Novel Synthesis Method to Produce Hybrid Nonribosomal Peptides (NRPs) with Enhanced Diversity and Functionality

Technology #17882

Applications

Nonribosomal peptides (NRPs) are structurally diverse molecules that have a broad range of biological activities and pharmacological properties. For example, they are widely used as pharmaceuticals (e.g., broad-spectrum antibiotics; anti-cancer drugs) and in the agricultural industry as insecticides. The ability to rationally engineer novel NRPs, especially those with structures that do not occur in nature, has an enormous impact in the expansion of the pool of chemical entities available. These entities can potentially be used to combat a variety of infections and diseases.

Problem Addressed

NRPs are a class of peptides produced in microorganisms such as bacteria and fungi. As opposed to ribosome-based synthesis, NRPs are produced by multi- domain complexes called nonribosomal peptide synthetases (NRPSs) and clusters thereof. NRPSs catalyze the sequential addition of natural and unnatural amino acids into a growing peptide chain. To this chain they can also add specific moieties (e.g. methyl groups and sugars) to specific atoms.

NRPs exhibit a wide range of bioactivities, and biomedical, agricultural and environmental applications. However, the discovery and production of native and new NRPs is notoriously difficult in a laboratory setting and often delivers a very low product yield. Existing methods of chemical synthesis are similarly impractical or not yet elucidated, due to the structural complexity of many NRPs. These drawbacks have led to the use of surrogate hosts (e.g., E. coli) for the heterologous production of NRPs. NRP biosynthesis pathways can be introduced into E. coli in their original form (e.g. gene clusters) or, alternatively, the pathways can be optimized for synthesis, product yield or size. Compressing multiple NRP biosynthesis pathways, as described within, makes it possible to easily generate non-naturally occurring nonribosomal molecules, in a controlled fashion. Furthermore, it allows to precisely control in vivo the assembly of the molecule designed in silico. The molecules exhibit an array of functions, with various bioactivities and applications. This living factory is conveniently an E. coli strain built especially for this purpose, and is an amenable and safe organism.

Technology

This technology is a method to produce a wide range of novel nonribosomal molecules by compressing two existing heterologous biosynthesis pathways and supplementing the growth medium with a precursor. The system is a modified strain of E. coli engineered to express a biosynthetic pathway composed of four components: 1) biosynthetic genes from one species encoding enzymes for the assembly of a nonribosomal molecule, 2) biosynthetic genes from a second species encoding enzymes for the assembly of a different nonribosomal molecule, 3) a gene encoding an amide synthase, and 4) exogenously supplied building blocks. The building blocks are

255 Main Street, room NE 18-501
Cambridge, MA 02142-1601
Phone: 617-253-6966 Fax: 617-258-6790
http://tlo.mit.edu
Contact the Technology Manager: tlo-inquiries@mit.edu

selected based on their potential to endow the hybrid molecule with desired functionalities (e.g., metal chelation; fluorescence; bactericidal or virucidal properties). The two molecule intermediates and one building block molecule are condensed via the aforementioned amide synthase to generate one hybrid nonribosomal molecule. As such, this method allows for the rational design of novel nonribosomal molecules with hybrid functionality not found in a natural environment.

Advantages

- Allows for the hands-off and controlled production of a diverse range of pre-designed novel nonribosomal molecules

Categories For This Invention:

Life Sciences
Biotechnology
Chemicals
Clinical Applications
Infectious Disease
Synthetic Biology
Bacterial
Therapeutics
Antibiotic
Peptide

Intellectual Property:

Compressed pathways for nonribosomal molecular biosynthesis
PCT
2016-196940
Compressed pathways for nonribosomal molecular biosynthesis
US Patent Pending
2018-0155400

Inventors:

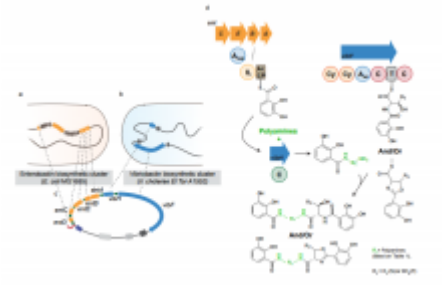
Timothy Lu
Sara Cleto

External Links:

Synthetic Biology Group
http://www.rle.mit.edu/sbg/

Image Gallery:

255 Main Street, room NE 18-501
Cambridge, MA 02142-1601
Phone: 617-253-6966 Fax: 617-258-6790
http://tlo.mit.edu
Contact the Technology Manager: tlo-inquiries@mit.edu



255 Main Street, room NE 18-501
Cambridge, MA 02142-1601
Phone: 617-253-6966 Fax: 617-258-6790
http://tlo.mit.edu
Contact the Technology Manager: tlo-inquiries@mit.edu