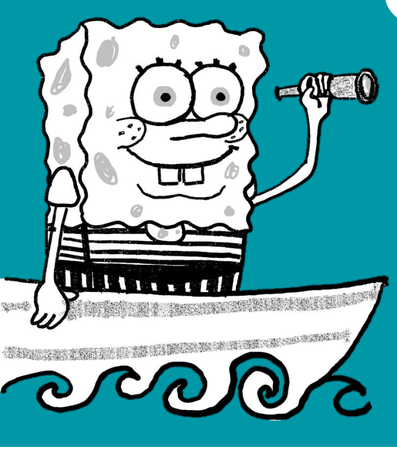
We're searching for **new antibiotics** in deep sea sponge bacteria



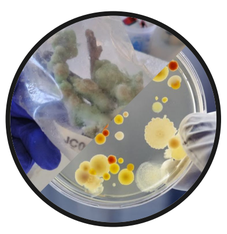
Antibiotic Discovery from the Abyss

***Henry Stennett**, Sam Williams, Catherine Back, Luoyi Wang, Paul Curnow, Chris Willis, Angela Essex-Lopresti, Paul Race.*

Introduction

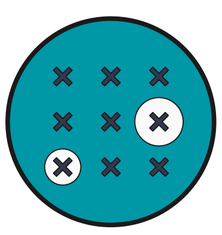
- **Antibiotic resistance** is getting worse and we need new antibiotics.
- **Natural products** have been the best source of antibiotics - they are evolutionarily optimised as drug-like molecules.
- Most of the living space on the planet is in the **deep sea**, and the extreme conditions there have led to metabolic innovation.
- A third of marine natural products were discovered in **sponges**, and are thought to be produced by members of the **microbiome**.

Methods



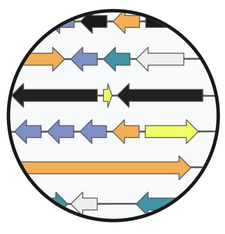
Isolation

Activity screening



Analytical chemistry

Genome assembly

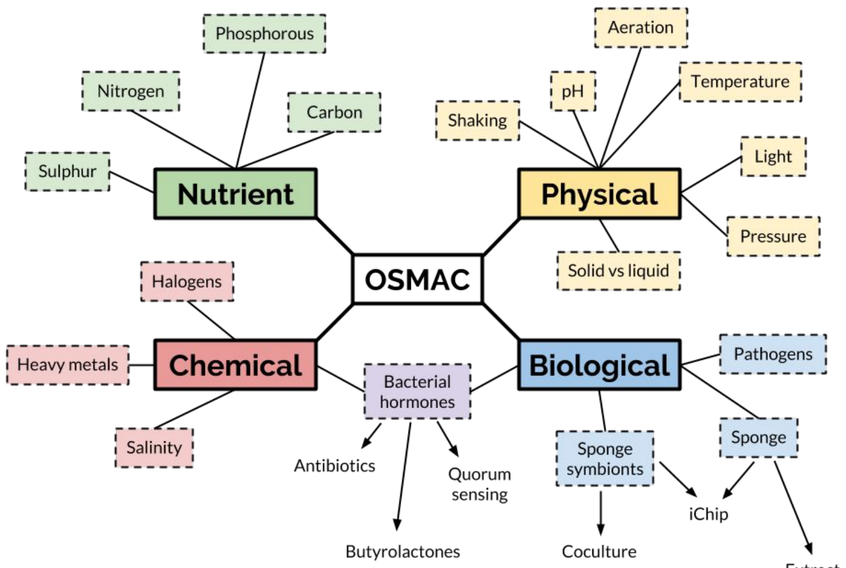


Genome mining

Transfer to heterologous host

We have established a pipeline from sponge to antibiotic.

OSMAC (One Strain Many Active Compounds) - Bacteria have the genetic potential to produce more natural products than we can isolate. Silent gene clusters can be awakened by changing culture conditions.



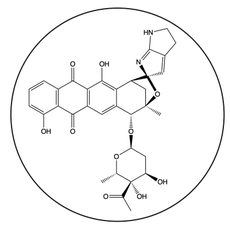
Results

Our initial screen of 487 isolates identified two hits (0.4%):

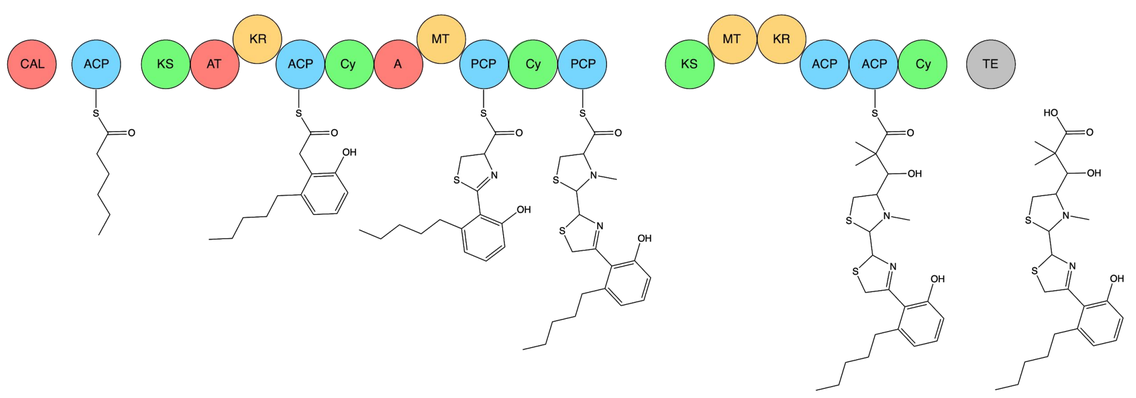
- *Bacillus pumilus* - a well known producer of antibiotics.
- *Micromonospora* sp. - a **likely novel species** from the second most prolific genus of antibiotic producers.

We rediscovered the quinocycline antibiotic **kosinostatin** from our *Micromonospora* sp. and found its biosynthetic gene cluster in the **completed genome**.

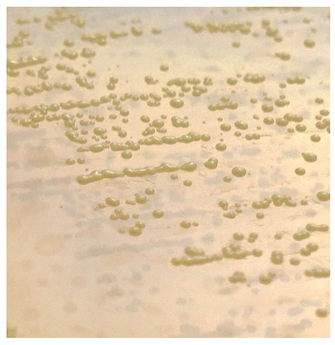
Drug \ MIC (uM)	MRSA	*A. bau*	*K. pneu*	*E. coli*	*E. coli eff* KO	*E. coli* IMP	HepG2
Kosinostatin	0.156	25	12.5	> 100	12.5	< 0.2	13.3
Sitafloxacin	0.156	0.078	< 0.02	< 0.02	< 0.02	< 0.02	-
Thioridazine	-	-	-	-	-	-	22.5

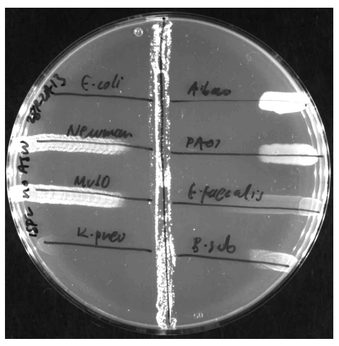


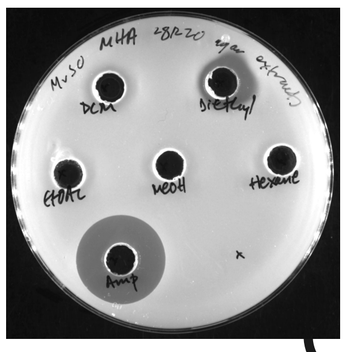
Our OSMAC screen of 90 isolates identified seven new hits (8%). We rediscovered **agrochelin** from *Stappia indica* and showed it has antibiotic activity for the first time. We also identified its putative biosynthetic gene cluster for the first time.



We have also identified a strain of *Kocuria rhizophila* that preferentially inhibits the growth of **Gram-negative** pathogens.

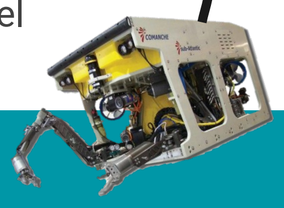






Future work

- Isolate active compounds from our remaining hits.
- Transfer biosynthetic gene clusters to heterologous hosts to link genotype to phenotype and discover novel products (**TAR cloning**).



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