

Viridicatumtoxin and Griseofulvin Biosynthesis in *Penicillium aethiopicum*

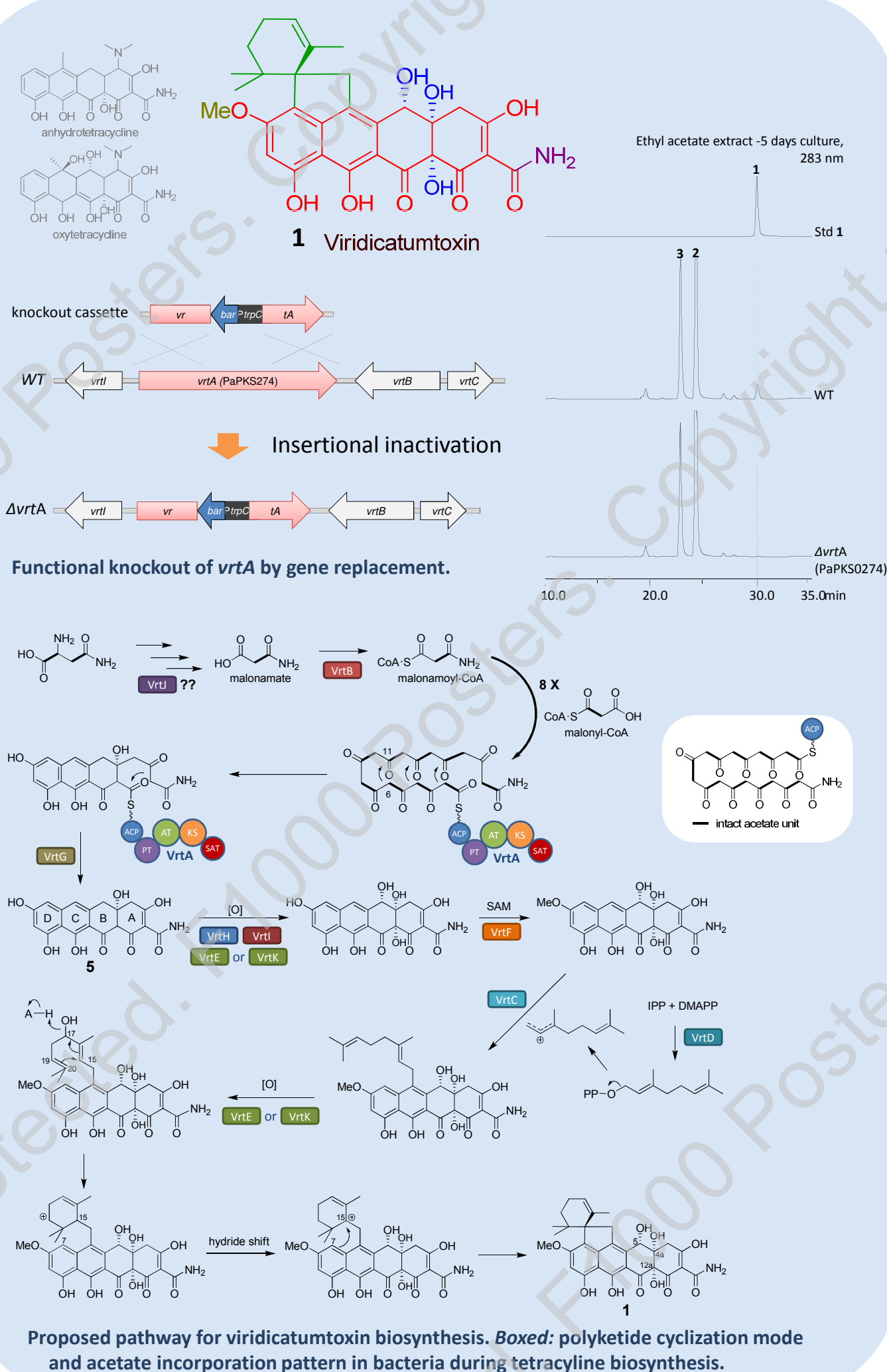
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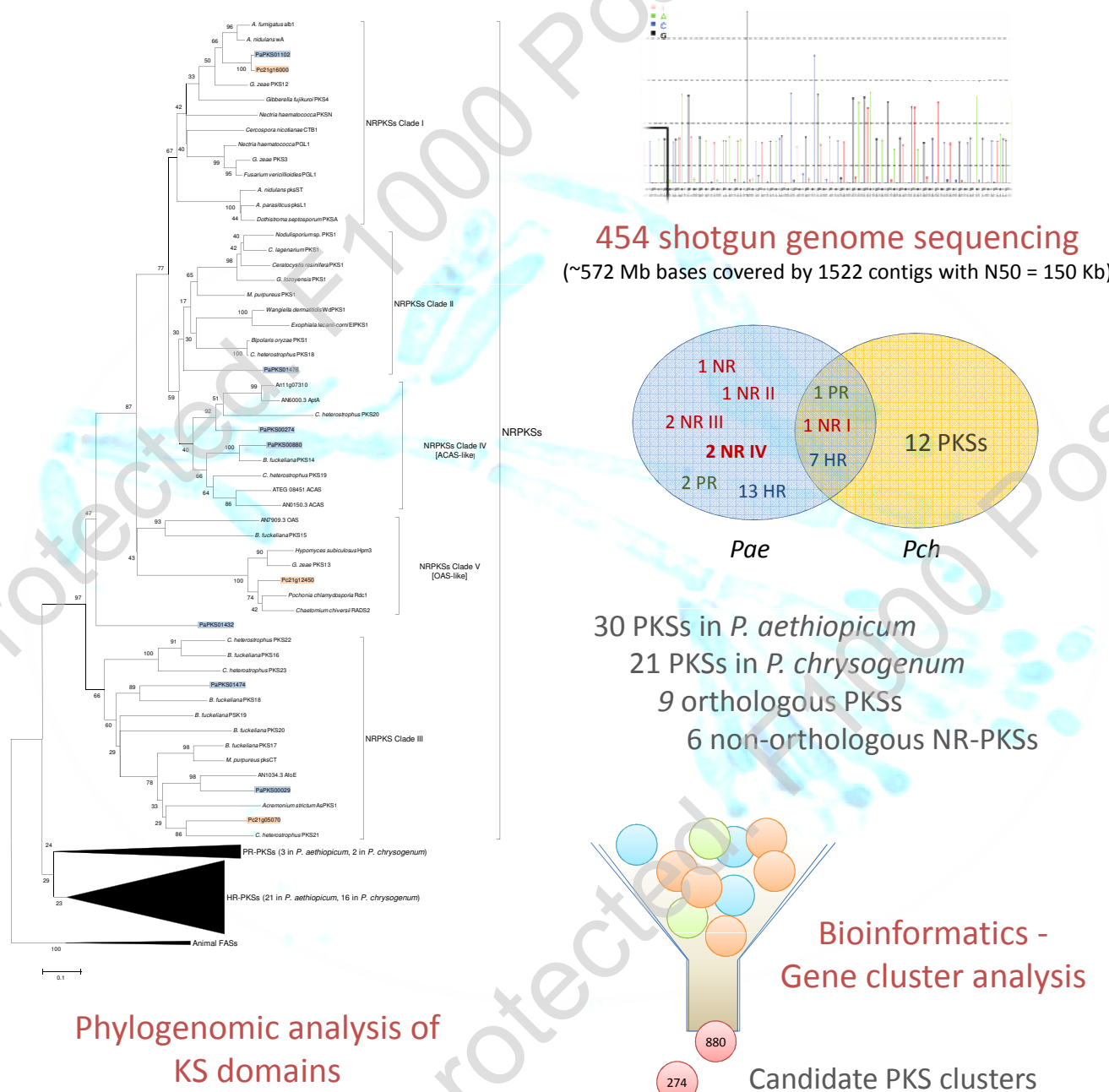
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Summary¹

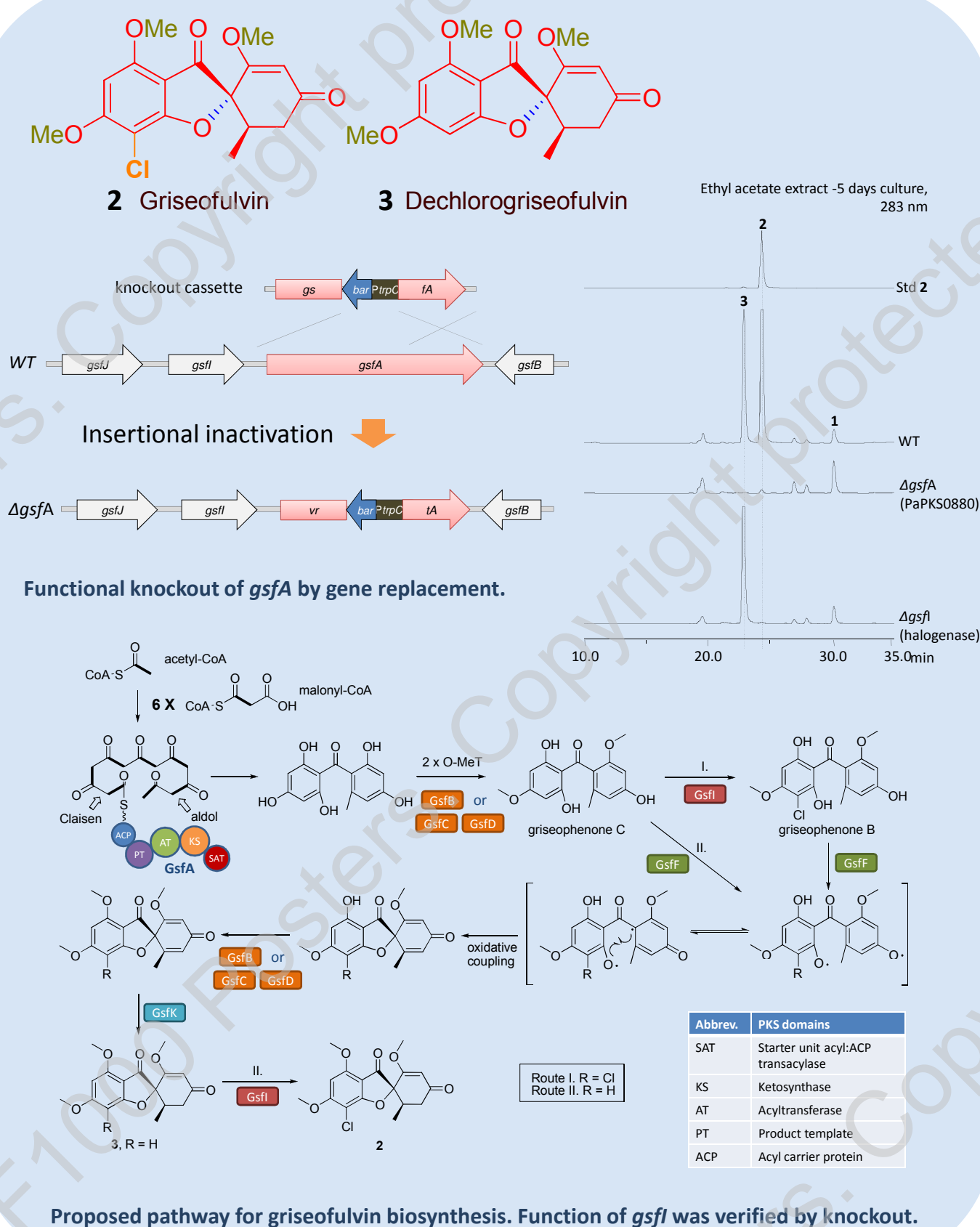
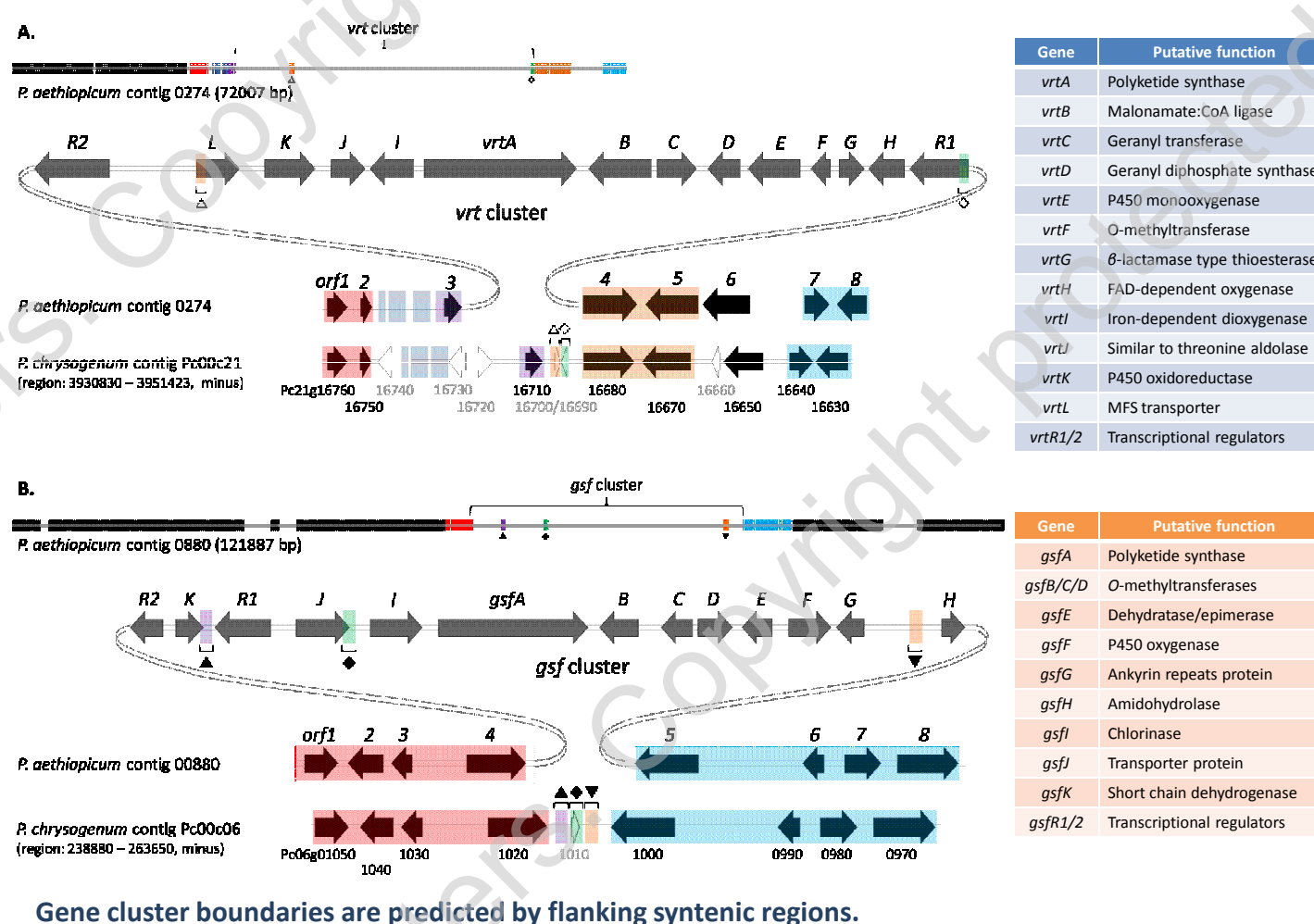
- *P. aethiopicum* produces viridicatumtoxin **1**, griseofulvin **2**, and tryptoquialanine
- **1** shared key structural features with anhydrotetracycline and possesses anti-MRSA
- **2**, a classical polyketide, is an antifungal agent and is investigated as antitumor
- 454 sequencing unveiled the gene clusters for **1** and **2** respectively
- *vrt* and *gsf* clusters lie within conserved syntenic regions of *P. aethiopicum* genome
- VrtA and GsfA are nonreducing PKSs required for biosynthesis of **1** and **2** respectively
- Knockout confirmed *gsfI* encodes chlorinase involved in the biosynthesis of **2**



Comparative genomics as tools for target-driven biosynthetic gene cluster discovery



vrt and *gsf* clusters are embedded within conserved syntenic regions of *P. aethiopicum* genome



Questions remained to be answered

Viridicatumtoxin

- The synthesis of the malonamyl starter unit. Which and how many enzymes involved?
- The last ring Claisen cyclization, facilitated by the β -lactamase type TE (VrtG)?
- The unusual cyclization of the geranyl moiety, what mechanism and which enzyme?
- Can we use the fungal viridicatumtoxin pathway enzymes and bacterial tetracycline tailoring enzymes for combinatorial synthesis of novel tetracycline analogs?

Griseofulvin

- How does GsfA performed both Claisen and aldol condensations without Claisen cyclase/thioesterase? Any other enzyme assists the cyclizations?
- The role and mechanism of the P450 oxygenase (GsfF) in formation of the grisan ring.
- The native substrate for GsfI. Griseophenone C or dechlorogriseofulvin?

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