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### **ACCEPTED MANUSCRIPT**

Engineering microbes for isoprene production Lidan Ye<sup>1,2</sup>, Xiaomei Lv<sup>1</sup>, Hongwei Yu<sup>1\*</sup>

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#### Abstract

Isoprene is facing a growing global market due to its wide industrial applications. Current industrial production of isoprene is almost entirely petroleum-based, which is influenced by the shrinking C5 supply, while the natural emission of isoprene is predominantly contributed by plants. To bridge the need gap, a highly efficient fermentation-based process for isoprene production might be a suitable and sustainable solution, and extensive research works have been performed to achieve this goal. Here we review the accomplishments in this field by summarizing the history and prospects of microbial isoprene production. The natural producers and biosynthesis pathways of isoprene, the key enzyme isoprene synthase and the metabolic engineering strategies adopted for developing isoprene-producing microorganisms are introduced. In particular, strategies employed for achieving engineered strains with improved performance indices are discussed based on the published papers and patents. The perspectives on further performance improvements and potential future strategies are presented as well.

Keywords: isoprene; metabolic engineering; protein engineering; isoprene synthase; yeast; bacteria

#### 1. Introduction

Isoprene ( $C_5H_8$ ), also known as 2-methyl-1,3-butadiene, has a wide scope of industrial applications, ranging from the production of synthetic rubber for tires and coatings, to use in adhesives and development of specialty elastomers, and also has the potential to be developed as fuel additive for gasoline, diesel, or jet fuel (Bentley et al., 2014). At the moment, isoprene is produced almost entirely from petrochemical sources, mainly by direct isolation from C5 cracking

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