UNIVERSITY OF OXFORD

OSCAR

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RECENT OSCAR publications

OSCAR ACADEMIC Seminar Series

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CONTENTS

Recent OSCAR publications

Research article from Professors Luet Wong and Jeremy Robertson's group published in Nature Synthesis

Professors Luet Wong and Jeremy Robertson's research team at Oxford University and OSCAR have recently reported a new approach to accelerate enzyme evolution for targeted, selective C–H oxidation of cyclic amines and potentially many other substrates. This work was published online at *Nature Synthesis* on 29th September 2022.

nature synthesis

Article https://doi.org/10.1038/s44160-022-00166-6

Enantioselective oxidation of unactivated C–H bonds in cyclic amines by iterative docking-guided mutagenesis of $P450_{BM3}$ (CYP102A1)

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In this work, the research team used a combined substrate and enzyme engineering approach to achieve enantioselective functionalization of all unreactive C–H bonds of a collection of cyclic amines by cytochrome $P450_{BM3}$ (CYP102A1). Substrate docking into molecular-dynamics-simulated structures of enzyme variants is shown to be useful for designing mutations to increase product selectivity and enzymatic activity. The synthetic application of selective C–H bond activation of cyclic amines is exemplified by the synthesis of anisodamine via enantioselective hydroxylation of N-Boc-nortropinone.

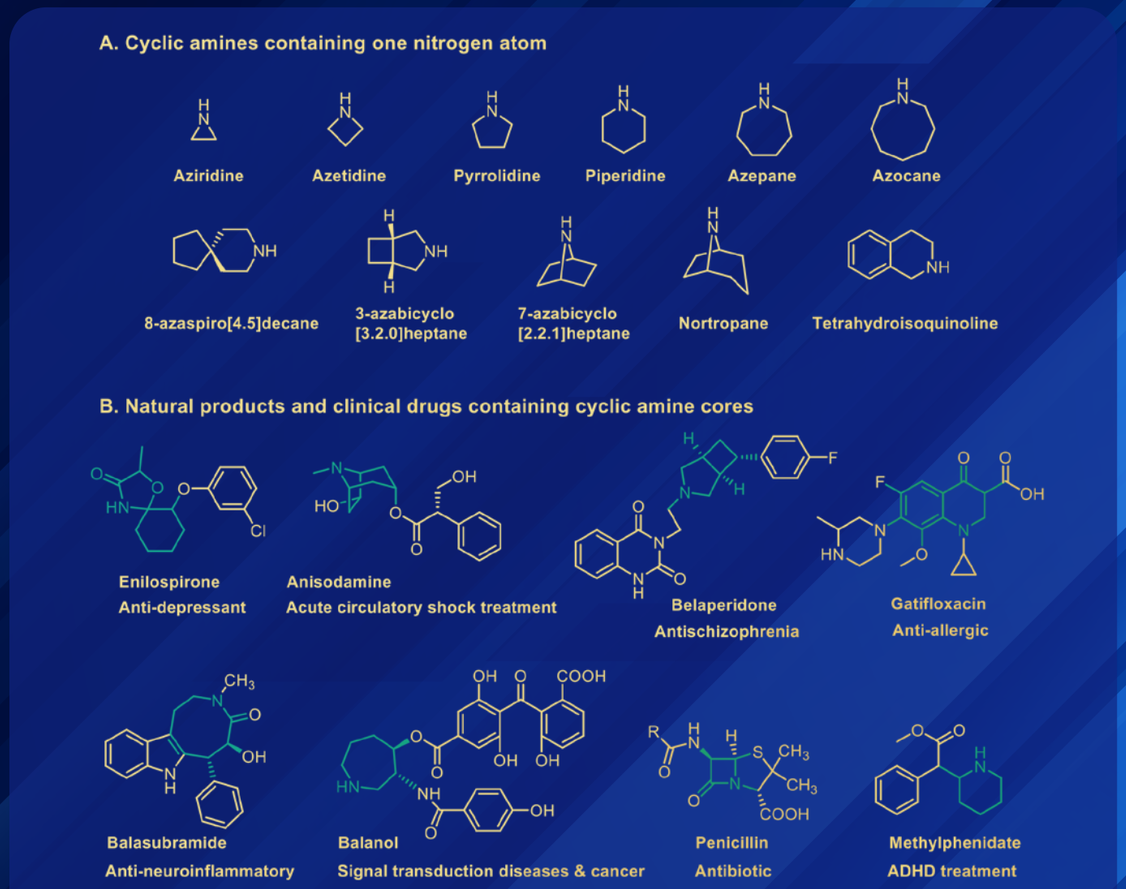

Figure 1 Examples of (A) cyclic amines and (B) clinical drugs containing cyclic amine cores.

Cyclic amines (Figure 1A) are versatile intermediates in drug synthesis and important fragment molecules in drug discovery, which have numerous applications across the chemical, agricultural and pharmaceutical industries. For example, ~60% of US Food and Drug Administration-approved small-molecule drugs have nitrogen heterocycles in their structures (Figure 1B). The Chinese medicine anisodamine which contains bicyclic amine core is used for the treatment of septic shock and circulatory disorders.

In an interview with Chemistry World, Prof. Jeremy Robertson says, 'Without any other functional groups within these molecules, all of the chemistry happens at either the nitrogen atom or the adjacent C–H bonds.'

"For the synthesis of cyclic amines, the nitrogen centre is a natural point of attachment, but target compounds usually include additional connections at one or more of the carbon atoms in the heterocycle. If not imported within one of the starting materials, each connection point must be introduced by a process that converts a C–H bond into an appropriate synthetic handle, such as a hydroxy (OH) group. Although chemical reagents can reliably oxidize positions adjacent to nitrogen, effecting selective catalytic hydroxylation reactions at every remote position in a variety of cyclic amine classes is a considerable challenge. Meeting the challenge would make available the complete set of mono-hydroxylated derivatives of a given cyclic amine to enable further diversification or incorporation into complex-molecule synthesis". With their mild reaction conditions and evolvable substrate specificity and product selectivity, P450 enzymes are attractive systems for functionalizing cyclic amines.

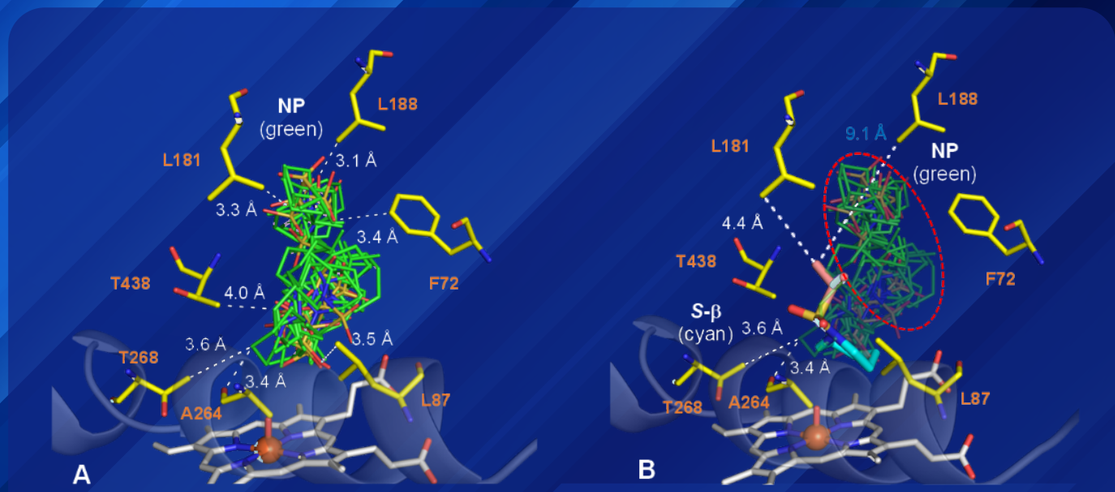

Figure 2 Examples of substrate docking analysis and design of mutations, showing the result from N-Ips-azepane docked with the MD-simulated structure of the GV/A184I/I263G/A328G variant.

'We wanted to understand what interactions are involved in holding the substrate in one particular orientation,' explains Prof. Luet Wong to Chemistry World, 'We then tried to disfavour any other orientations which would lead to unwanted products.'

The research team have extensive experience in $P450_{BM3}$ enzyme engineering; their initial panel of 48 $P450_{BM3}$ variants oxidized all but one of the remote C–H bonds in their four cyclic amines with moderate to high regio- and enantio-selectivity (with up to 99% e.e.). With most variants, changing the *N*-modifying group resulted in different product selectivity. After the initial screening, they utilized MD-simulation and substrate docking to identify potential binding modes (poses) of substrates within the active site of selective enzyme variants. Mutations were then designed to increase both the product selectivity and enzymatic activity.

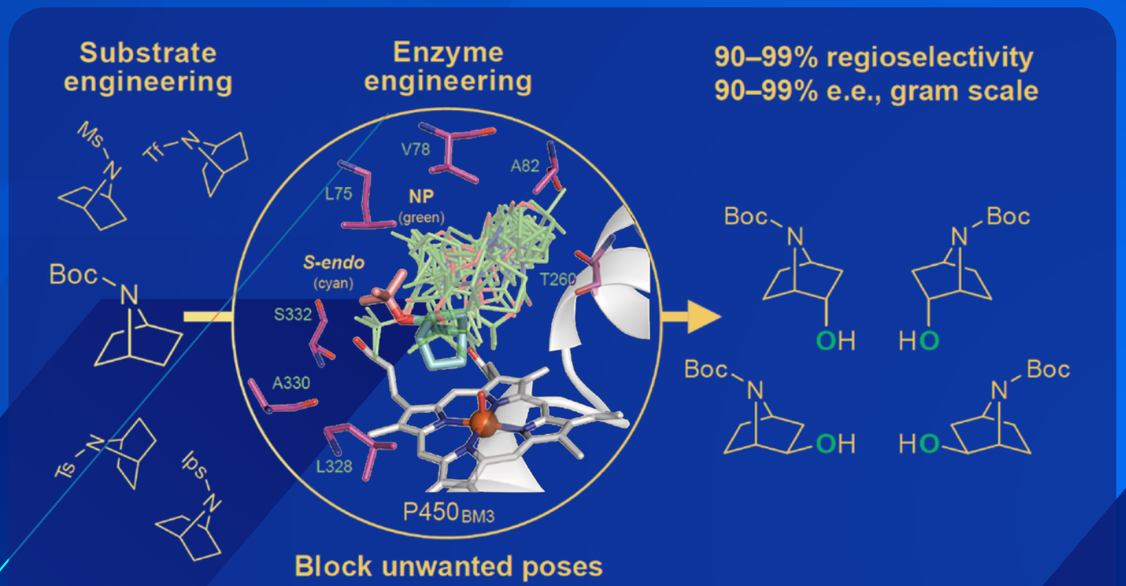

Figure 3 Schematic representations of the overall methodology of this publication – the combined strategy of using different N-modifying groups and docking-guided mutagenesis led to highly selective oxidation of cyclic amines.

This docking-guided mutagenesis approach led to enantioselective oxidation, in most cases with >90% e.e., of all unactivated C–H bonds of single-ring, bridged bicyclic and spirocyclic amines by $P450_{BM3}$ variants. The alcohol products are valuable synthetic intermediates for drugs and functionalized fragment molecules. Their stereoselective synthesis of anisodamine showed a good example of the elaboration of a single enzyme product to a defined product. The production of a set of hydroxylated isomers derived from a single cyclic amine is the first step to rapid molecular diversification to compound libraries for drug discovery etc.

The full article is available online: Zhang *et al*, "Enantioselective oxidation of unactivated C–H bonds in cyclic amines by iterative docking-guided mutagenesis of $P450_{BM3}$ (CYP102A1)" *Nat. Synth.* 2022. DOI: 10.1038/s44160-022-00166-6.

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Accelerated enzyme evolution for targeted C–H oxidation in cyclic amines. Nat. Synth (2022). https://doi.org/10.1038/s44160-022-00170-w

Research article from Professor Zhongmin Qian's research team published in Proceedings of the Royal Society A

Professor Zhongmin Qian's research team at University of Oxford and OSCAR have recently established a novel random vortex system to represent solutions of the three-dimensional (3D) Navier-Stokes equations. This representation paves the way to design Monte-Carlo simulations for turbulent flows. The research has been published in the Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences.

PROCEEDINGS A

royalsocietypublishing.org/journal/rspa

Random vortex dynamics via functional stochastic differential equations

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The new random vortex method provides numerical schemes to efficiently approximate the 3D incompressible fluid flows by Monte Carlo simulations. Compared with the 2D Navier-Stokes equation, the difficulty of the 3D Navier-Stokes equation lies in the non-linear stretching of vorticity. To address this stretching term, a system of stochastic differential equations is coupled with a functional ordinary differential equation into the 3D random vortex system.

Two main tools are developed to derive the new dynamics: the first is the investigation of pinned diffusion measures, which describes the duality among conditional distributions of diffusions in turbulence, and the second is a forward-type Feynman Kac formula for nonlinear Partial Differential Equations (PDEs), which utilizes the duality of the pinned diffusion measures to overcome the time reversal issue in PDE.

Despite the emphasis on the Navier-stokes equations, the tools set out in this paper are quite general and likely to be applied to other nonlinear PDEs, thereby providing respective numerical schemes.

The full article is available online and in print: Qian Zhongmin, Süli Endre and Zhang Yihuang 2022Random vortex dynamics via functional stochastic differential equations. Proc. R. Soc. A.4782022003020220030 http://doi.org/10.1098/rspa.2022.0030

OSCAR Academic Seminar Series

On Friday 9th September, OSCAR held its 3rd Academic Seminar of the year. The seminar was the 13th of its kind to date for OSCAR, attended virtually by participants in the UK, Switzerland, and China. The two speakers invited to showcase their academic achievements were **Lee Ann Laurent-Applegate**, Professor of Regenerative Therapy at Lausanne University Hospital, Switzerland and Visiting Professor at OSCAR, and **Dr. Kamran Khan**, Research Scientist with Professor Mark Moloney's Functional Materials research group at OSCAR.

Prof. Moloney is the Deputy Director and a PI of OSCAR. He chaired the meeting.

Talk 1 - "Industrialisation of cellular therapy in modern medicine"

The industrialisation of cellular source manufacture and processing has had a pivotal impact in health care over the past hundred years, with potent and stable cell sources vital for vaccine development, drug discovery and testing assays, and more recently for patient-targeted cell therapies for disease treatments. The Covid-19 pandemic has led towards more than 100 clinical trials being initiated for Covid-19 patient treatments using different cell sources, dosages, and administration modalities to the patient. Cell culture standardization and methods for out-scaling have become particularly important as more cell therapies are utilized in disease management. Cellular-based therapies provide an alternative means to classical medications and can easily be implemented in parallel and provide important surgical-assisted measures for the repair and regeneration of tissues.

Great strides have been made in recent decades in the comprehension of the potential of targeted cell-based therapies. Aesthetic and reconstructive applications have led the charge, due to the particular challenges presented from injury, loss of circulatory capacity, degenerative paths and repair, which put high demands on optimal approaches to structural and regenerative needs.

At this seminar, Professor Lee Ann Laurent-Applegate shared 25 years of experience illustrating the potential for using targeted cellular therapies to treat cutaneous (skin-related) and chondral (cartilage) afflictions at the Lausanne University Hospital in Switzerland and her vision for future innovations in this research area.

Talk 2 - "Surface modification of common materials and their application as antimicrobials"

The worldwide spread of the new coronavirus, its derivatives, and other novel viruses, has stimulated research in the design and development of novel antiviral, and viricidal agents, with a broad spectrum of antiviral activity. The current challenge lies in the development of universal virus repudiation systems that are reusable and capable of inactivating pathogens, thus reducing the risk of infection and transmission.

In his talk, Dr. Kamran Khan shared a green antimicrobial coating technology that he and his colleagues have developed. The coating technology can cover a variety of materials including polypropylene, polycarbonate, polythene, cellulose, polyamide, glass, and silver. Additionally, this coating has long-lasting (up to 12 months) antiviral and antibacterial effects against viruses, bacteria, and fungi. Its effectiveness was externally validated for personal protective equipment (PPE), filtration systems, and textiles. Dr. Khan provided his insight into the vast number of applications and industries that could benefit and find uses for this novel technology going forward.

About the speakers

Prof. Lee Ann Laurent-Applegate

earned her doctorate at the University of New Mexico. She moved to Switzerland for an International Fellowship for Cancer Research Award in 1989 and is currently the director of the Unit of Regenerative Therapy (UTR) in the Service of Plastic, Reconstructive and Hand Surgery in the Department of Musculoskeletal Medicine at the University Hospital of Lausanne, Switzerland. She holds joint appointments at EPFL and the University of Zurich. Prof. Laurent-Applegate has developed cellular therapies for different clinical applications since 1993 using progenitor cells from musculoskeletal tissues and particularly for the treatment of burn patients, with a special interest in the safety and stability of cellular therapies.

Dr. Kamran Khan

is currently working as a research scientist at OSCAR. He obtained his doctorate from the Chinese Academy of Sciences in Biochemical Engineering. He worked as a postdoc at the Department of Chemical Engineering at Tsinghua University. His research work focuses on surface functionalization and its applications in PPE, therapeutics, proteins purification, antimicrobials and water purification.

Meet OSCAR's New Researcher

Dr. Alexander Vasilyev joined OSCAR in September as a Research Scientist in Prof. David Clifton's Digital Health group. He earned his Ph.D. in July 2020 at the School of Computer Science of Queen Mary University of London. His research during his doctoral study was focused on the development of computational models of human eye movements and the design of psychophysical experiments. Prior to his doctoral years, Alexander had 2 years of work experience in the drug discovery company Gero.ai as a researcher and later as a team leader of the science team.

Dr. Alexander Vasilyev
Research Scientist in Prof. David Clifton's group

Alexander says "Prof. Clifton's group employs the brightest people in the field and has a vast collaboration network within academia and the healthcare industry. My research focus here will be the application of reinforcement learning for decision-making for the treatment of patients with various medical conditions. This could potentially improve the well-being of patients and reduce the workload of hospitals. "

Alexander comes from Russia. He accepted the offer to work at OSCAR back in mid-2021, without knowing that he would then embark on a 16-month odyssey trying to secure a visa and arrange a trip to China. For both Alexander and Miaoqing, OSCAR's Senior HR Supervisor, it was a protracted battle working around fluid COVID-19 restrictions, lockdowns, and border closures since the onset of the pandemic. Alexander said this whole process would never have worked out without the all-round help of Miaoqing, who not only arranged the visa application and supporting documents but also went to great lengths to assist him in many difficult situations on arrival in China and Suzhou. Alexander on the other hand didn't give up during this overwhelming process. He said, it is because he had learned the quality of determination during his Ph.D. course, that success is only possible if efforts are applied for a prolonged period of time.

OSCAR Outreach and Collaboration

Alex Yang, Head of Research Cooperation

Yang Cao, Research Scientist with Prof. Luet Wong's group

Dr. Chenbo Wang, Research Scientist with Prof. Mauro Pasta's group

Co-hosting a sci-tech innovation forum with Oxford & Cambridge Alumni Network Jiangsu-Zhejiang and the Suzhou Association for Young Talents in Science, OSCAR welcomed dozens of Oxford and Cambridge Universities alumni and local young scientists on 17th September. The forum was designed to encourage participants' insights into the development of innovative technologies and their social and economic impact.

OSCAR Head of Research Cooperation Alex Yang, Research Scientists Dr. Yang Cao and Dr. Chenbo Wang were invited to present recent successes in scientific research and technology commercialisation.

Did you know this about SIP?

Three emerging industries of SIP
- Biomedical industry

The Ministry of Science supports SIP in its efforts to develop into a National Bio-Medicine Technological Innovation Centre.

SIP aims to become a world-class source of biopharmaceutical technology innovation, focusing on **drug target discovery, new drug R&D, key reagents and excipients, new processing technologies**.

- Industry output **100 Billion CNY** in 2020 with a growth rate of **15%**.
- **1800+** enterprises, **10** of the Global Top 20 companies were attracted to SIP.
- **80%** of Jiangsu's Category 1 New Drug Clinical Approvals were made in SIP
- **1000+** Medical Device Product Registration Certificates acquired
- Nearly **40000** practitioners , total of **16** listed enterprises

New Drug R&D

Medical Devices

Biological Technology

Biomedical industry in SIP
- Pharmaceutical manufacturing

- **280** clinical approvals were for Category I biological medicines;
- In 2020, **26%** of total new Category I biological medicine clinical approvals in China were from SIP.

Lilly, Lonza, SANOFI, Santen, 住友制药, 恒瑞医药 HENGRUI MEDICINE, Innovent 信达生物制药, 基石药业 CSTONE PHARMACEUTICALS, Eisai Co., Ltd., zoetis, CMAB 苏桥生物, 东曜药业 TOT BIOPHARM COMPANY LIMITED, EDDING 亿腾 PHARM, zai Lab 再鼎医药, BeiGene, 君实生物 TopAlliance, HARBOUR BIOMED

- Medical devices manufacturing

- In total **1044** Product Registration Certificates acquired with **311** class Ⅲ Certificates;
- Output value reached RMB **15.6 Billion** in 2020.
- **17** products entered the "Green Channel" of national medical device innovation product examination and approval, representing **39%** of Jiangsu Province.
- **45** registered Class III medical device certificates acquired in 2020, representing 5% of the country.

Johnson & Johnson, Roche, ThermoFisher SCIENTIFIC, BECKMAN COULTER, BD, stryker, Baxter, B BRAUN SHARING EXPERTISE, 恒瑞医药 HENGRUI MEDICINE, 迈瑞 mindray, PHILIPS, MicroPort 微创医疗, HITACHI, BARCO, Philips Medisize a molex company, smith&nephew

- Academic environment

- Forums

DeviceChina 中国医疗器械高峰论坛

CMP 从创新到产业 From Innovation to Industry
中国国际医疗器械创新合作洽谈会
CHINA MEDTECH PARTNERING

CHINA HEALTHCARE INVESTMENT CONFERENCE

10TH ANNUAL INTERNATIONAL PARTNERING CONFERENCE
CHINABIO PARTNERING FORUM

DIA

PhIRDA 中国药促会

- Institutes

CSH Asia 冷泉港·亚洲 Cold Spring Harbor Asia

ISM 苏州系统医学研究所

苏州先进技术研究院 ADVANCED TECHNOLOGY INSTITUTE OF SUZHOU

SIMM

中国科学院 苏州纳米技术与纳米仿生研究所 Suzhou Institute of Nano-tech and Nano-Bionics, Chinese Academy of Sciences

- Sino-foreign cooperation

- Cooperation between Johnson & Johnson and CAS on nano-coating solution.

Johnson & Johnson × 中国科学院 苏州纳米技术与纳米仿生研究所 Suzhou Institute of Nano-tech and Nano-Bionics, Chinese Academy of Sciences

- Cooperation between Eli Lilly and Hutchison MediPharma on cancer solution.

Lilly × HUTCHINSON

- Cooperation between Eli Lilly and Innovent on tumor solution.

Lilly × Innovent 信达生物制药

- IP Protection

- SIP values and encourages IP protection. **57541** patents have been licensed in SIP.
- Suzhou Industrial Park Court established the **SIP Intellectual Property Rights Judicial Protection Public Service Platform** to specialize in handling corporate intellectual property disputes.
- The **Suzhou Intellectual Property Court** was unveiled in January 2017 and was one of the first 4 IP courts established in mainland

- Higher Education Support

- Xi'an Jiaotong Liverpool University (XJTLU) Wisdom Lake Academy of Pharmacy started to enroll undergraduate, graduate, and PhD students in 2021.
- Focusing on training SIP Bio-Pharm industrial talents and cultivating R&D environment in the Academy.
- Cooperating closely with local innovative Bio-Pharm enterprises.
- Research in three directions: New Therapeutic Drugs; AI in the field of medicine; Clinical Pharmacy.