

**MS6-O3** The Architecture of Fully Reducing Polyketide SynthasesDominik A. Herbst<sup>1</sup>, Roman P. Jakob<sup>1</sup>, Franziska Zähringer<sup>2</sup>,  
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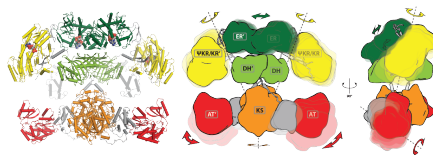
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Polyketides are a diverse family of potent bioactive microbial secondary metabolites and amongst the most successful compound classes in drug discovery, including many clinically relevant drugs. They are assembled via stepwise precursor elongation by giant polyketide synthases (PKSs)<sup>1</sup>. PKSs combine all enzymatic domains for a single-step of precursor elongation and modification in one module, which features a structural and functional separation into a product condensing and a modifying region as observed for fatty acid synthases. The product of each PKS module is determined by its specificity for the precursor and elongation substrate as well as the extent of product modification, encoded in the variable domain composition of the modifying region. The maximum extent of product modification is observed in reducing PKS, which employ two reductase and one dehydratase domain for full reduction of the intermediate to an elongated acyl chain. PKS modules either operate iteratively in iterative PKS or as part of a multimodular assembly line, with directed transfer of substrates between modules. The product diversity of PKS is thus directly encoded in their molecular organization.

Here, we report<sup>2</sup> a hybrid model of a reducing mycocerosic acid synthase-like PKS (MAS-PKS)<sup>3</sup>, which represents a large family of closely related mycobacterial PKS, based on overlapping crystal structures of its condensing and modifying regions. A comparison of a large set of experimentally observed MAS-PKS conformations provides a visualization of structural dynamics and conformational coupling in PKSs. Our data reveal a close relationship of individual domains of MAS-PKS and multimodular PKS. The modifying region of MAS-PKS adopts a unique dimeric linker-based organization devoid of stable interactions between different domain types. Comparative small angle X-ray scattering (SAXS) demonstrates that this architecture is common also to multimodular PKS. The linker-mediated construction principle provides a rationale for the characteristic variability of PKS modifying regions as a main contributor to the evolution of product diversity. Our comprehensive model of PKS architecture will contribute to the functional dissection and targeted re-engineering of PKSs for enabling combinatorial biosynthesis.

## References

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**Figure 1.** Hybrid model and conformational variability of a reducing mycocerosic acid synthase-like PKS.

**Keywords:** Polyketide Synthase, PKS, Molecular Machine, Architecture