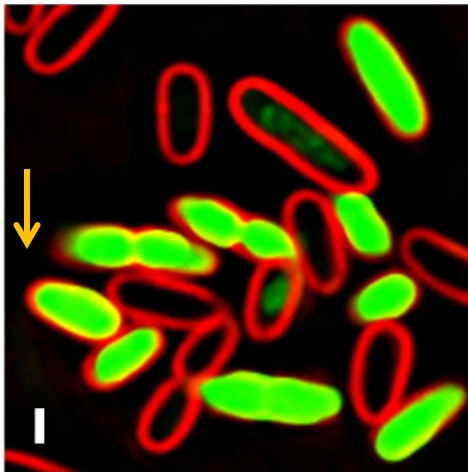
## Cytology profiling

Translation Inhibitor



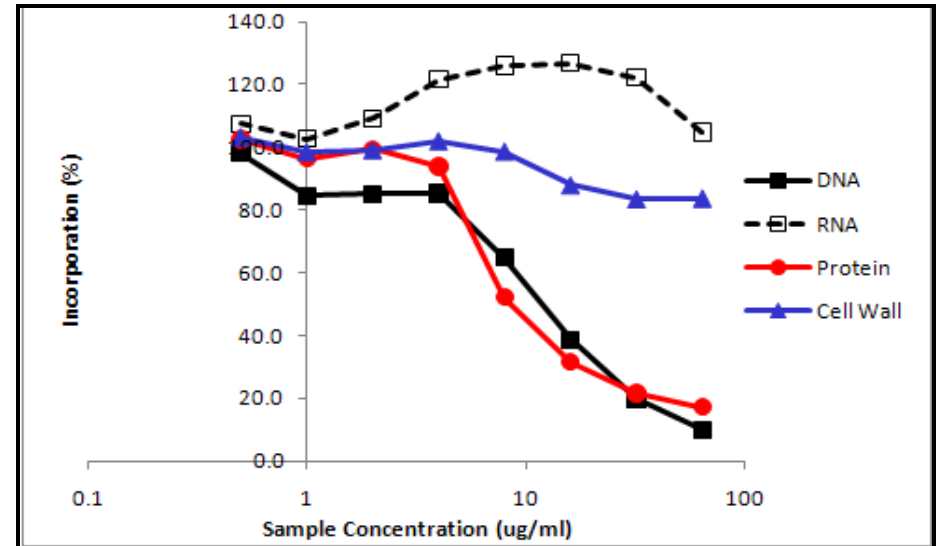
DAPI

Membrane active

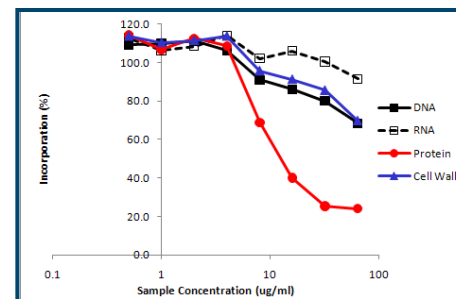


Sytox Green

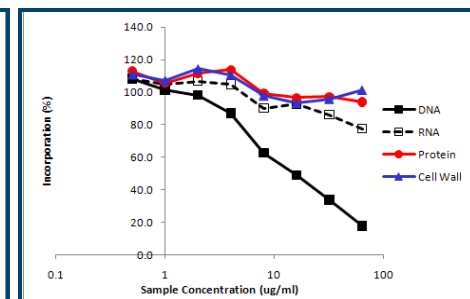
## Macromolecular labeling



Two mechanisms observed in crude



Fraction 1  
DNA synthesis



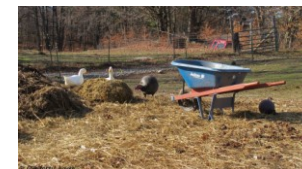
Fraction 2  
Protein synthesis

## Future Directions: Genes → Compounds

- Low cost genome sequencing has revealed the ability of Actinomycetes to produce many more secondary metabolites than have been detected
  - Combination of sequence tags and analytical data allows ID of compounds
  - Limited by throughput

## Summary:

- Natural products continue to be a diverse source of novel chemistry and a complement to small molecule approaches
- Dereplication bottlenecks can be solved using the following approaches:
  - Metabolomic analysis tools
  - Mechanism of action studies in crude extracts
  - Advances in whole genome sequencing
- This may will reduce the “jackpot” nature of natural products and help us find gold in our BAARN





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