In recent years, the crude oil price has been surging to reach over US$60 per barrel. Crude oil is the most important energy source and many industries are heavily relying on the use of chemicals derived from crude oil. The finite nature of oil reserves, coupled with increasing concerns on our environmental damages, urge us to develop a sustainable way of securing these chemicals and energy. White biotechnology, which is a European terminology for industrial biotechnology, is thus drawing much attention as a solution to produce energy, chemicals and other materials from renewable resources.

White biotechnology provides significant benefits over the conventional chemical industry because it allows production of chemicals and energy from annually renewable resources in a more energy-effective manner. Also, decreased generation of wastes, reduced CO$_2$ formation, and increased product yield and purity for some of the products are additional advantages of white biotechnology. Until now, white biotechnology has been successful in fine chemical and pharmaceutical industries leading to approximately 15% of total market (Table 1). The market portion of the current white biotechnology-based products is approximately 5% of the total chemical market. According to McKinsey and Company, the biotechnological feedstock will become ca. 20% and 75% of the total chemical feedstock by 2010 and 2050, respectively, with the help of technologies such as systems biotechnology and metabolic engineering (Fig. 1).

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Global annual production and market price (million tons / US$ per kg)</th>
<th>Microrganisms (processes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Glutamic acid</td>
<td>1,500 / 1.44</td>
<td>Bacteria (aerobic)</td>
</tr>
<tr>
<td>Citric acid</td>
<td>1,000 / 0.96</td>
<td>Yeast (aerobic)</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>150 / 2.16</td>
<td>Bacteria (anaerobic)</td>
</tr>
<tr>
<td>Gluconic acid</td>
<td>100 / 1.8</td>
<td>Yeast (aerobic)</td>
</tr>
<tr>
<td>L-Lysine</td>
<td>700 / 2.4</td>
<td>Bacteria (aerobic)</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>80 / 9.6</td>
<td>—</td>
</tr>
</tbody>
</table>

The global chemical industry produced approximately US$1.9 trillion worth of products through conventional petrochemical-based processes using more than 2 billion barrels of crude oil in 2005. The processes are energy intensive and environmentally unfriendly emitting about 1.5 billion tons of CO$_2$. With the growing environmental concerns and rapid increase in oil price, much effort is being devoted worldwide to develop cost-competitive and energy-effective processes using renewable resources. In particular, it is urgent to develop innovative processes for the production of bulk chemicals, which accounts for more than 95% of all chemicals produced. Among
the various technologies to accomplish this bio-based chemicals vision, metabolic engineering will play the most important role as it allows development of strains that are capable of enhanced production with less byproducts from various renewable raw materials. Recent developments in the area of systems biology are further advancing the strategies for metabolic engineering by providing genome-scale and holistic information of a given organism; I prefer to call this systems biotechnology, which is the development of biotechnological processes using systems biological approaches (Fig. 2). Among the various chemicals that can be produced by white biotechnology (Fig. 3), some of them are briefly described below.

Bioethanol is the best developed bio-based bulk chemical produced by white biotechnology. Recently, the US government decided to fund additional research in ‘cutting-edge methods’ for producing ethanol (2006 U.S. President’s annual address). The goal is to make ethanol more practical and competitive to replace the crude oil imports. Bioethanol is commonly produced from the carbon sources from crop plants (maize and sugar plant) by fermentation. It is one of the most cost-effective renewable transport fuels. From a practical viewpoint, 10% ethanol can be used in modern vehicles without any appreciable changes in performance. Traditionally, yeast has been used for ethanol production. However, metabolically engineered bacterial strains (e.g., Zymomonas mobilis and Escherichia coli) have been developed to efficiently produce bioethanol.

Glycerol is another promising chemical to be produced by microbial fermentation. More than 600,000 tons of glycerol was produced in 2001, and used as a feedstock for the production of various chemicals. Although glycerol had been commercially produced by microbial fermentation during the World War I, it has been synthesized from allyl alcohol or by the oxidation or chlorination of propylene after the World War II. Numerous genetically modified bacterial or yeast strains have been developed by overexpressing and/or knocking-out the genes associated with the glycerol formation pathways to enhance the cell’s ability to produce glycerol. The best microorganism
Fig. 2: Concept of white biotechnology: Integration of upstream (strain development), midstream (fermentation) and downstream (recovery) strategies is important for the development of successful and commercially viable processes.

Fig. 3: Representative products of white biotechnology. Renewable raw materials are converted to various chemicals ranging from primary to secondary metabolites.
for the production of glycerol is an osmotolerant yeast strain, *Candida glycerinogenes*, isolated from glazed fruit in southern China. As the price of crude oil rapidly increases, more than 10,000 tons of glycerol is produced by fermentation of *C. glycerinogenes* in China for the domestic usage.

Lactic acid is also one of the main products produced by white biotechnology. Annually, 130,000 tons of lactic acid is produced, most of which is used by the food industry. Future demand on lactic acid is expected to increase with the introduction of polylactic acid into the market. Polylactic acid is a biodegradable (and now more perferably called high-performance) plastic that has the advantages, compared to the existing plastics, of being biodegradable and manufactured from renewable resources. Various bacteria have been reported to produce lactic acid with high yield and productivity. By employing different strains, a desired lactic acid enantiomer such as L(+)-, D(-)-, or DL-lactic acid can be produced. The development of specialty polymers from lactic acid has triggered increased interest in the production of specific enantiomers. The dimers, LL, DD, and DL, can be used as building blocks of polylactic acid possessing different physical properties. Recently, homofermentative production of lactic acid by metabolically engineered *E. coli* has also been developed.

1,3-propanediol has a wide range of applications such as composites, adhesives, laminates, monomers of polymers, solvents and anti-freezing agent. Currently, it is produced by chemical synthesis, but there has been growing interest for its biotechnological production. Until now, various microorganisms including *Klebsiella*, *Enterobacter*, *Citrobacter*, *Lactobacilli* and *Clostidia* have been reported to produce 1,3-propanediol under anaerobic condition using glycerol as an carbon source. Considering the high price of glycerol, many researchers have considered *E. coli* as a host strain for the production of 1,3-propanediol from glucose.

As mentioned earlier, the production of biodegradable polymer is one of the main goals of white biotechnology. While lactic acid and 1,3-propanediol serve as monomers for polymerization, polyhydroxyalkanoates (PHAs) are a family of naturally synthesized polymer in a wide variety of bacteria as an energy and/or carbon storage material. PHAs possess material properties similar to various petrochemical-based synthetic thermoplastics and elastomers currently in use. They are also completely degradable to water and carbon dioxide (and methane under anaerobic condition) by microorganisms in various environments. Recent advances in our understanding of the PHAs biosynthetic pathways, and cloning and molecular characterization of key genes have allowed the construction of various bacterial strains for the enhanced production of PHAs. The production cost of PHAs is still two to three times higher than petroleum-based polymers, but this situation may change as the price of crude oil goes up further.

Another good example of chemicals produced by white biotechnology is 3-hydroxypropionic acid, which is a key intermediate for several commercially important chemicals including acrylic acid, acrylamide, and 1,3-propanediol. Codexis and Cargill developed a microbial process which utilizes low-cost and clean agricultural feedstocks (corn sugar) to produce 3- hydroxypropionic acid.

Succinic acid is a four-carbon dicarboxylic acid, which can be used as a precursor of many industrially important chemicals in food, chemical and pharmaceutical industries. It is expected that the current petroleum-based succinic acid process will be replaced by the fermentative succinic acid production system in the foreseeable future. Several promising
succinic acid producers include Actinobacillus succinogenes, Anaerobiospirillum succiniciproducens, Mannheimia succiniciproducens and recombinant Escherichia coli.

There is no doubt in that white biotechnology will become an essential technology paradigm for the sustainable growth using renewable materials. However, the efficiency of the processes for the production of the diverse chemicals needs to be improved. For the time being, the products of white biotechnology have to compete with the products from the petroleum-based industry. This is why there is still hesitation in the global chemical industry for actively adopting white biotechnology. However, as repeatedly stated, white biotechnology is a key solution for the sustainable growth. As the first group of foreseeing companies are already developing more and more bio-based processes, there may be no second chance left for the other chemical companies in the near future. White biotechnology! It is an essential technology for our future.

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References


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