



Understanding bacterial regulation systems to unlock the production of novel “cryptic” antibiotics

Vincent Poon^{1,2}, Dr. Jonathan Moore¹ and Dr. Christophe Corre²

Vincent.Poon@Warwick.ac.uk

¹Warwick Systems Biology Centre, University of Warwick

²School of Life Sciences / Department of Chemistry, University of Warwick

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WARWICK

Aims of the project

- To understand regulatory systems involved in controlling production of antibiotic-like compounds in *Streptomyces* bacteria.
- To exploit our understanding to unlock the production of novel antibiotics.

1. Introduction

Up to two thirds of today’s clinically approved antibiotics originate from soil-living *Streptomyces* bacteria (Fig 1) [1]. While each species is predicted to produce dozens of drug-like compounds, the production of compounds is often tightly controlled by DNA-binding regulators (Fig 2).

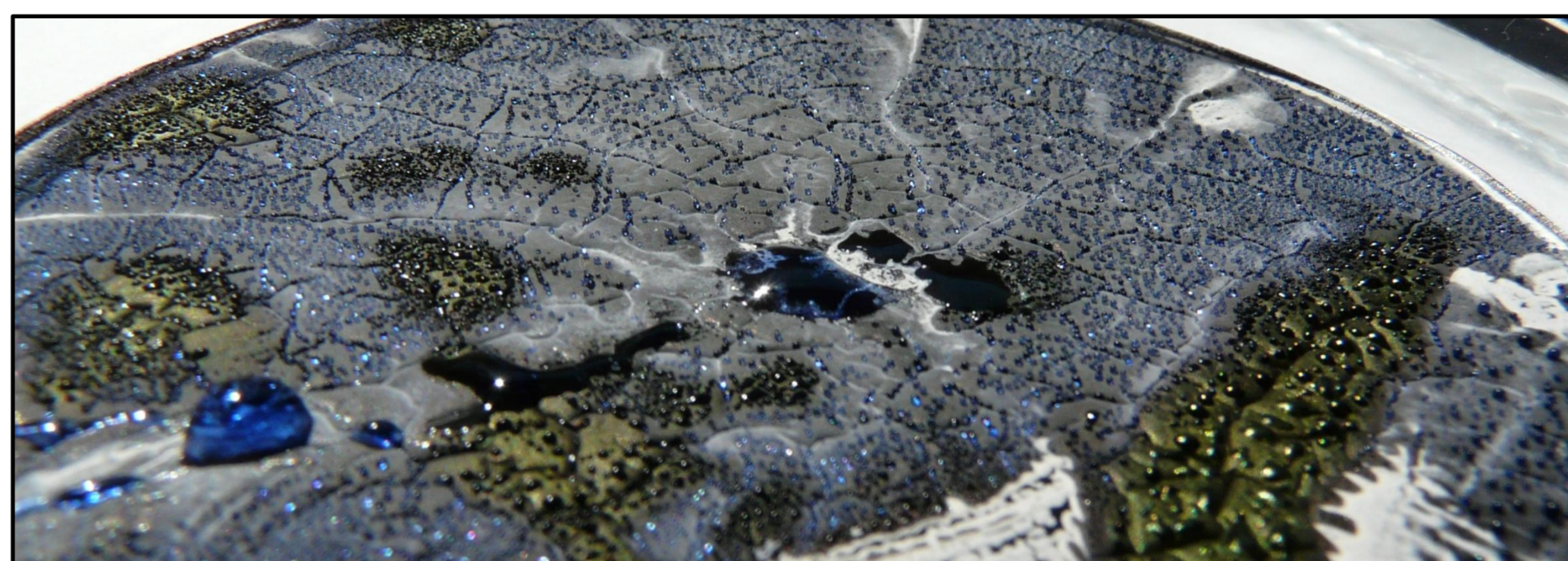


Fig 1. *Streptomyces* secreting blue pigmented antibiotic

2. Antibiotic-producing gene clusters controlled by conserved regulatory systems

In diverse *Streptomyces* bacteria, the production of drug-like compounds is regulated by a conserved set of 5 genes. These regulatory genes are clustered with genes that direct the assembly of antibiotic-like compounds (Fig 2) [2]. By understanding how the production of compounds is regulated, genetic manipulations can be carried out in these gene clusters to discover new natural drug compounds.

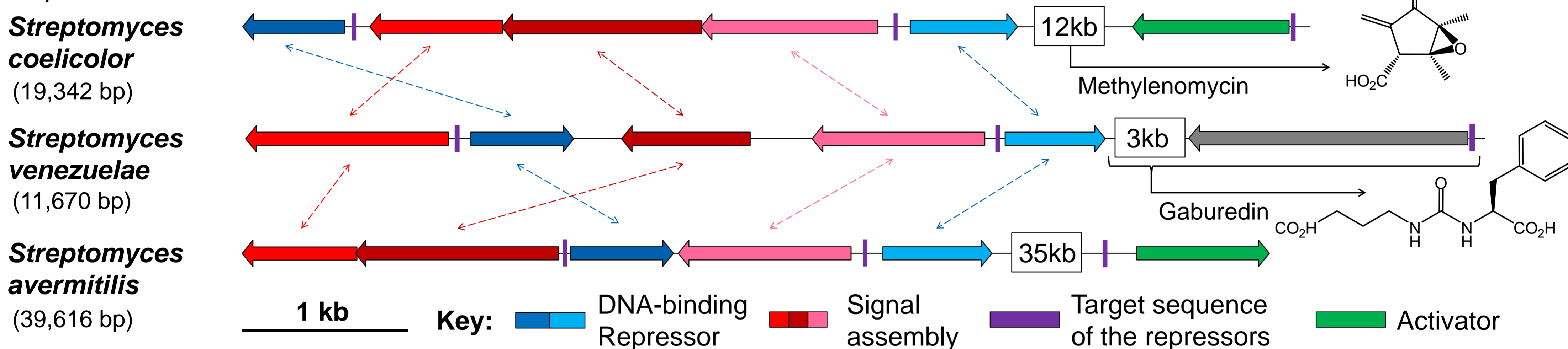


Fig 2. Gene clusters involved in regulating the production of drug-like compounds in *Streptomyces* bacteria

3. Predicted novel valanimycin-like compounds in *Streptomyces avermitilis* gene cluster

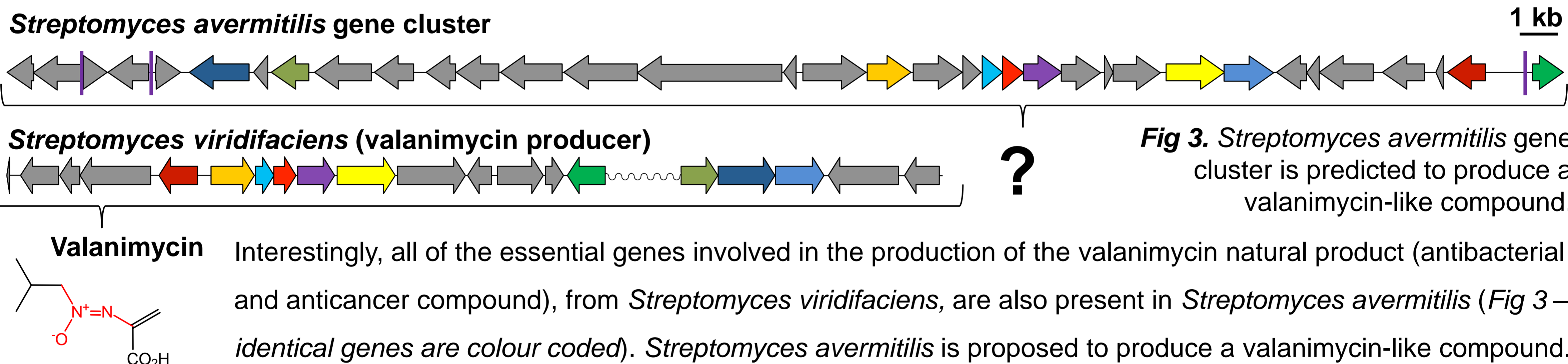


Fig 3. *Streptomyces avermitilis* gene cluster is predicted to produce a valanimycin-like compound.

4. Synthetic biology - “Playing” with regulators

In *Streptomyces coelicolor* and *Streptomyces venezuelae* (Fig 2), the deletion of regulators over-produces the compound. The rational genetic manipulation of the homologous regulator in *Streptomyces avermitilis* is expected to over-produce new valanimycin-like compounds.

5. Conclusions and Future works

An untapped source of drug compounds is waiting to be discovered in *Streptomyces* [2]. Using a synthetic biology approach, *Streptomyces avermitilis* is being manipulated and is expected to produce valanimycin-like compounds.

References

[1] Bentley, S.D. et al. (2002). *Nature*. [2] Corre, C. et al. (2008). *Proc. Natl. Acad. Sci.* [3] Ling, L.L. et al. (2015). *Nature*.

Acknowledgements

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