VUW-OUC Joint Symposium on Marine Drugs

Program on Tuesday February 28, 2023

Opening Ceremony	
Time: **9:00-9:20, February 28**	
Meeting ID: TBA	
Opening Ceremony Host: Xiaoyi Guan	
9:00-9:10	Paul Teesdale-Spittle (*Victoria University of Wellington, NZ*)
9:10-9:20	Dehai Li (*Vice Dean, School of Medicine and Pharmacy, Ocean University of China, CHN*)
Academic Symposium	
Time: 9:20-12:10, February 28	
Academic Host: Chao Cai	
9:20-9:40	**Title**: Heparan Sulfate, the Next Polymer Paradigm in Therapeutics **Speaker**: Simon Hinkley (*Victoria University of Wellington, NZ*)
9:40-10:00	**Title**: The Effects of Algae-derived Polysaccharides to Intestinal Microbiota **Speaker**: Guangli Yu (*Ocean University of China, CHN*)
10:00-10:20	**Title**: Drug Discovery of Btk Inhibitors Based on Fungal Natural Product (-)-TAN-2483B **Speaker**: Joanne Harvey (*Victoria University of Wellington, NZ*)
10:20-10:40	**Title**: Collective Total Synthesis of Penicimutanin A and its Congeners **Speaker**: Tao Xu (*Ocean University of China, CHN*)
10 mins Break	
Academic Host: Robert Keyzers	
10:50-11:10	**Title**: Nodulisporic Acid Biosynthesis: A Multifunctional Monooxygenase Delivers a Complex and Highly Branched Array **Speaker**: Alistair T. Richardson (*Victoria University of Wellington, NZ*)

11:10-11:30	**Title**: Searching Marine Natural Products Using Genome Mining and Synthetic Biology Tools **Speaker**: Guojian Zhang (*Ocean University of China, CHN*)
11:30-11:50	**Title**: Finding the Unknown: Developing an Unbiased Screen for Immunoregulation **Speaker**: Anne Camille La Flamme (*Victoria University of Wellington, NZ*)
11:50-12:10	**Title**: Study of a Marine Candidate Drug 1778 with Antitumor Effect by Activating NK Cells **Speaker**: Jing Li (*Ocean University of China, CHN*)
Closing Remarks	

Speakers Introduction and Presentation Abstracts

Invited Speaker

Simon Hinkley

Assoc. Professor, Ferrier Research Institute,
Victoria University of Wellington, New Zealand.
Tel: *+6427 501 8811;* ***Email:*** *simon.hinkley@vuw.ac.nz*

Education

1988-1991: B.Sc(Hons) University of Otago, New Zealand
1992-1995: PhD, University of Otago, New Zealand

Research Career

1997-1999 Post-doctoral scientist, University of Maryland at College Park, MD, USA.
1999-2006 Pharmaceutical engineering, IRL-BioPharm, New Zealand
2007-2013 Research scientist, Industrial Research Limited, NZ.
2014-2023 Assoc. Professor, Victoria Univiersty of Wellington, NZ.

Research Interests

Research completed in our group has a range of topics from natural product small molecule characterisation to polysaccharide analysis and organic synthesis:

- Natural products chemistry focused on the identification, isolation and characterisation of high-potency fungal metabolites.
- Complex carbohydrate analyses tackling:
  - Cell wall carbohydrate separation and characterisation
  - Sulfated seaweed polysaccharides
  - Glucosaminoglycan analyses and modifcation
- Organic synthesis of heparan sulfate mimetics.

Selected publications

1. Qasim, M.; Clarkson, A. N.; Hinkley, S. F. R., Green Synthesis of Carbon Nanoparticles (CNPs) from Biomass for Biomedical Applications. *International Journal of Molecular Sciences* **2023,** *24* (2), 1023.
2. Novis, P. M.; Bell, T. J.; Fraser, P.; Luiten, C. A.; Hinkley, S. F.; Borges, H.; Schallenberg, M., Nuisance mucilage produced by *Lindavia intermedia* (Bacillariophyceae) in New Zealand lakes. *Inland Waters* **2022,** *12* (2), 232-244.
3. Kidgell, J. T.; Carnachan, S. M.; Magnusson, M.; Lawton, R. J.; Sims, I. M.; Hinkley, S. F. R.; de Nys, R.; Glasson, C. R. K., Are all ulvans equal? A comparative assessment of the chemical and gelling properties of ulvan from blade and filamentous Ulva. *Carbohydr Polym* **2021,** *264*, 118010.

Heparan sulfate, the next polymer paradigm in therapeutics

Simon Hinkley
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The anticoagulant Heparin is the most widely used natural product human therapeutic. Application as an anticoagulant commands an international market worth US$ ~10 B.[4] The most negatively charged natural polymer[5] is arguably the most information-rich biomolecule in nature. However, while only mast cells produce Heparin, and it is present in our body in very small amounts, *every* cell generates the closely related heparan sulfate.

Our research focuses on the chemical composition of heparan sulfates.[6] The goal is to generate, for the first time, a therapeutic based on heparan sulfate that capitalizes on this molecules ability to bind selectivity to specific growth factors. As heparan sulfate is ubiquitous in the body it exhibits perfect biocompatibility; therefore, such a technology could direct cellular repair and speed tissue regeneration without any undesirable side-effects.

The characterization of this highly complex class of molecule, its application in a wound repair technology[9] and research towards wholly synthetic variants will be presented.

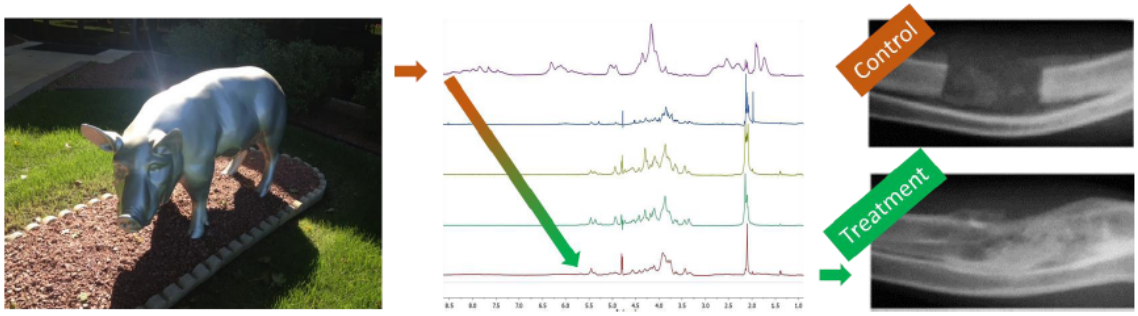

Figure 1. Porcine derived heparan sulfate with processing can promote rapid bone repair.[7,8]

Acknowledgements

This work is supported by the Ministry of Business, Innovation and Employment Endeavour Programme *Regenerative Therapies* (RTVU1706).

References

4. Zhu, Y.; Zhang, F.; Linhardt, R. J., Heparin contamination and issues related to raw materials and controls. In *The Science and Regulations of Naturally Derived Complex Drugs*, Sasisekharan, R.; Lee, S. L.; Rosenberg, A.; Walker, L. A., Eds. Springer: 2019; Vol. 32, pp 191-206.
5. Baytas, S. N.; Linhardt, R. J., Advances in the preparation and synthesis of heparin and related products. *Drug discovery today* **2020,** *25* (12), 2095-2109.
6. Sargison, L.; Smith, R. A.; Carnachan, S. M.; Daines, A. M.; Brackovic, A.; Kidgell, J. T.; Nurcombe, V.; Cool, S. M.; Sims, I. M.; Hinkley, S. F., Variability in the composition of porcine mucosal heparan sulfates. *Carbohydrate polymers* **2022,** *282*, 119081.
7. Wijesinghe, S. J.; Ling, L.; Murali, S.; Qing, Y. H.; Hinkley, S. F.; Carnachan, S. M.; Bell, T. J.; Swaminathan, K.; Hui, J. H.; van Wijnen, A. J., Affinity Selection of FGF2 - Binding Heparan Sulfates for Ex Vivo Expansion of Human Mesenchymal Stem Cells. *Journal of cellular physiology* **2016,** *10.1002/jcp.25454*.
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Invited Speaker

Guangli YU

Professor, Ocean University of China, School of Medicine and Pharmacy; Director, Key Laboratory of Marine Drugs, Ministry of Education of China; Shandong Provincial Key Laboratory of Glycoscience and Glycotechnology; Qingdao National Laboratory for Marine Science and Technology; No.5 Yushan Road, Qingdao 266003, China.

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Education

1984-1988: B.Sc. College of Marine Chemistry, Qingdao Ocean University, China

1993-1996: M.Sc. College of Food Engineering, Qingdao Ocean University, China

1998-2004: Ph.D. School of Medicine and Pharmacy, Ocean University of China

Academic Careers

1999 - 2000: Visiting Scholar, College of Pharmacy, University of Iowa, USA

2007.1-3: Visiting Professor, Université de Bretagne Occidentale, France

2008.7-8: Visiting Professor, Imperial College London, UK

2002 -present: Professor, Ocean University of China

Awards/Honors

First-class Prize of the State Technological Invention, 2009

Second-class Prize of National Oceanic Administration S&T Innovation Award, 2018

Second-class Prize of Shandong Provincial Scientific and Technological Progress, 2019

Taishan Scholar of Shandong Province, 2015-2020

Shandong Taishan Scholars Climbing Plan,2021-2025

Research Interests

The preparation and structural studies of marine poly/oligosaccharides; Structural studies of GAGs and N/O-glycans in biomass; Glycochip study and interaction of glycans with functional proteins; Relationship studies of glycans with human gut microbiota; Research and development of carbohydrate-based drugs.

Selected publications

1. Mingfeng Ma, Tianyu Fu, Y. Wang, A. Zhang, P. Gao, Q. Shang* and G. Yu*， Polysaccharide from Edible Alga Enteromorpha clathrate Improves Ulcerative Colitis in Association with Increased Abundance of Parabacteroides spp. in the Gut Microbiota of Dextran Sulfate Sodium-Fed Mice, ***Marine Drugs***, 2022, 20, 20, 764.
2. L. Pan，T. Fu, H. Cheng, J. Mi, Q. Shang*, G. Yu*， Polysaccharide from edible alga Gloiopeltis furcata attenuates intestinal mucosal damage by therapeutically remodeling the interactions between gut microbiota and mucin O-glycans，***Carbohydrate Polymers***，2022, 278：118921.
3. Lin Pan, Xuze Ai, Tianyu Fu, Li Ren, Qingsen Shang*, Guoyun Li*, G. Yu*， In vitro fermentation of hyaluronan by human gut microbiota: Changes in microbiota community and potential degradation mechanism，***Carbohydrate Polymers***，2021, 269：118313.

4. Lin Pan#, Chao Cai#, Chanjuan Liu, Di Liu, Guoyun Li, Robert J Linhardt，G. Yu*，Recent Progress and Advanced Technology in Carbohydrate-Based Drug Development，***Current Opinion in Biotechnology***，2021, 69:191–198
5. Chen Wang，Guoyun Li, Kaige Cui, Zihan Chai, Ziyu Huang, Yue Liu, Shang Chen, Haoyan Huang, Kaiyue Zhang, Zhibo Han, Yuhao Li, Guangli Yu, Zhong-Chao Han, Na Liu*, Zongjin Li*， Sulfated glycosaminoglycans in decellularized placenta matrix as critical regulators for cutaneous wound healing，***Acta Biomaterialia，2021***，122: 199-210
6. Lin Pan，Weixia Sun, Qingsen Shang, Qingfeng Niu, Chanjuan Liu, Guoyun Li*, Guangli Yu*，In Vitro Fermentation and Isolation of Heparin-degrading Bacteria from Human Gut Microbiota，***Anaerobe***, 2020，102289
7. Xindi Shan, Xueliang Wang, Hao Jiang, Chao Cai, Jiejie Hao, Guangli Yu*, Fucoidan from *Ascophyllum nodosum* Suppresses Postprandial Hyperglycemia by Inhibiting Na+/Glucose Cotransporter 1 Activity, ***Marine Drugs***, 2020, 18(9): 485
8. Chendong Yang, Lei Gao, Meng Shao, Chao Cai*, Lihao Wang, Yifan Chen, Jianghua Li, Fei Fan, Yubing Han, Ming Liu*, Robert J. Linhardt and Guangli Yu*， End-functionalised glycopolymers as glycosaminoglycan mimetics inhibit HeLa cell proliferation， ***Polymer Chemistry***，2020，11:4714
9. Jianghua Li，Yang Zhang，Chao Cai*, Xiaozhi Rong, Meng Shao, Jiarui Li, Chendong Yang and Guangli Yu*，Collaborative assembly of doxorubicin and galactosyl diblock glycopolymers for targeted drug delivery of hepatocellular carcinoma，***Biomater. Sci***., 2020, 8, 189–200
10. Jun Li，Chao Cai*, Lihao Wang, Chendong Yang, Hao Jiang, Miaomiao Li, Ding Xu, Guoyun Li, Chunxia Li, Guangli Yu*，Chemoenzymatic Synthesis of Heparan Sulfate Mimetic Glycopolymers and Their Interactions with the Receptor for Advanced Glycation End-Product，***ACS Macro Lett.*** 2019, 8, 1570−1574.
11. Yi Yang，Xiaoliang Zhao, Jia Li, Hao Jiang, Xindi Shan, Ya Wang, Wenbang Ma, Jiejie Hao*, Guangli Yu*， A β-glucan from Durvillaea antarctica exerts immunomodulatory effects on RAW264.7 macrophages via Toll-like receptor 4，***Carbohydrate Polymers***, 2018,191:255-265.
12. Qingsen Shang, YaWang, Lin Pan, Qingfeng Niu, Chao Li, Hao Jiang, Chao Cai, Jiejie Hao, Guoyun Li and Guangli Yu*，Dietary Polysaccharide from Enteromorpha Clathrata Modulates Gut Microbiota and Promotes the Growth of Akkermansia muciniphila, Bifidobacterium spp. and Lactobacillus spp. ***Mar. Drugs***, 2018, 16, 167
13. W. Wang, J. Wu, X. Zhang, C. Hao, X. Zhao, G. Jiao, X. Shan, W. Tai, G. Yu*, Inhibition of Influenza A Virus Infection by Fucoidan Targeting Viral Neuraminidase and Cellular EGFR Pathway. ***Sci. Rep***., **2017**, *7*, 40760.
14. Lang Ding, Xindi Shan, Xiaoliang Zhao, Hualian Zha, Xiaoyu Chen, Jianjun Wang, Chao Cai *, Xiaojiang Wang, Guoyun Li, Jiejie Hao, Guangli Yu*, Spongy bilayer dressing composed of chitosan-Ag nanoparticles and chitosan-Bletilla striata polysaccharide for wound healing applications， ***Carbohydrate Polymers***, 2017,157: 1538-1547.
15. X. Zhang, X. Zhao, Y. Lang, Q. Li, X. Liu, C. Cai, J. Hao, G. Li, G. Yu*，Low Anticoagulant Heparin Oligosaccharides as Inhibitors of BACE-1, the Alzheimer's β-Secretase. ***Carbohydrate Polymers***, **2016**, 151, 51-59.

The Effects of Algae-derived Polysaccharides to Intestinal Microbiota

Guangli Yu[1,2], Qingsen Shang[1,2], Chao Cai[1,2], Guoyun Li[1,2], Hao Jiang[1,2]

[1]Key Laboratory of Marine Drugs of Ministry of Education of China, and Shandong Provincial Key Laboratory of Glycoscience and Glycotechnology, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, P. R. China

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There are over 1000 species bacteria in healthy human gut, and the total sum of colon bacteria up to 100 trillion. These bacteria contain over 3-millions genes, which can produce diverse of proteinase, lipases and carbohydrate hydrolyses etc. All these enzymes are essential for the gut to offer differet nutrients for human body. Many papers reported that, the abnormal gut bacteria are associated with inflammation, obesity, diabetes, Alzheimer's and tumors. Polysaccharides are essential nutrients for gut bacteria, and different sugar may affect different bacteria. Marine algae are very good sources of polysaccharides, such as the agarose and carrageenan are from red algae, the alginate and fucoidan are from brawn algae, and the ulvan from green algae. Although the above polysaccharides are traditionally used as food additives, but their effect to the gut microbiota are still not very clear. I will show our research works of the effects of marine polysaccharides (agar, alginate, fucoidan, carrageenan, Ulvan) to the intestinal microbiota.

References

1. Donaldson GP, Lee SM, Mazmanian SK. Gut biogeography of the bacterial microbiota. ***Nat Rev Microbiol,*** 2016, 14: 20-32.

2. Mingfeng Ma, Tianyu Fu, Y. Wang, A. Zhang, P. Gao, Q. Shang* and G. Yu*. Polysaccharide from Edible Alga Enteromorpha clathrate Improves Ulcerative Colitis in Association with Increased Abundance of Parabacteroides spp. in the Gut Microbiota of Dextran Sulfate Sodium-Fed Mice, ***Marine Drugs***, 2022, 20, 764.

3. Qingsen Shang, Ya Wang, Lin Pan, Qingfeng Niu, Chao Li, Hao Jiang, Chao Cai, Jiejie Hao, Guoyun Li and Guangli Yu*. Dietary Polysaccharide from Enteromorpha Clathrata Modulates Gut Microbiota and Promotes the Growth of *Akkermansia muciniphila, Bifidobacterium spp. and Lactobacillus spp*. ***Mar. Drugs***, 2018, 16, 167.

4. Qingsen Shang, Weixia Sun, Xindi Shan, Hao Jiang, Chao Cai, Jiejie Hao, Guoyun Li, Guangli Yu*. Carrageenan-induced colitis is associated with decreased population of anti-inflammatory bacterium, *Akkermansia muciniphila*, in the gut microbiota of C57BL/6J mice. ***Toxicology Letters***, 2017, 279: 87-95.

5. Qingsen Shang, Guanrui Song, Meifang Zhang, Jingjing Shi, Cuiying Xu, Jiejie Hao, Guoyun Li, Guangli Yu*. Dietary fucoidan improves metabolic syndrome in association with increased Akkermansia population in the gut microbiota of high-fat diet-fed mice. ***Journal of Functional Foods***, 2017, 28, 138.

6. Miaomiao Li, Qingsen Shang, Guangsheng Li, Xin Wang *, Guangli Yu *. Degradation of marine algae-derived carbohydrates by Bacteroidetes isolated from human gut microbiota. ***Marine Drugs***, 2017, 15(4), 92.

Invited Speaker

Joanne HARVEY

Associate Professor, School of Chemical and Physical Sciences, Victoria University of Wellington, NEW ZEALAND
***Tel:** +64(4)4635956； **Email:** joanne.harvey@vuw.ac.nz*

Education

1992-1995: BSc. Hons in Chemistry Victoria University of Wellington

1997-2000: PhD in Chemistry, Australian National University

Academic Positions

2020-present: Associate Professor of Chemistry, Victoria University of Wellington.

2010-2019: Senior Lecturer in Chemistry, Victoria University of Wellington.

2004-2010: Lecturer in Chemistry, Victoria University of Wellington.

2001-2004: Postdoctoral Research Fellow, University of York (Professor Richard J. K. Taylor)

1996-1997: Research Chemist, Carbohydrate Chemistry Team, Industrial Research Ltd.

Awards and Fellowships

2015: GWW Victoria Academic Staff Development Award

2015-current: Fellow of the New Zealand Institute of Chemistry (FNZIC)

2014-current: Awarded Fellowship of the Royal Society of Chemistry (FRSC)

Research Interests

My core skills and expertise are in organic chemical synthesis, determination of properties and structural characterisation of complex organic molecules. These are deployed in many different settings, from nature-inspired drug discovery through medicinal chemistry to development of new chemical methodologies for accessing novel molecular structures.

Selected publications

1. Gold(I)-catalyzed, one-pot, oxidative formation of 2,4-disubstituted thiazoles: Application to the synthesis of a pateamine-related macrodiolide. T. Xu, C. Cuyamendous, S. L. Brown, S. K. Andreassend, H. Cumming, G. B. Evans, P. H. Teesdale-Spittle, J. E. Harvey. *Tetrahedron* **2021**, *88*, 132109. https://doi.org/10.1016/j.tet.2021.132109

2. Total Synthesis and Bioactivity Studies of Fungal Metabolite (-)-TAN-2483B. Jordan A. J. McCone, Kalpani K. Somarathne, Christopher L. Orme, Russell J. Hewitt, Elysha-Rose Grant, Kelsi R. Hall, David F. Ackerley, Anne C. La Flamme, Joanne E. Harvey. *Org. Lett.* **2020**, *Org. Lett.* **2020**, 22, 9427–9432. https://pubs.acs.org/doi/10.1021/acs.orglett.0c03303

3. A colourful azulene-based protecting group for carboxylic acids. Thomas W. Bevan, James Francis-Taylor, Helena Wong, Peter T. Northcote, Joanne E. Harvey. *Tetrahedron* **2018**, *74*, 2942-2955. https://doi.org/10.1016/j.tet.2018.04.066

Drug discovery of Btk inhibitors based on fungal natural product (-)-TAN-2483B

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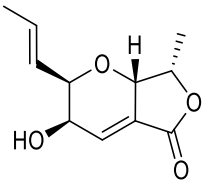
The natural product (-)-TAN-2483B was isolated from a Japanese filamentous fungus extract that inhibits *c*-src kinase and PTH-induced bone resorption.[1] Our total synthesis of the natural product enabled determination of its bioactivity, which included inhibition of bacterial pathogens, immunomodulatory effects and inhibitor of the kinase Btk (Bruton's tyrosine kinase) but not *c*-src.[2] Btk is of particular interest as a validated drug target for B-cell cancers.[3] Following from our initial SAR studies of side-chain analogues of (-)-TAN-2483B,[4] computational structure-based drug design and additional analogue synthesis have enhanced our understanding of the structural features in the TAN-2483B system that are necessary for Btk inhibition. This presentation will cover our synthetic, modelling and screening work involving the natural product and side-chain analogues, as well as exploration of second-generation analogues of TAN-2483B.



(-)-TAN-2483B

Reference*s*

1. Hayashi, K.; Takizawa, M; Noguchi, K. TAN-2483-Related Compound, Its Production and Use. Japanese Patent JP10287679 (A), 27 October, **1998**; *Chem. Abstr.* **1999**, *130*, 3122e.
2. McCone, J. A. J.; Somarathne, K. K.; Orme, C. L.; Hewitt, R. J.; Grant, E.-R.; Hall, K. R.; Ackerley, D. F.; La Flamme, A. C.; Harvey, J. E. *Org. Lett.* **2020**, *22*, 9427**–**9432.
3. Lucas, F.; Woyach, J. A. *Targeted Oncology* **2019**, *14*, 125**–**138.
4. Somarathne, K. K.; McCone, J. A. J.; Brackovic, A.; Rivera, J. L. P.; Fulton, J. R.; Russell, E.; Field, J. J.; Orme, C. L.; Stirrat, H. L.; Riesterer, J.; Teesdale-Spittle, P. H.; Miller, J. H.; Harvey, J. E. *Chem. – Asian J.* **2019**, *14*, 1230–1237.

Invited Speaker

Tao XU

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***Tel:** +86(532)85906822； **Email:** xutao@ouc.edu.cn*

Education/Acdemic Training

2002-2006: B.Sc. School of Chemical Engineering, Dalian University of Technology, China

2006-2011: Ph.D. School of Chemistry, Peking University, China

2011-2015: Postdoc, Dept. of Chemistry, University of Texas at Austin, Texas, USA

Academic Careers

2015 --present: Professor, School of Medicine and Pharmacy, Ocean University of China

Awards/Honors

2022 **Thieme Chemistry Journal Award**

2022 The 12th **Shandong Youth Scinece and Technology Prize**

2021 **Excellent Young Scientists Fund**, NSFC, China

2020 The Natural Science Fund for **Distinguished Young Scholars**, Shandong province.

2019 Recipient of the **Natural Science Award, Qingdao** Municipal Government

2016 Recipient of the Taishan Youth Scholar Award, Shandong Government, China

Research Interests

My research focuses on developing new methodologies employing transition metal catalysis in generating versatile molecular skeletons, which could be ultimately applied in complex bioactive natural products and/or pharmaceutically active intermediate synthesis.

Selected publications

[1] "Regioselective Activation of Benzocyclobutenones and Dienamides Lead to anti-Bredt Bridged-Ring Systems by a [4+4] Cycloaddition." Zhang, J.; Wang, X.; **Xu, T.*** ***Nat. Commun.* 2021,** *12,* 3022.

[2] "Rh-Catalyzed Cascade C–C/C_{olefin}–H Activations and Mechanistic Insight." Wang, Y.; Qiu, B.; Hu, L.; Lu, G.;*** Xu, T.*** ***ACS Catal.* 2021,** *11,* 9136-9142.

[3] "Total Synthesis of (–)-Penicimutanin A and the Related Congeners." Yu, H.; Zong, Y.; **Xu, T.*** ***Chem. Sci.* 2020,** *11,* 656-660.

[4] "Total Synthesis of Galanthamine and Lycoramine Featuring an Early-Stage C–C and a Late-Stage Dehydrogenation via C–H Activation." Zhang, Y.; Shen, S.; Fang, H.; **Xu, T.*** ***Org. Lett.* 2020**, *22,* 1244-1248.

[5] "Rh^{I}-Catalyzed Carboacylation/Aromatization Cascade Initiated by Regioselective C−C Activation of Benzocyclobutenones" Sun T.; Zhang, Y.; Qiu, B.; Wang, Y.; Qin, Y.; Dong, G.*; **Xu, T.*** ***Angew. Chem. Int. Ed.* 2018**, *57,* 2859-2863.

Collective Total Synthesis of Penicimutanin A and its Congeners

Tao Xu[1,2]

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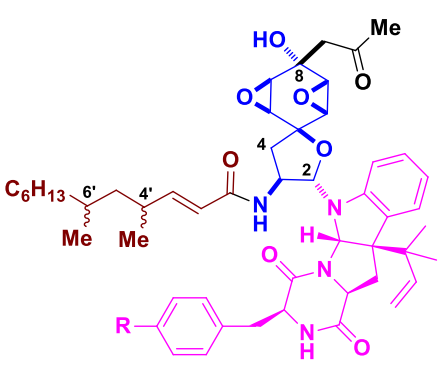
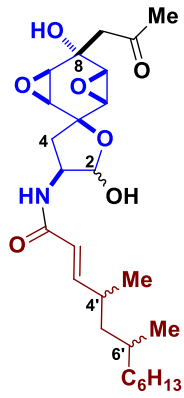
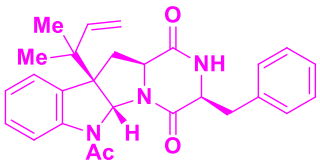


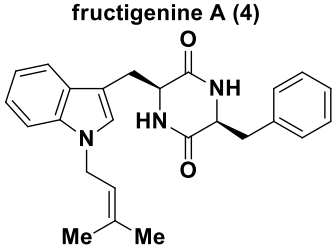
R= H, penicimutanin A (1)
R=OH, penicimutanin B (2)



penicimutanolone (3)



fructigenine A (4)



penicimutatin (5)

Fungi have been exploited as rich sources to generate structurally appealing molecules featuring synthetically challenging motifs and consecutive stereocenters, which often displayed promising bioactivities towards life-threatening diseases. In particular, for deep sea-derived fungi strains, chemical mutagenesis is commonly used to activate “muted genes” for discovery of new natural products. Penicimutanin A (**1**) and B (**2**) were two representative secondary metabolites reported by Cui and coworkers in 2014, isolated from a marine-derived fungal strain identified as Penicillium purpurogenum G59 through chemical mutagenesis.[1] In addition to 1, penicimutanolone (**3**) and penicimutatin (**5**) together with known fructigenine A (**4**) were also isolated alongside, indicating their biosynthetic interrelationship. These secondary metabolites and their congeners were found to possess a range of biological activities from anti-fungal as a histidine kinase inhibitor to anti-inflammatory as well as anti-tumor effects. However, these natural products suffered from limited supplies from natural sources. In addition, the absolute configuration of penicimutanin A and penicimutanolone remained undetermined.[2]

References

[1] Fang, S.-M.; Wu, C.-J.; Li, C.-W.; Cui, C.-B. *Mar. Drugs*, **2014**, *12*, 1788-1814;

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Alistair T. Richardson

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Education

2012-2015: Bsc(Hons) Chemistry, University of Otago, New Zealand
2016-2019: PhD Chemistry, University of Otago, New Zealand

Academic Career

2019-2021: Postdoctoral Research Fellow, Ferrier Research Institute Victoria University of Wellington
2021-present: Scientist, Ferrier Research Institute Victoria University of Wellington

Research Interests

Biosynthesis of high value natural products with commercial potential. Currently focused on investigating the biosynthesis of indole diterpenes in filamentous fungi.

Publications

1. Richardson, A. T., et al. (2022). "Biosynthesis of Nodulisporic Acids: A Multifunctional Monooxygenase Delivers a Complex and Highly Branched Array." Angewandte Chemie International Edition **n/a**(n/a): e202213364.
2. Bundela, R., et al. (2023). "Generation of Alternate Indole Diterpene Architectures in Two Species of Aspergilli." Journal of the American Chemical Society **145**(5): 2754-2758.

Nodulisporic Acid Biosynthesis: A Multifunctional Monooxygenase Delivers a Complex and Highly Branched Array

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Nodulisporic acids are structurally complex indole diterpenes renowned for their potent anti-insect properties. We previously reported the biosynthetic gene cluster for these metabolites in *Hypoxylon pulicicidum* and now report the complete elucidation of their biosynthesis through heterologous expression of cluster encoded gene products in *Penicillium paxilli*.

The complex and highly branched nature of this biosynthetic pathway arises due to modification of the carboxylated prenyl tail by a single promiscuous P450 monooxygenase, NodJ. Through heterologous recombination and feeding studies we have shown that NodJ acts on a key intermediate, NAD_4 (nodulisporic acid D_4), to generate four distinct products (Figure 1), NAD, NAD_1, NAD_5 and NAD_6.

The catalytic promiscuity of NodJ can be rationalized as oxidation at two separate sites, with additional complexity introduced through formation of an allylic radical intermediate which partitions to either NAD through loss of hydrogen or to NAD_6 through reaction with an iron-bound hydroxyl radical. This mechanistic bifurcation is crucial to the generation of chemical diversity in nodulisporic acid biosynthesis giving rise to the metabolic grid that characterises this pathway and is unprecedented in indole diterpene biosynthesis.

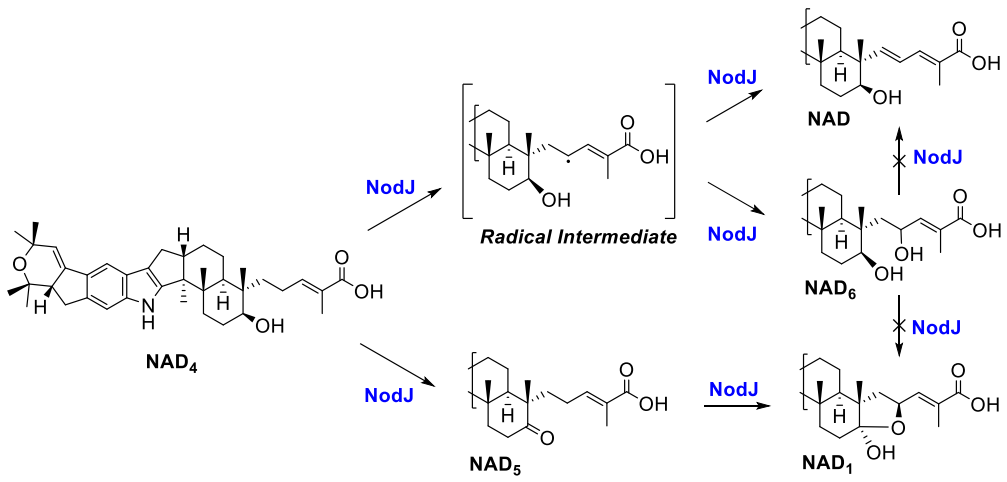

Figure 1. *Monooxygenase NodJ acts on biosynthetic intermedaite NAD_4 to give four distinct products.*

Invited Speaker

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Education

2002-200.6: B.Sc. College of Marine Life Sciences, Ocean University of China, China

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Academic Careers

2011.12-2014.12: Postdoc, Department of Chemical and Biological Engineering, SUNY at Buffalo, USA

2014.12-2016.10: Postdoc, Department of Biochemistry, University of Oklahoma, USA

2016.10-2017.6: Postdoc, Department of Chemical and Biological Engineering, SUNY at Buffalo, USA

2017.7-2022.12: Associate Professor, School of Medicine and Pharmacy, Ocean University of China

2022.12--present: Professor, School of Medicine and Pharmacy, Ocean University of China

Awards/Honors

Taishan Scholar Youth Expert Program in Shandong Province, 2020

Research Interests

Discovery and Biosynthesis of bioactive natural products which includes: 1) Using genome mining and synthetic biology methods combined with traditional natural product chemistry tools to discover bioactive compounds from marine microorganisms; 2) Using metabolic engineering and combinatorial biosynthesis methods to rebuild the biosynthetic pathway in native or heterologous host to produce bioactive compounds and analogues.

Selected publications

1. Guowei Liu, Dan Liu, Zongyuan Li, Jieying Jiao, Xuewen Hou, Xiaomin Zhang, Qian Che, Tianjiao Zhu, Dehai Li, **Guojian Zhang***. Overexpression of transcriptional regulator and tailoring enzyme leads to the discovery of anti-inflammatory meroterpenoids from marinederived fungus *Alternaria alternata* JJY-32. *Fron. Mar. Sci.*, 2022, DOI: 10.3389/fmars.2022.1015684.
2. Kaijin Zhang#, **Guojian Zhang#**, Xuewen Hou, Chuanteng Ma, Junyu Liu, Qian Che, Tianjiao Zhu, Dehai Li*. A Fungal Promiscuous UbiA Prenyltransferase Expands the Structural Diversity of Chrodrimanin-Type Meroterpenoids. *Org. Lett.*, **2022**, 24, 2025−2029.
3. Yimin Chang, Qian Che, Li Xing, Chuanteng Ma, Yaxin Han, Tianjiao Zhu, Blaine A. Pfeifer, Jixing Peng, **Guojian Zhang*** and Dehai Li*. Antibacterial p-Terphenyls with rare 2,2'-bithiazole moiety

isolated from marine-derived actinomycete *Nocardiopsis* sp. HDN154086. *J. Nat. Prod*., **2021**, 84(4):1226–1231.

4. Chuanteng Ma, Kaijin Zhang, Xianyan Zhang, Guowei Liu, Tianjiao Zhu, Qian Che, Dehai Li, **Guojian Zhang***. Heterologous expression and metabolic engineering tools for improving terpenoids production. *Curr. Opin. Biotech*., **2021**, 69, 281-289.
5. Ruonan Sun, Yanyan Feng, Hengyi Xu, Xuewen Hou, Tianjiao Zhu, Qian Che, Blaine Pfeifer, **Guojian Zhang*** and Dehai Li*. An Efficient Marker Recycling System for Sequential Gene Deletion in a Deep Sea-derived Fungus *Acremonium* sp. HDN16-126. *Synth*. *Syst. Biotechnol.*, **2021**, 6, 2, 127-133.
6. **Guojian Zhang**, Yi Li, Lei Fang and Blaine A. Pfeifer. Tailoring Pathway Modularity in the Biosynthesis of Erythromycin Analogues Heterologously Engineered in *E. coli. Sci. Adv.*, **2015**, 1, e1500077.

Searching Marine Natural Products Using Genome Mining and Synthetic Biology Tools

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It is a certain challenge to obtain metabolites from microorganisms derived from the marine environments due to a large part of the metabolic potential of such microorganisms are not released under the conventional laboratory cultivations. This problem could be alleviated by using genome mining and synthetic biology tools which either facilitate the activation of target gene clusters in situ or expressing them in heterologous hosts. We have set up the natural product isolation and characterization, biosynthetic study and metabolic engineering platforms which are effective on searching of bioactive compounds from marine environments such as deep sea, polar regions and mangrove ecosystems. In our recent work, heterologous expression of a type II PKS biosynthetic gene cluster (BGC) cloned from a marine derived actinomycete strain *Streptomyces* sp. led us to isolate and characterize a series of cytotoxic angucycline derivatives including spirocyclione A (**1**), with a novel oxaspiro[benzochromene-2,1'-cyclohexane] architecture, and spirocyclione B (**2**), with an intriguing di-carboxylic substituted benzochromene scaffold. Biosynthesis studies confirmed the unique structures of **1** and **2** were produced from unprecedented flavin-dependent oxidation steps where SpiH3 catalyzed the oxidative cleavage of the C12-C12a bond of an early angular intermediate to form the oxaspiro structure in **1**, and SpiH1, a new member of BVMOs in the antibiotic biosynthesis monooxygenase (ABM) superfamily, was responsible for the C12a-C12b bond cleavage of **1** to give the A-ring opened product of **2**. Above work reveals an unprecedented pattern of post-PKS modification on angucycline skeletons that contribute structural diversity and complexity to aromatic polyketides.

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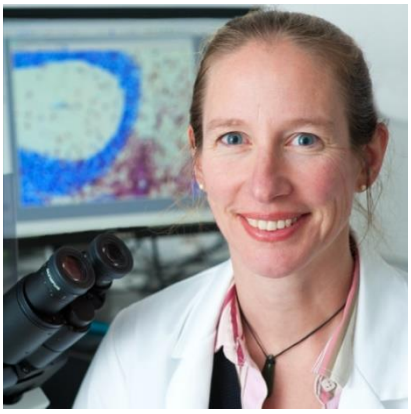
6 H. L. Wang, Z. Li, R. Jia, Y. Hou, J. Yin, X. Y. Bian, A. Y. Li, R. Müller, A. F. Stewart, J. Fu, Y. M. Zhang, *Nat. Protoc*., 2016, **11**, 1175-1190.



Anne Camille La Flamme, PhD. Prof La Flamme received her BSc in Life Sciences from the Massachusetts Institute of Technology (MIT) followed by an MSc in Molecular Parasitology and PhD in Immunoparasitology from the University of Washington, Seattle. After receiving her doctorate, Prof La Flamme spent several years at Cornell University studying how schistosome worms alter the host's immune response and cause immune-mediated pathology. From this work, she developed a research programme investigating how to regulate the immune system to treat immune-mediated diseases such as multiple sclerosis. Additionally, in collaboration with national and international medicinal and natural product chemists, she has been investigating the immunoregulatory potential of novel compounds and their potential in treating diseases mediated by dysfunctional immune responses. Currently, she is a Professor in the School of Biological Sciences at Victoria University of Wellington and leads the Multiple Sclerosis Research Programme at the Malaghan Institute of Medical Research. This research programme combines the use of experimental models to understand human disease processes with the translation of these basic research findings into clinical applications.

Finding the unknown: developing an unbiased screen for immunoregulation

Anne C La Flamme

Victoria University of Wellington

In searching for new compounds to regulate or activate the immune system, many researchers are focused on a single target or activity because that targeted pathway has been shown to be important in a particular disease. Thus, the screens developed for this application focus solely upon one pathway without any appreciation for the wider impacts that bioactive compounds may have on the network of cellular processes. To balance this target-guided approach, we have been building a discovery platform to understand the immunomodulatory potential of novel compounds in a more unbiased manner. This tiered screening approach is being developed and optimized to characterize the individual immunomodulatory activity of single compounds but also to build a wider understanding of how immunological networks interact. Together, this approach will facilitate the identification of compounds' mechanisms of action and may help predict side effects mediated by "off-target" activities.

Invited Speaker

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Education

1987-1991: B.Sc. College of Food Engineering, Qingdao Ocean University, China
1995-1998: M.Sc. Institute of Marine Medicine and Food, Ocean University of China
2003-2008: Ph.D. School of Medicine and Pharmacy, Ocean University of China

Academic Careers

2011--present: Professor, Ocean University of China
2018--present: Secretary General of Marine Pharmaceutical Pharmacology Committee of Chinese Pharmacological Society
2018--present: Executive Director of Shandong Pharmacological Society
2017--present: Vice Chairman of Qingdao Physiological Society
2016--present: Deputy Director of Pharmacology Professional Committee of Qingdao Pharmaceutical Association
2005—present: Editorial Board Member of " Chinese Journal of Marine Drugs"

Research Interests

Pharmacological study for development anticancer drug from marine nature products. Identification of new target molecules for anticancer drug. Study of cancer immunological therapy based on NK cells.

Selected publications

1. Wu Y, Ma Z, Mai X, Liu X, Li P, Qi X, Li G, Li J*. Identification of a Novel Inhibitor of TfR1 from Designed and Synthesized Muriceidine a Derivatives. *Antioxidants (Basel)*. **2022** Apr 25;11(5):834.
2. Wenjiao Xia, Xin Qi, Mingfeng Li 1, Yu Wu, Lulu Sun, Xinglong Fan, Yuan Yuan, Jing Li*, Metformin promotes anticancer activity of NK cells in a p38 MAPK dependent manner. *OncoImmunology*, **2021**, 10(1): e1995999.
3. Wang Yuying, Sun Lulu, Yu Guihong, Qi Xin, Zhang Aotong, Lu Zhimin, Li Dehai, LiJing*. Identification of a novel non-ATP-competitive protein kinase inhibitor of PGK1 from marine nature products, *Biochemical Pharmacology*, **2021,** 17(183): 114343
4. Du Fu, Qi Xin, Zhang Aotong, Sui Fanfan, Wang Xuemin, Proud. Christopher G, Lin CuNzhi, Fan, Xinglong, Li, Jing*. MRTF-A-NF-kappa B/p65 axis-mediated PDL1 transcription and expression contributes to immune evasion of non-small-cell lung cancer via TGF-beta, *Experimental and Molecular Medicine*, **2021**.12, 53(9): 1366-1378.
5. Dai Jiajia, Chen Ao, Zhu Meilin, Qi Xin, Tang Wei, Liu Ming, Li Dehai, Gu Qianqun, Li Jing*. Penicisulfuranol A, a novel C-terminal inhibitor disrupting molecular chaperone function of Hsp90 independent of ATP binding domain, *Biochemical Pharmacology*, **2019**, 163: 404-415.

Study of a marine candidate drug 1778 with antitumor effect by activating NK cells

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Immunotherapy has become the most advanced means of anti-tumor. However, there are still some disadvantages, such as less response population, drug resistance and high price for PD-1/PD-L1 antibody drug developped from T cells. NK cells are the core cells of the innate immune system and the innate counterpart of cytotoxic T cells. Recent years, the development of immunotherapeutic drugs based on NK cells is a hot spot in the field of antitumor research. At present, cell therapy, antibody and cytokine drugs for NK activation are developing rapidly, while small molecule drugs are still in the early stage of discovery. We found that **1778**, a novel small molecule compound with azaphilone structure from marine fungi, effectively and selectively enhanced activation of NK cells with maximum efficiency equivalent to IL-15. Moreover, **1778** exhibited potential inhibition effects in the lymphoma growth and melanoma metastasis, and **1778** promoted anticancer efficacy of anti-PD1 antibody with improvement of tumor microenvironment. The mechanism study showed that this effect was dependent on a new signaling pathway of Jak1/Jak2-STAT5 evoked by **1778**. The study is of great significance for the development of **1778** as a new immunotherapeutic drug.

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1. Wenjiao Xia, Xin Qi, Mingfeng Li 1, Yu Wu, Lulu Sun, Xinglong Fan, Yuan Yuan, Jing Li*, Metformin promotes anticancer activity of NK cells in a p38 MAPK dependent manner. *OncoImmunology*, **2021**, 10(1): e1995999.
2. Du Fu, Qi Xin, Zhang Aotong, Sui Fanfan, Wang Xuemin, Proud. Christopher G, Lin CuNzhi, Fan, Xinglong, Li, Jing*. MRTF-A-NF-kappa B/p65 axis-mediated PDL1 transcription and expression contributes to immune evasion of non-small-cell lung cancer via TGF-beta, *Experimental and Molecular Medicine*, **2021**.12, 53(9): 1366-1378.