Advanced Drug Delivery Reviews 105 (2016) 96–106

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Biosynthesis of therapeutic natural products using synthetic biology☆

Ali R. Awan, William M. Shaw, Tom Ellis *

Centre for Synthetic Biology and Innovation, Imperial College London, London SW7 2AZ, UK
Department of Bioengineering, Imperial College London, London SW7 2AZ, UK

ARTICLE INFO

Article history:
Received 25 November 2015
Received in revised form 24 March 2016
Accepted 10 April 2016
Available online 16 April 2016

Keywords:
Synthetic biology
Natural products
Therapeutics
Polyketides
Nonribosomal peptides
Terpenoids
Alkaloids

ABSTRACT

Natural products are a group of bioactive structurally diverse chemicals produced by microorganisms and plants. These molecules and their derivatives have contributed to over a third of the therapeutic drugs produced in the last century. However, over the last few decades traditional drug discovery pipelines from natural products have become far less productive and far more expensive. One recent development with promise to combat this trend is the application of synthetic biology to therapeutic natural product biosynthesis. Synthetic biology is a young discipline with roots in systems biology, genetic engineering, and metabolic engineering. In this review, we discuss the use of synthetic biology to engineer improved yields of existing therapeutic natural products. We further describe the use of synthetic biology to combine and express natural product biosynthetic genes in unprecedented ways, and how this holds promise for opening up completely new avenues for drug discovery and production.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Synthetic Biology: Innovative approaches for pharmaceutics and drug delivery".
* Corresponding author at: Centre for Synthetic Biology and Innovation, Imperial College London, London SW7 2AZ, UK.
E-mail address: t.ellis@imperial.ac.uk (T. Ellis).

http://dx.doi.org/10.1016/j.addr.2016.04.010
0169-409X/

1. Introduction

1.1. Natural products as therapeutics

Chemicals found in nature have been used for therapeutic purposes since ancient times. The ancient Egyptians and Greeks used salicylic acid from the bark of the willow tree to treat aches and pains [1]. In the 19th century, chemists at Bayer modified this substance to make aspirin. Natural products like salicylic acid are small molecules produced by plants, bacteria, and fungi that have been selected by evolution for stability and interaction with biological polymers (proteins, nucleic acids, carbohydrates, and lipid membranes) [2]. Their importance to human health is underscored by the fact that natural products and their derivatives comprise over 40% of drugs, including antibiotics and antitumour and cholesterol-lowering agents [3,4]. The major classes of therapeutic natural product, along with an illustrative member of the class and the organism it was discovered in is given in Fig. 1.

One class of therapeutic drug in particular, the antibiotics, has relied heavily on natural products. The discovery of penicillin in 1928 heralded the "Golden Era" of natural products as antibiotics [5]. In the decades since the 1980s, however, fewer and fewer new antibiotics were being discovered in nature [6]. This situation led to a prioritising of pharmaceutical drug discovery towards completely synthetic chemical avenues [7]. However, several recent trends have motivated a move back to exploiting natural products [2]. This review focuses on one of these developments: the application of synthetic biology towards the production of natural product-derived therapeutic drugs.

1.2. Synthetic biology for therapeutic production

Synthetic biology has several definitions. Here we adhere to the definition that the goal of synthetic biology is to extend or modify the behaviour of organisms using molecular biology to perform new tasks in a predictable manner [8]. The relevant task in this case is the production of therapeutic natural products at commercially viable yields by a suitable host organism.

Natural products are mostly produced by the action of multiple genes [9]. In the simplest scenario each gene encodes an enzyme that converts an input chemical into an output chemical acted upon by the next enzyme until the final natural product is produced, in assembly-line fashion. Together, these biosynthetic genes comprise a pathway. To produce natural products at high yields, a synthetic biologist must balance pathway gene expression and host cell growth. This endeavour must acknowledge the burden caused by the pathway gene expression, both via siphoning away of host resources and via the build-up of toxic pathway intermediate products [10]. In order to achieve this balance and maximise pathway yield, synthetic biology has developed tools to allow finely-tuned control over pathway behaviour.

These tools fall into two main categories. The first category of tools has roots in the older disciplines of genetic engineering and metabolic engineering and includes simple mutation and screening, rational modulation of host organism gene expression, protein engineering, directed evolution, and optimisation of growth conditions [11]. The second class of tools can be viewed as purely belonging to synthetic biology. These tools are based on adapting naturally occurring biological molecules at the DNA, RNA, and protein levels to confer the desired behaviour to pathway function [12].

When it comes to optimising the production of natural products, the distinction between the terms "metabolic engineering" and "synthetic biology" is breaking down, as these terms are increasingly being used interchangeably in the literature [13,14]. Thus, this review discusses both categories of tools mentioned above, but specifically using cases concerning the production of natural products with therapeutic value.

2. Known natural products

In the majority of cases taken on by synthetic biology, the chemical structure of the natural product is known. The main tasks faced by synthetic biologists in these cases are threefold. The genes encoding enzymes that will convert starting chemicals into the final natural product must be selected, and a host organism must be chosen. Finally, ways must be found to control the expression of these genes to optimally balance pathway yield and host organism growth. These tasks are not

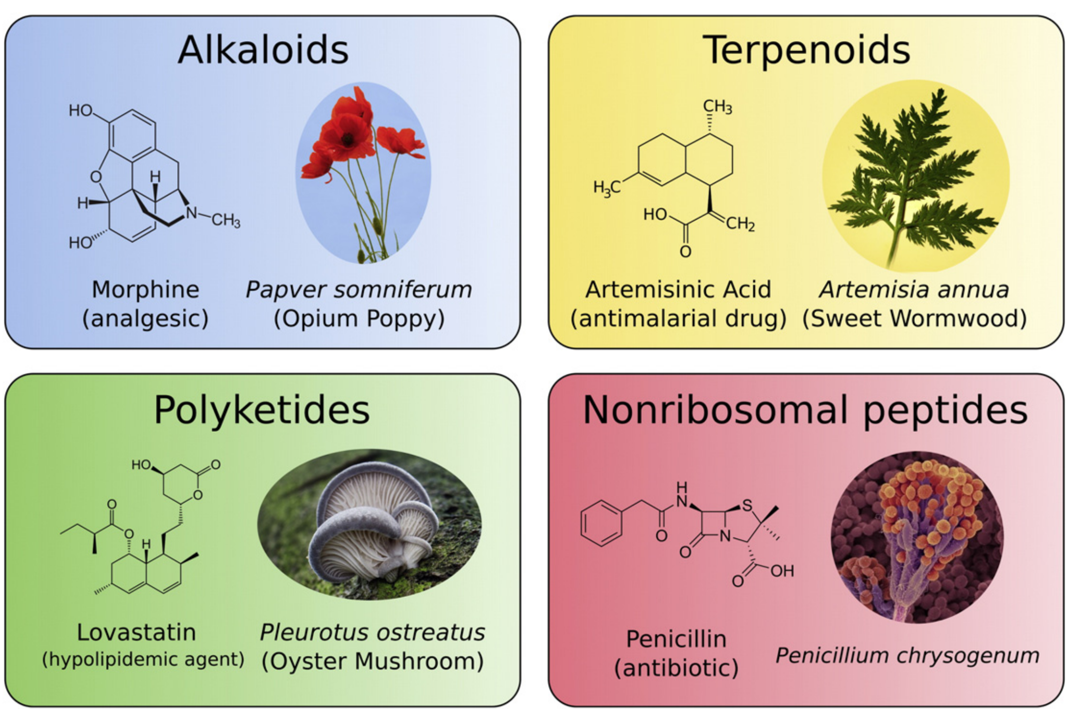

Fig. 1. *The major classes of natural product.* The four major classes of natural product are shown. For each class, a member with therapeutic properties is given along with the producing organism.