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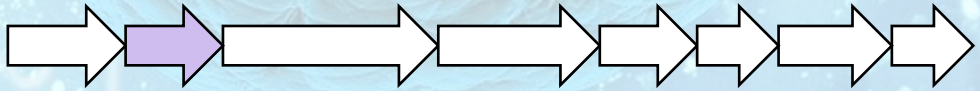
Accessing Hidden Therapeutics in Nature



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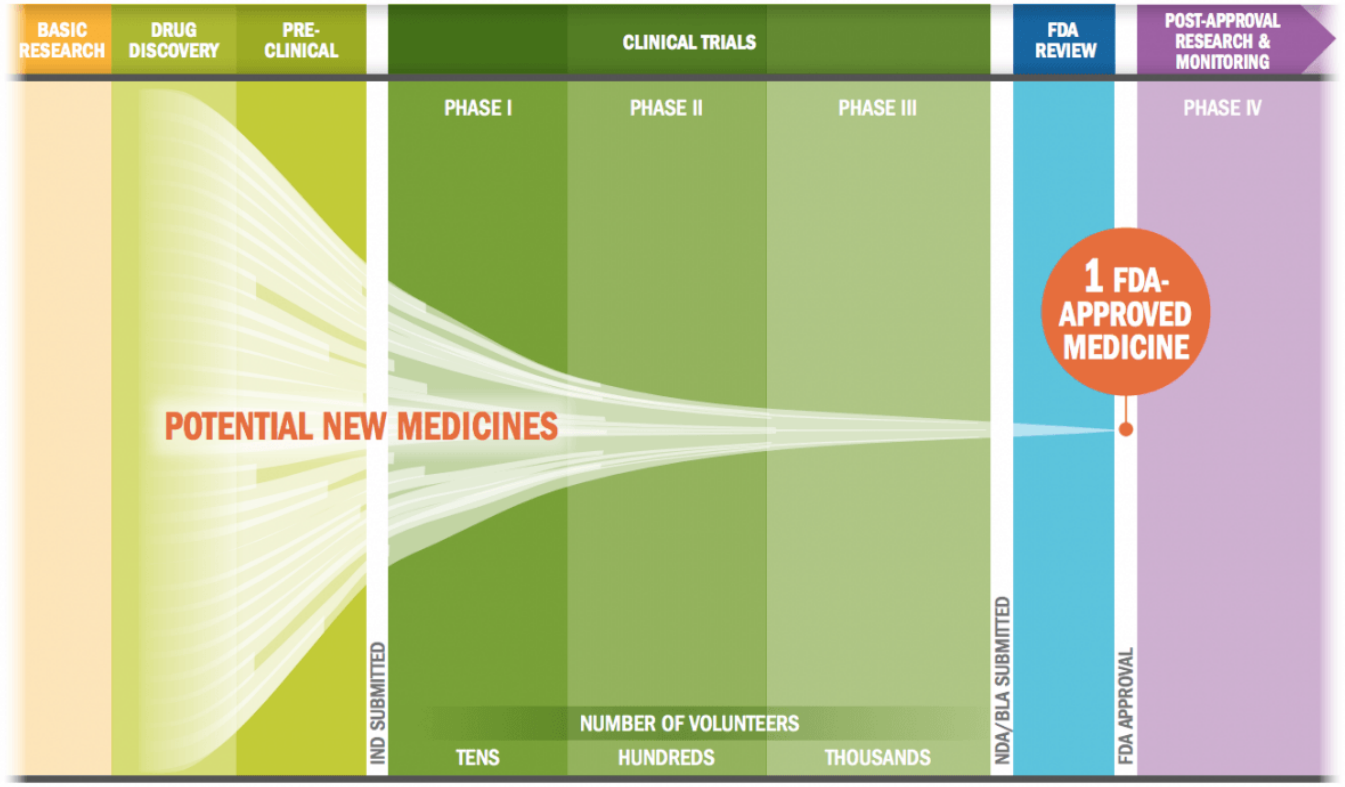
The Current Drug Discovery Paradigm: Slow and Costly

Synthetic drug leads

- Expensive
- Time-consuming
- Require extensive R & D
- Low hit-rate

What if we supply the drug discovery pipeline with a much larger drug-like chemical space?



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

- It takes $2.6 billion & 10-12 years to develop a drug
- No adequate treatment for 2/3 of all diseases

Source: PhRMa's 2015 "Biopharmaceutical Research & Development" PDF report

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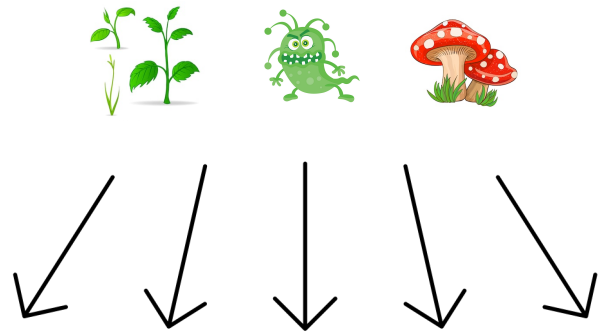
Microbial Natural Products: Most Diverse Reservoir of Evolved Therapeutic Agents

✓ >50% of FDA-approved drugs in the past 40 years are derived from natural products (from plants, bacteria, and fungi)



Paclitaxel
$1.1B in sales

Tacrolimus
$4.6B in sales

Azithromycin
$2.8B in sales

Cyclosporine
$2.5B in sales

Daptomycin
$1.2B in sales

✓ Natural products have better drug properties than synthetic drugs:

- Unmatched chemical diversity
- Difficult to conceive of and produce synthetically
- Higher hit-rate

✓ Big pharma divested from natural product programs due to the costly rediscovery of known compounds

✓ This is in part due to the silent or 'cryptic' nature of most biosynthetic genes: conventional methods only capture

~10% of a bacterium's biosynthetic potential

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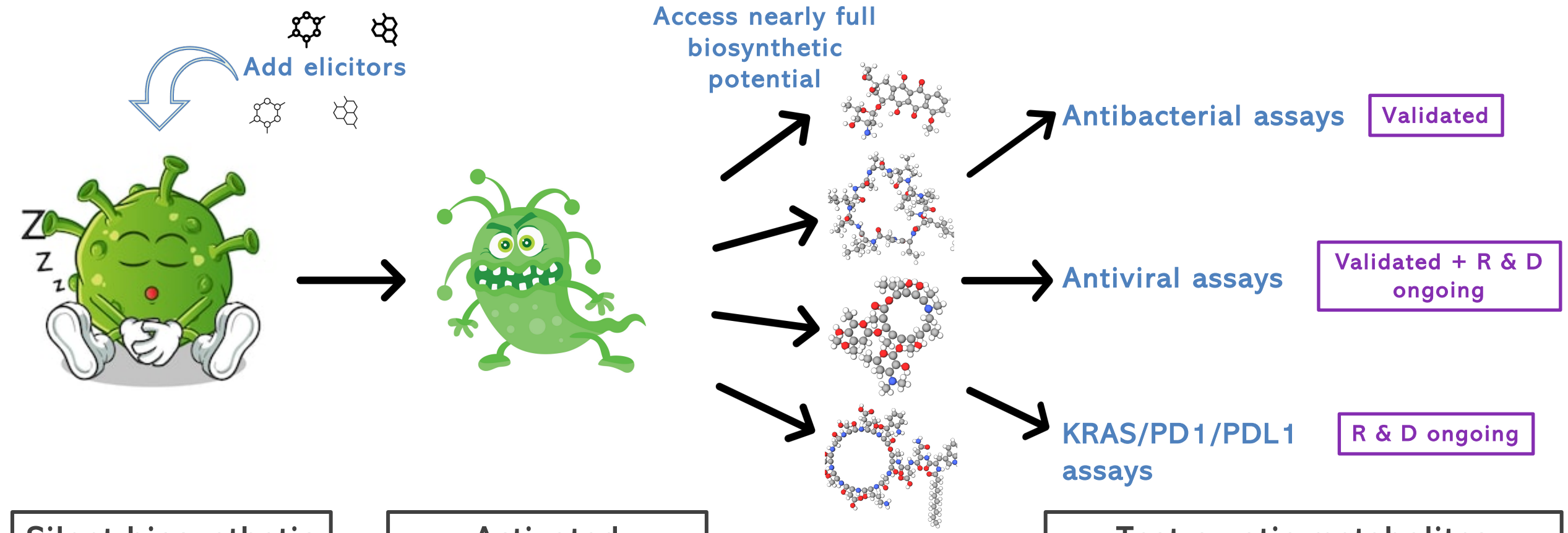
HiTES: High-Throughput Elicitor Screening

The HiTES Platform accesses up to 90% of this silent biosynthetic potential



Patented methodology: WO 2019/027877

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HiTES Anti-Infective Pipeline

Threat	Standard of care (SoC)	Problems with SoC	Our solution
Clostridium difficile Urgent CDC threat 223,900 cases in 2017 & 12,800 fatalities	Vancomycin; fidaxomicin; metronidazole	High resurgence; broad-spectrum (not-specific)	**Cryptyx-1k** (WO2019027877A1): **5-fold > metronidazole & vancomycin** **3-fold > fidaxomicin**
Neisseria gonorrhoeae Urgent CDC threat Drug-resistance on the rise with 500,000 cases yearly	Ceftriaxone + azithromycin	Rising resistance; parenteral administration; increased adverse effects with increasing doses	**Cryptyx-2t** (US20170022532A1): **high selectivity**
Mycobacterium tuberculosis **(TB)** Serious CDC threat 1.4 million fatalities, 214,000 fatalities from drug-resistant TB	RIPE therapy: rifampicin, isoniazid, pyrazinamide, ethambutol	Long treatment (min. 6 mo.) high rate of relapse; development of resistance	**Cryptyx-3k** (Drafting PCT): **high potency against drug-resistant TB;** **low toxicity**
Respiratory syncytial virus (RSV) Nearly all children are infected with RSV by age 2	No specific therapy, but Ribavirin is generally employed	Ribavirin is not recommended for infants	**Cryptyx-4k:** **20-fold > ribavirin**
Melioidosis Over165,000 worldwide cases and ~89,000 fatalities.	Ceftazidime and/or meropenem	High rate of relapse	**Cryptyx-5td:** **high potency; high selectivity**

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Timeline for Lead Development

Cryptyx-4k
RSV antiviral
20-fold > Ribavirin
Drafting PCT

Cryptyx-1k
C. Diff antibiotic
5-fold > Metronidazole
WO2019027877A1

Cryptyx-2t
Neisseria antibiotic
Highly selective
US20170022532A1

Stage I:
~4 months

Bacterial growth and compound isolation

Stage II
~6 months

Pharmacokinetics + Pharmacodynamics

Stage III
~6-12 months

Mouse Studies + Further Assessment

Pursue IND

Competitive Advantage of HiTES

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Hexagon Bio

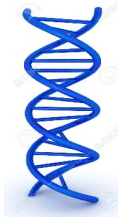
Lodo Therapeutics

unnatural products

Competing Workflow

Soil & other sources

1 mo.



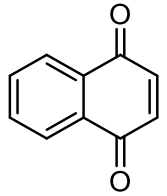
Sequence

1 mo.

3 mo.

3-6 mo.

1 mo.



Data science + synthetic biology to produce desired compound

Our Proprietary Workflow

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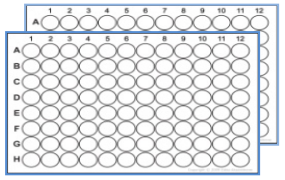
Soil & other sources

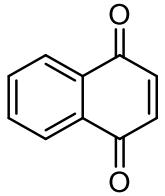
1 wk.



HiTES

1 mo.

1 mo.



Scaled production & isolation of desired compound

At least one year faster than competitors

Competitive Landscape
The Only Genetics-Free Bioactivity-First Platform

	Cryptyx Bioscience	Lodo Therapeutics	ADAPSYN	Magellan BioScience	Hexagon Bio	LifeMine
Proprietary Platform	✓	✓	✓	✓	✓	✓
Genetics-Free/ Cloning-Free	✓	✗	✗	✗	✗	✗
Bioactivity First	✓	✗	✗	✗	✓	✗
Sequencing required	✗	✓	✓	✓	✓	✓

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Deep Natural Product Drug Discovery Expertise

Mo Seyedsayamdost, PhD; Co-founder

Training: MIT, Harvard Medical School

Associate Professor at Princeton

MacArthur Fellow

Developed Technology Based on his Lab's Pioneering Research

Maryam Elfeki, PhD; Co-founder

Training: UIC, Princeton

Postdoctoral Fellow at Princeton

Technology Transfer and Late-Stage Biotech Investment Experience

Chari Smith, PhD; Scientific Advisor

Training: Cornell, Brandeis, UCLA

Drug Discovery Consultant

10+ years in GSK

5+ early-stage drug discovery consultant

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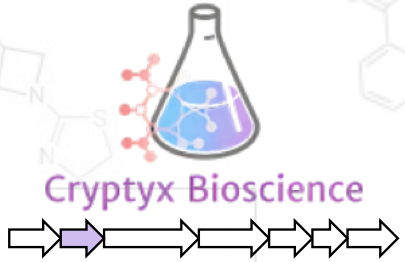
Combating Disease with Cryptic Metabolites



Awakening silent genes opens a new path to natural product drug discovery

APPENDIX

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Why Natural Products?

Natural products have more favorable drug characteristics than synthetic compounds:

	Synthetic/Combinatorial	Natural
Chemical diversity	Limited	No known limits
Polarity	Limited	Wide range
Intracellular target	Limited	Wide range
Molecular size	Small	Wide range
Three-dimensional complexity	Low	High
Aromatic rings	Common	Fewer
Chiral centers	Few	Many
Oxygen content	Low	High
Nitrogen content	High	Low
Macrocyclic aliphatic rings	Small/Uncommon	Large/Common

Biomed. Rep. 2017, 6:612–614; *Bioorg. Med. Chem. Lett.* 2015, 25:4802–4807; *J. Nat. Prod.* 2020, 83:770–803

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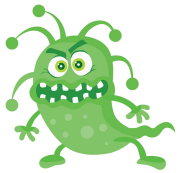
Why Microbial Natural Products?

- Plants, bacteria, and fungi are all prolific producers of biologically active natural products.
- **Bacteria are the oldest organisms.** They have been on earth for billions of years. They have evolved to live independently and as symbionts of diverse micro- and macroorganisms.

- Bacteria are less burdensome to work with than higher organisms (i.e. higher eukaryotes). They typically produce natural compounds at higher concentrations than plants, whose organic components are difficult to separate using conventional column chromatography.



- Some bacteria dedicate a relatively large percentage of their genome to biosynthesizing complex natural products, also referred to as secondary metabolites.

J. Ind. Microbiol. Biotechnol. 2014, 41:185–201.

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If Microbial Natural Product Show Such Great Potential, Why is Not Everyone Working With Them?

- Everyone should! However, most natural product biosynthetic genes were undiscovered until the advent of next-generation DNA sequencing technologies.
- Since then, scientists have discovered that bacteria have a much larger potential for natural product biosynthesis than previously anticipated, even well-studied bacteria explored for decades in bioproduction and other applications!
- Most natural product biosynthetic genes are silent or poorly expressed under normal laboratory growth conditions (monoculture in standard nutrient broth).
- Many scientists raced to discover the products of these genes, and the field regained new attention with many spin-off companies gaining traction (Lodo Therapeutics, Hexagon Bio, LifeMine Therapeutics, etc).
- However, the majority of these companies rely on genetic engineering and heterologous expression in non-natural hosts for the production of these compounds.
- We believe the native host is the best producer of its own compounds. **We are the only company that does not rely on heterologous expression to access 'hidden' natural products.**

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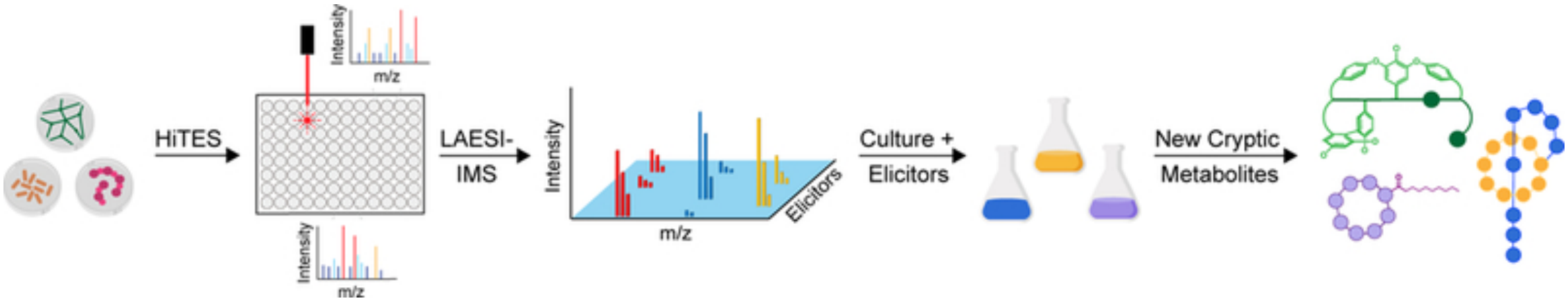
HiTES Platform: Tapping into the Largest Reservoir of Biologically Relevant Molecules

HiTES proof-of-concept pipeline



Select 'talented' bacterial producer

Bacterial producer arrayed in 96-well plates; small molecule elicitors are added

Global MS-based or bioactivity assay-based metabolome

Large scale fermentation

Novel metabolites

Each microbial strain screened with HiTES has produced a dozen or more cryptic metabolites

Patent # US20170022532A1

PNAS 2014, 111:7266–7271; *Nat. Chem. Biol.* 2019, 15:161–168; *ACS Chem. Biol.* 2019, 14:767–774