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SYNTHEThIC BIOLOGY APPROACHES IN TERPENOID RESEARCH

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Specialized plant metabolites have numerous applications as pharmaceuticals, flavors, fragrances, and even biofuels. Yet, their application is limited due to low availability from natural sources, inefficient chemical synthesis, and untapped chemical diversity. Production of these compounds in engineered microbes can provide a sustainable solution. However, the availability of the building blocks for natural products biosynthesis in heterologous hosts remains a major constrain. We addressed this challenge by engineering a complete synthetic orthogonal pathway for monoterpenoid production based on synthesis of an isomeric isoprenoid building block or by repurposing yeast peroxisomes as building block-synthesizing microfactories. Moreover, the chemical space occupied by specialized metabolites, and, thus, their application potential, is limited because their biosynthesis is based on only a handful of building blocks. Thus, we demonstrated the re-design of existing biological systems to acquire new functions by engineering yeast cells to synthesize a non-canonical building block with 11 and 16 carbons. These approaches enabled production of more than 100 new-to-nature C11 and C16 terpene scaffolds that can form the basis for entire new terpenoid classes. By combining gene mining with protein and metabolic engineering, we converted C10 plant monoter-pene synthases to C11-specific enzymes through a single-residue switch, and constructed variants that selectively produce seven non-canonical isoprenoid building blocks with 16 carbon atoms.

Dr. Codruta Ignea undertook her PhD at the University of Crete, where she worked with Prof. Nick Panopoulos on natural products biosynthesis. As Postdoctoral researcher she engineered heterologous production of terpenes in yeast, developed efficient production platforms, and demonstrated the usefulness of Synthetic Biology approaches in biosynthetic pathways elucidation. She was awarded a Postdoctoral fellowship from Novo Nordisk Foundation to move to the University of Copenhagen, where she has carried out pioneering work on Synthetic Metabolism, constructing metabolic pathways not found in nature. In 2018, she received a highly prestigious Marie Sklodowska-Curie Fellowship to study the regulation of biosynthetic pathways at molecular level. Her research work has led to high profile, first author publications in Nature Chemical Biology, Nature Communications and PNAS.

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