Chemistry
IN NEW ZEALAND

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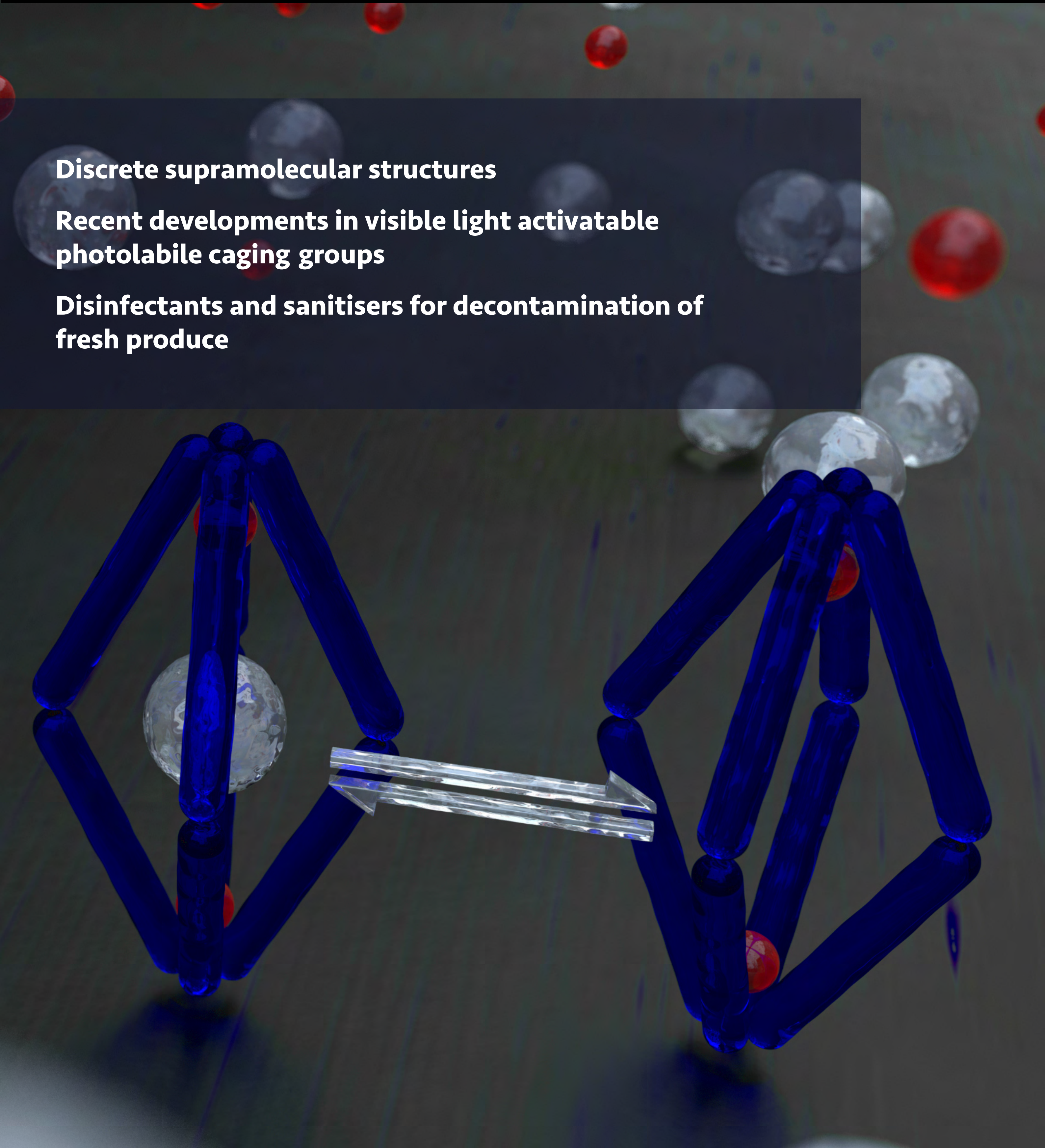

Discrete supramolecular structures

Recent developments in visible light activatable photolabile caging groups

Disinfectants and sanitisers for decontamination of fresh produce

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NZIC Chemistry IN NEW ZEALAND

Volume 85, No.2, April 2021

Articles and features

Other Columns

Comment from the President

Kia ora koutou

Hello everyone

By the time you read this, universities and schools will be well underway for the year and research institutes and businesses will also have been running in a year which is still greatly affected by the COVID-19 pandemic and prolonged border closures. However, on a brighter note, vaccinations have started (for essential workers at time of writing) and hopefully all of us will soon have the opportunity to also be vaccinated.

We had our Council meeting of the Executive in Christchurch on 19 February which involved a passing of the presidential chains from past president Sarah Masters to me (see photo!). Once again I thank Sarah for her great work over the past two years and I look forward to her ongoing support this year as past president. It was also great to meet the other delegates face to face as a group and to find out more about some of the Institute's activities that have been occurring around the country in spite of the border closures. For instance, the 3rd IUPAC Global Women's Breakfast was a great success with the Auckland, Waikato, Manawatu, Canterbury and Otago branches reporting excellent participation in this event.

I feel it is worth mentioning, especially to student members, that despite overseas travel to conferences and meetings remaining a challenge, domestic travel is still possible, at least while areas of the country are under alert levels 1 and 2 (although participant numbers are restricted at level 2). Travel grants for students for domestic conferences can still be applied for where applicable in local branches. With that said, the possibility of virtual conference participation should also be considered where conventional face to face participation in conferences is still basically impossible. On this note, it was reported at the Council meeting that the Hawaii-based Pacifichem conference (postponed in 2020 due to COVID) will be going ahead now “no matter what” with physical or virtual participation being possible. Although virtual participation in any conference has its limitations and disadvantages from a social and networking point of view, the virtual option does have some benefits from an equity point of view, improving accessibility to an international conference to present research that might have been impossible due to economic reasons or through the difficulty of being granted visas to enter the US. The Institute would be open to funding student participation via branch student registration fees (for NZIC members) as the Pacifichem registration fees for students are heavily subsidised. As a student member it is also worthwhile considering because some participation in the international scientific community via a conference is better than none at all and it would be a good addition to the CV in a time when international

networking activities and travel are restricted.

On the subject of networking, we would also like to mention again the great efforts of the Auckland branch in putting on a career evening where students and industrial representatives from chemistry-based industries were able to meet and mingle. About 190-200 people attended this event and it showcased the great diversity of companies with which chemistry students could find careers. It was suggested in the Council meeting that this be an event worthy of emulating (or adapting for purpose/scale) by other branches in order to afford students opportunities and to allow better networking. For businesses this can be particularly valuable when finding suitably skilled employees (such as our chemistry graduates) is challenging due to recruitment from overseas being severely limited by COVID-19.

Another important item discussed at our Council meeting was the digitisation of our *Chemistry in New Zealand* journal. The plan to do this had been discussed in the previous year. A number of you still receive the paper copy which can limit the level of interactive content that can be produced. In 2021 we will be moving toward a complete digitising of the journal so it is delivered online via an email to your inbox. We will make a gradual move to this format. It will allow interactive content to be more easily delivered to members and for this we invite contributions from Institute members to make it possible in future editions.

Council meeting and passing of the "Presidential Chains", 19 February 2021, Christchurch.

Noho ora mai

Michael Mucalo

NZIC President

AUCKLAND

The University of Auckland

Events

The School of Chemical Sciences will be publishing a yearly research review highlighting research success, new staff and domestic and international collaborations. This review will be distributed to key figures in industry, academia and government.

UniBound Faculty of Science Experience
The UniBound faculty of science experience for Pasifika students took place on 13-14 January. 26 UniBound students enjoyed their introductory experience to SCS and took part in demonstrations, experiments and interacted with real scientists.


Students at UniBound

Research Fellow *Joel Rindelaub* had his study on air pollution from Guy Fawkes celebrations featured by Radio NZ in a recent news article. Joel's work was originally published in *Environmental Science and Pollution Research*, a journal of the European Chemical Society.

School of Chemical Sciences Seminars
A series of short talks under the Food, Food Production and Nutrition theme were given in November by staff from SCS, including Dr *Davide Mercadante*, Dr *Kang Huang*, Dr *Amy Zhu*, and Dr *Rebecca Jelly*. These talks were designed to be accessible to a general science audience and to identify opportunities for collaboration.

Staff Successes
Two academic staff associated with the School were awarded New Year Honours. Professor *Juliet Gerard* was named a Dame Companion of the New Zealand Order of Merit. She is the third School member to receive this high honour - Professor *Charmian O'Connor* became a Dame in 2018 and Professor *Margaret Brimble* received the same honour in 2019. Juliet is the Prime Minister's Chief Science Advisor and has advised the Government and public on other topics from the impacts of plastic pollution to the possible impacts of legalising cannabis. Juliet's academic research is focussed on fundamental and applied protein science. She has more than 175 publications, including three books. She has also founded and directed her own company Hi-Aspect, which produces protein nanofibres for medical and other uses.

Dr *SallyAnn Harbison* was named as a Member of the New Zealand Order of Merit. SallyAnn is a Senior Science Leader in the Forensics section of ESR and has been an honorary lecturer with the Forensic Science programme since its inception in 1996. She is an expert in forensic biology, and most recently has been setting up the capability for the Auckland ESR site to conduct genomic sequencing of SARS-CoV-2, the virus that causes COVID-19. SallyAnn has supervised more than 60 MSc and PhD students in the Forensic Science programme and has over 60 publications.

Brent Copp was named on the annual list of Highly Cited Researchers 2020 from Clarivate. He was recognised in the Pharmacology and Toxicology category. The highly anticipated annual list identifies researchers who have demonstrated significant influence in their chosen field(s) through the publication of multiple highly cited papers during the last decade. Their names are drawn from the publications that rank in the top 1% by citations for field and publication year in the Web of Science citation index.

Margaret Brimble gave the Cornforth Lecture as part of the Life Sciences Symposium at the University of Sussex (online).

Margaret Brimble presented the Cornforth Lecture online at the University of Sussex

Funding

Muhammad Hanif and several colleagues were awarded a Faculty Teaching Development Fund grant for their project, *Using 3D printed molecular models as pedagogical aids in large undergraduate teaching spaces*.

Lisa Pilkington received a Faculty Teaching Development Fund award for her application entitled, *Bespoke R manual for chemistry students*. This project will be focused on developing learning resources for statistics and chemometrics.

Margaret Brimble, *Paul Harris* and *Sharma Dissnayake* were awarded $109,999 from Cure Kids for their project, *Development of novel peptidomimetics against pediatric dental caries*.

Paul Harris was awarded $90,000 from Lottery Health towards the purchase of shared equipment.

Student Successes

PhD Student Prizes

Faculty of Science poster competition

The following students received merit prizes and were selected to participate in the University poster competition: Alex Mayer, Courtney Lynch, Dhanisha Patel, Jessie Davys, Lewis Green, Olivia Johnson and Timothy Christopher.

Lewis Green was also placed third in the People's Choice award with his poster, *Immunogenic cell death: reawakening the immune system to cancerous threats with metal complexes*.

AUT

New Faces

Ema Maretic will be doing her Honours dissertation this year with Professor *Nicola Brasch* and will be synthesising and studying the properties of alkene derivatives of vitamin B12, intermediates of B12-catalased dehalogenation reactions in bacteria.

Cailin Carmichael is starting her Honours project with Dr *Cassandra Fleming*. Cailin is working on the development of organelle-targeted photolabile caging groups.

Olivia Matich will be doing her Honours project with Dr *Jack Chen*, working on *Dynamically assembled phosphate receptors.*

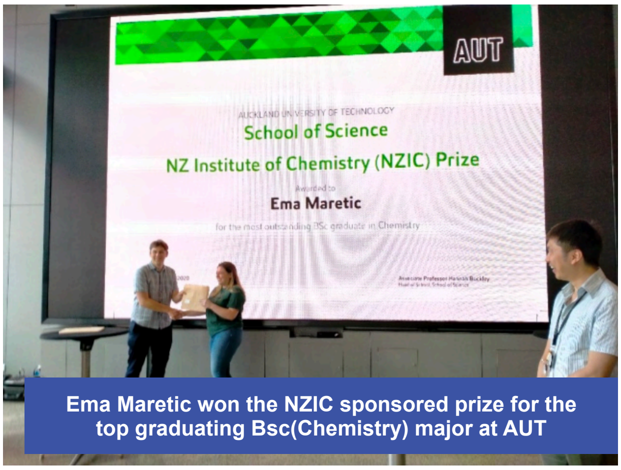
Events

Associate Professor *Marcus Jones* has established a laser lab @AUT (catchier name pending!), which will soon be equipped with a purpose-built time-resolved fluorescence system capable of visible and near IR excitation and detection. Time resolution will be a few tens of ps with time windows as long as ms. Initially we will be able to study ensemble liquid and thin film samples, but single molecule capability will be added at a later date.

Chloe Zhijun Ren, supervised by Dr *Jack Chen*, gave a talk at the RACI Supramolecular Group Virtual Symposium entitled, *Dynamic and modular formation of a synergistic transphosphorylation catalyst*. AUT hosted the IUPAC Global Women's Breakfast with the theme of *Empowering diversity in science*. The NZIC and IUPAC sponsored event was attended by all genders and Distinguished Professor Dame *Margaret Brimble* spoke about the important work of IUPAC and the benefits of being involved with IUPAC.

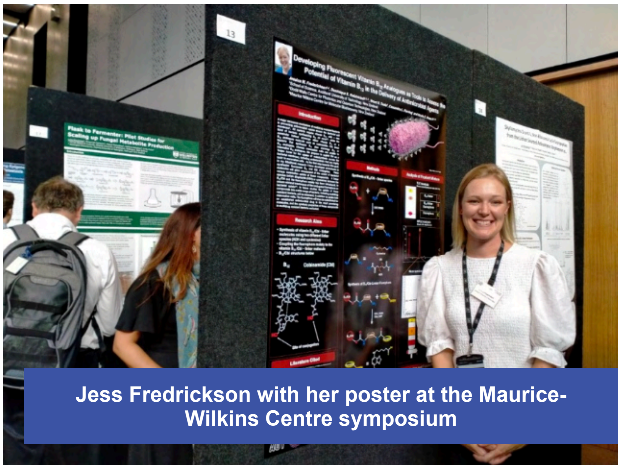
Congratulations

Ema Maretic received an "A" grade for her 3rd year research project and was awarded the NZIC sponsored prize for the top graduating BSc(Chemistry) major at AUT.



Ema Maretic won the NZIC sponsored prize for the top graduating Bsc(Chemistry) major at AUT

Jess Fredrickson and Professor *Nicola Brash* attended the Maurice-Wilkins Centre symposium in February. Jess presented a poster on her Honours research on fluorescent Vitamin B_{12} analogues.



Jess Fredrickson with her poster at the Maurice-Wilkins Centre symposium

CANTERBURY

NZIC

NZIC Canterbury would like to congratulate all the students who graduated in December 2020.

NZIC Canterbury AGM

The NZIC Canterbury branch AGM and Christmas function was held on 9 December 2020 at the University of Canterbury. It was noted at the AGM that some 3-4 ChemSoc members will be joining the NZIC Canterbury Branch committee next year. Concern was expressed at the AGM regarding the potential slipping of standards and the ability of high school students in chemistry, with New Zealand's 13-year-olds having recorded their worst ever results in a major international mathematics and science test, the Trends in International Mathematics and Science Study (TIMSS).

The Co-Treasurer, *Darren Saunders*, also noted that 2020/2021 was a transition year in which the move to the Xero accounting platform would be completed. In his opinion Xero has been greatly beneficial in terms of ease of generating GST returns and financial reporting.

Sarah Masters attended the Global Women's Breakfast in Alaska via Zoom

NZIC Presidential Address

Associate Professor *Sarah Masters*, School of Physical and Chemical Sciences, The University of Canterbury, gave the presidential address on *Resilience & opportunity in career pathways* at the NZIC Canterbury Branch AGM. Sarah outlined how the pathway that people take from school to their current job is generally different for all and academia is no exception. Whilst it can be perceived that the typical academic career pathway is Degree → PhD → Postdoc → Position, often this is not the case. The route to an academic job can include career breaks, fellowships, working in industry and working in education. More often than not those in academic positions have had to overcome hurdles and take diverse routes to their current roles. One thing that generally does unify everyone who has chosen academia as a career path is the need to be resilient and to overcome adversity, which can manifest itself in many forms. Another important consideration is that of opportunity; how to recognise it and how to take it!

IUPAC Global Women's Breakfast

This global networking event was held on 12 February and is designed to assist women in all areas of chemistry to expand their network of contacts, both locally and internationally. Women at different stages of their individual careers are encouraged to inform each other about their career progress, and together explore opportunities, for professional development in research and/or teaching.

The guest speaker, Rebecca O'Loughlin from Burnside High School, discussed her career progression and experience in different countries and cultures.

Associate Professor *Sarah Masters* also attended the breakfast in Alaska via Zoom to close the loop between the start of the breakfasts in NZ and the end of them in the USA. Kelly Drew gave a fascinating talk on ground squirrels and how understanding the chemistry of their hibernation could potentially lead to applications in space travel.

NZIC sponsored events

The Materials@UC annual conference was held on 19-20 November 2020 at the University of Canterbury. The aim of the conference is to bring together materials researchers from as many different fields as possible so that new ideas, new perspectives, and new collaborations can be developed. While largely targeted at postgraduate students, the goal is to bring together students, academics and industry professionals so that together we can shape the future of materials research and innovation in NZ.

The inaugural Materials@UC conference was held in 2018 as an event for the newly-formed Materials Cluster@UC. The resounding success of both the 2018 and 2019 meetings led to it becoming an annual fixture in the UC calendar, with the eventual goal of development into a national event. Since 2019, Materials@UC has been organised largely by postgraduate students. For more details see ***https://sites.google.com/view/materialsuc-2020/about-materialsuc***

MANAWATŪ

The Manawatū branch IUPAC Global Women's Breakfast on 9 February was a lovely success, with 12 people joining us for breakfast. *Nyree Parker* gave an inspiring talk about how she has built a successful career teaching chemistry and being the Puhoro Coordinator at Palmerston North Boys High School. *Evelyn Sattlegger* delivered a fascinating talk about how she developed her successful career researching and teaching metabolic biochemistry first in Germany, then the United States and finally at Massey University. *Heather Jameson* told us some exciting news about the development of the NZ branch of the International Younger Chemists Network. The breakfast was a fantastic opportunity for us to discuss how we can help support women working in the chemical and related sciences in our region. Thank you everyone for coming and making it such a great morning.


Attendees at the Manawatū Global Women's Breakfast

At the end of 2020, the APOBEC3 team consisting of Associate Professor *Vyacheslav V. Filichev*, Dr *Elena Harjes*, Professor *Geoff Jameson* (Massey University, Manawatu) and Dr *Wanting Jiao* (Ferrier Research Institute, Wellington) was awarded a grant of $250k for 24 months from The Health Research Council of New Zealand, Breast Cancer Cure and Breast Cancer Foundation NZ for the project entitled, *Stopping breast cancer evolution: evaluation of APOBEC3 inhibitors in live cells*. The team aims to develop new drugs that stop evolution of drug resistance and metastasis in cancer.

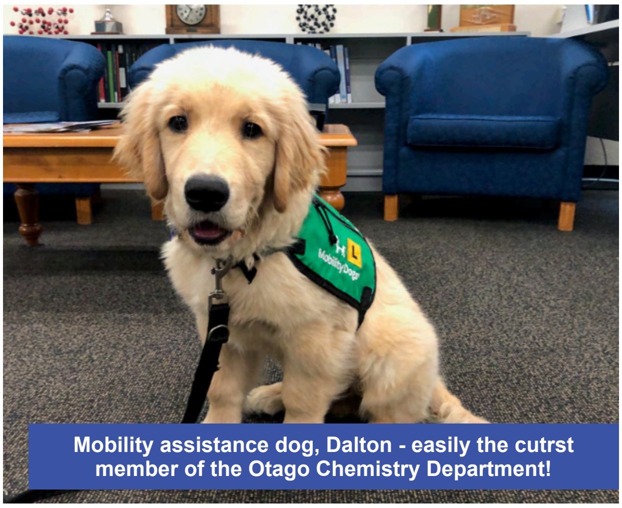
Maulik Mungalpara successfully defended his PhD thesis titled, *New routes to planar chiral ligands and their use in asymmetric catalysis*. Maulik was supervised by Associate Professor *Gareth Rowlands* and Professor *Paul Plieger*.

Liam Mowbray is working with Associate Professor *Mark Waterland* and Dr *Katherine Holt* on a MURF funded project titled, *IR and Raman chemometrics on monofloral New Zealand honeys*.

OTAGO

University of Otago, Department of Chemistry

Introducing Dalton, who is a obility assistance dog in training and being raised by *Andrea Vernall* in the Department of Chemistry. Dalton is getting into the swing of departmental meetings and is looking forward to attending lectures with Andrea shortly. The department personnel are doing a very good job of ignoring Dalton and admiring him from a distance.


Mobility assistance dog, Dalton - easily the cutrst member of the Otago Chemistry Department!

Jaydee Cabral participated in the Reverse Science Fair at the Otago Museum on 13 February for the International Day of Women and Girls in Science. At this event, local scientists showcased their fields to school students and the public. In Jaydee's exhibition, a hands-on mock 3D bioprinter was used to teach the concept of 3D printing and tissue engineering.


Jaydee Cabral showcasing a mock 3D bioprinter at the Otago Museum's Reverse Science Fair event

In news from Plant and Food Research, *David Rubin* has submitted his MSc thesis (and passed with flying colours) entitled, *Discoveries from the alpine daisy Celmisia viscosa: unique diterpenes and flavones, and variation within the species*. David, working with *Catherine Sansom*, *Nigel Perry* and many other chemists and botanists, discovered new diterpenes and flavonoids that probably contribute to the stickiness and ecological defence of this prominent plant. David has now moved to the US with his family.

PhD student *Lani Aloi* and *Nigel Perry* attended the Maurice Wilkins Centre Symposium in Auckland in February. Lani presented a poster on *Natural products from Samoan la'au fai vai* (medicinal plants), and discussed collaborations in this area with other MWC researchers.

Josh Bristowe completed a summer studentship on *Harakeke. Isolation and identification of potentially bioactive compounds* in collaboration with the Māori weavers group in Karitane. This project was supported by both the University of Otago Te Ngaru Paewhenua and the Ti Rito Plant & Food Research Māori summer studentship programmes.

The MacDiarmid Institute's annual symposium was held in Rotorua on 9-12 February. It was attended by PIs *Sally Brooker*, *Carla Meledandri* and *Anna Garden*, as well as students *Sandhya Singh*, *Abdullah Abudayyeh*, *Sriram Sundaresan*, *Caitlin Casey-Stevens* and *Charlie Ruffman*, all of whom gave a talk, and *Dan Ross* who presented a poster. Special mention to Charlie for winning a student talk prize and to Abdullah who received a prize at the dinner for the most recent thesis submission! We were extremely grateful for our first "big" conference in a while (although limited to 100 people) and especially inspired by the discussions around Mātauranga Māori, commercialisation and science communication, as well as the high-calibre scientific talks. During the symposium attendees also enjoyed a Whakarewarewa geothermal village tour, learning about the history and current utilisation of the geothermal resources in the village.


MacDiarmid Institute symposium attendees outside the wharenui at Whakarewarewa

WAIKATO

The winners of the undergraduate chemistry prizes for 2020 were as follows:

J.E. Allan Memorial prize (for best overall student at second year): **Robbie Maris.**

Dow Agrosciences Prize for best overall student at third year: **Siyuan Li.**


Attendees at the MacDiarmid Institute for Advanced Materials and Nanotechnology annual symposium

A very enjoyable breakfast was held at Jack's Coffee Lounge, Hamilton, in February as part of the Global Women's Breakfast event for female chemists. Although only a small group, we were very privileged to be able to meet in person, as most of the 306 individual events held globally were virtual. Given the time differences, we were also the very first breakfast to launch.

University of Waikato

It was congratulations then a sad goodbye to *Amanda French*. Amanda and her husband Thad welcomed baby Theodore in November but have now returned to the United States to be closer to family and for Amanda to take up a new position as a Research Scientist at Pacific Northwest National Laboratory in Washington State.

Congratulations to *Megan Grainger* who was awarded a Marsden Fast-Start grant entitled, *Metal incorporation into honeybee brains and cells: at what cost to the hive?* Michael Goblirsch (United States Department of Agriculture, Agricultural Research Service, USA) is collaborating on the project. This work will investigate if incorporation of heavy metals has an impact on individual bees and/or the entire hive.

Congratulations also to *Michael Mucalo* and *Graham Saunders* who are part of a large, successful MBIE proposal from the University. Their role will be to design new sustainable building materials from waste.

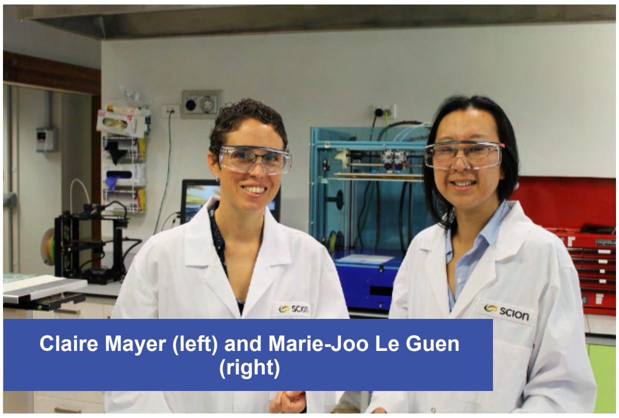
A number of students have successfully completed their research. Hayden Thomas has completed his doctoral studies on iridium and rhodium complexes of NHC ligands with fluorinated substituents with *Graham Saunders*. Nyssa Hewitt and Kaitlin Button have completed their Masters degrees with *Megan Grainger* and industry

Hamilton Global Women's breakfast participants

partners. Nyssa's thesis concerned chemical fingerprinting of a novel bioactive compound from a fermentation broth, while Kaitlin investigated various methods to convert a fresh distillate into a product that tastes like an aged whiskey. Kirstie Cochrane completed her Masters degree with *Megan Grainger* and *Amanda French* on the presence, speciation and movement of arsenic in Lake Tarawera. Claire Voogt and Taylor Farr have both completed their Masters degrees with *Michèle Prinsep* on marine algal chemical ecology and marine algal natural products respectively. Claire is now working for the patent office and Taylor is working for the Treasury (both in Wellington).

New doctoral students include Lauren Gris (from France) who is working with *Michèle Prinsep* on the chemical ecology of nudibranchs, Stephen Gardyne, working with *Bill Henderson* on coordination chemistry of polyether appended ligands and Kavitha Harshani Ranaweera (from Sri Lanka) who is working with *Michael Mucalo* on repurposing of waste materials.

New Masters students include Cynthia McConachy, working with *Graham Saunders* on superhydrophobic surfaces, Amanda Robinson, working with *Merilyn Manley-Harris* on quantifying cannabinoids, Emma Carroll, working with *Megan Grainger* and an industry partner and Brittany Jane, working with *Megan Grainger* on her Marsden project.



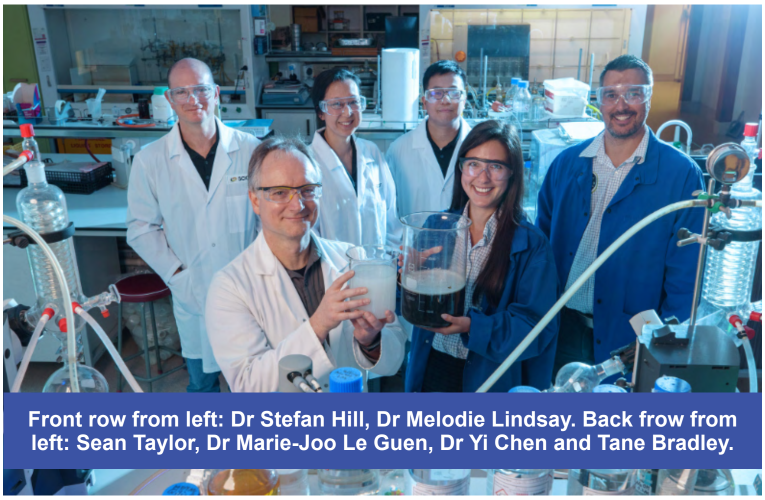
Claire Mayer (left) and Marie-Joo Le Guen (right)

Scion

Stefan Hill, *Marie-Joo Le Guen*, and *Yi Chen*, along with *Sean Taylor*, have developed a scalable method to generate nanocellulose from waste seaweed using mild chemicals in partnership with AgriSea New Zealand Seaweed Ltd. This process will be trialled at pilot plant scale at the Foodbowl (Massey University).

Claire Mayer has arrived in New Zealand ready to begin a two year research programme to explore the use of plant material in 4D printing with *Marie-Joo Le Guen*. Claire works for France's National Research Institute for Agriculture, Food and Environment (INRAe) and was awarded a Marie Skłodowska-Curie (MSC) fellowship in 2020.

Robert Abbel and *Mathias Sorieul* have developed an electrically conductive biobased and biodegradable polymer following green chemistry principles. A key advantage is the self-healing properties of the material. The polymer can be cut and pressed together with mild heating to restore the initial conductivity.



Front row from left: Dr Stefan Hill, Dr Melodie Lindsay. Back frow from left: Sean Taylor, Dr Marie-Joo Le Guen, Dr Yi Chen and Tane Bradley.

Jose Quinsaat recently completed his two year postdoctoral fellowship supervised by *Kirk Torr* (Scion) and Dr Richard Vendamme (VITO, Belgium). His project on thermoplastic and thermoset biobased polymers derived from depolymerised native softwood lignin was part of an ongoing collaboration between Scion and VITO. Jose moves to Massey University to start a new postdoctoral fellowship with *Shane Telfer* on metal-organic frameworks.

Discrete supramolecular structures

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Keywords: *metallo-supramolecular, tetrahedral, helices, cage, self-assembly*

Introduction

Inorganic supramolecular chemistry is concerned with the self-assembled larger arrangements of metal ions and organic ligand building blocks. There are two main fields: divergent ligands forming metal–organic frameworks (MOFs), and convergent ligands, with at least two (ditopic) coordination sites, forming discrete 2D or 3D molecular entities of supramolecular coordination complexes (SCCs).[1] The metals and basic organic ligands act as building blocks that organise themselves with little intervention from humans or machines[2] through the spontaneous formation of non-covalent intermolecular interactions including hydrogen bonding, metal coordination, pi-pi bonds and electrostatic interactions.[3] The overall final architectural design is 'programmed' into the components, along with the directional, complimentary non-covalent interactions they have the potential to form.[2] Over the last few decades an endless array of SCCs have been synthesised, including grids, helices and cages.[4,5]

SCCs have many unique chemical and physical properties due to the different intrinsic properties of their components. Building blocks can be rationally mixed and matched to provide structures with a wide range of properties that have been used to develop functional supramolecular architectures for use in host–guest applications, catalysis, switches, redox, extraction and sensors.[4,6] They have potential applications in a range of future materials and devices, in areas of supramolecular photonics, electronics, crystal engineering and biology.[3,7]

Supramolecular polygons based on metal–ligand coordination initially emerged in part as a result of studies in the 1960s by Pedersen *et al.* which demonstrated that complementary small molecules could exhibit intermolecular recognition via noncovalent interactions forming larger overall structures.[8] However, the process behind this was not looked into and not developed as a field until the laboratory of Jean-Marie Lehn introduced the concept of supramolecular chemistry and its connection to functional structures as 'chemistry beyond the molecule' work recognised with a Nobel Prize.[2]

This review will look at some of the discrete supramolecular structures developed though coordination driven self-assembly and give examples from New Zealand's contributions to the growing library of these structures.

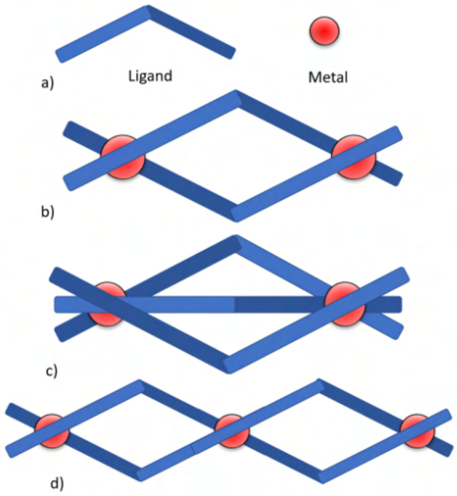

Fig. 1. Schematic of various helicates: a) the linear structure represents the organic ligand and the circle represents the metal, b) [M_2L_2] bimetallic double stranded helicate, c) [M_2L_3] bimetallic triple stranded helicate, and d) [M_3L_2] trimetallic double stranded helicate.

Helicates

An early example of a structure reported by New Zealand researchers comes from Coles *et al.* at Victoria University of Wellington in 1969[9] and consists of two copper atoms held by two very simple bridges [M_2L_2]. There is no twist in the ligands so it is simply a dimer. Aside from simple one-ligand, mono-metallic [M_1L_1] structures, helicates are the simplest discrete SCCs.

Helicates are discrete mono-directional, helical complexes of one or more covalent ligand strands wrapped about and coordinated to a series of metal ions in a helical axis.[10,11] This wrapping can be controlled by the metal ion coordination or other interactions such as hydrogen bonds. Entropy may be harnessed as a driving force in the context of helicates as well as in mononuclear complexes, leading them to be the more common SCC formed.[5] If ligands are too long and flexible, single nucleated structures would form enthalpically instead of multi-nucleated structures. The greater the rigidity of the ligand the more it will coordinate to separate metal centres.[12]

Different types of helicates of different proportions of metals and ligands are shown in Fig. 1. The widespread occurrence and importance of helicates in nature has provided insight into the process of self-assembly and the potential use of helicates as components in functional molecular devices.[13]

Metal coordination

The successful directing, formation and self-correction of a particular SCC depend heavily on the ligand design, choice of metal ion and the metal–ligand.[14] If attraction between the ligand coordination site and the metal ion is too weak, bonds and hence structures will not form. If the bonds are too strong, ligands will not be able to self-correct into discrete shapes, but will instead create continuous chains of ligands and metal into large entanglements.

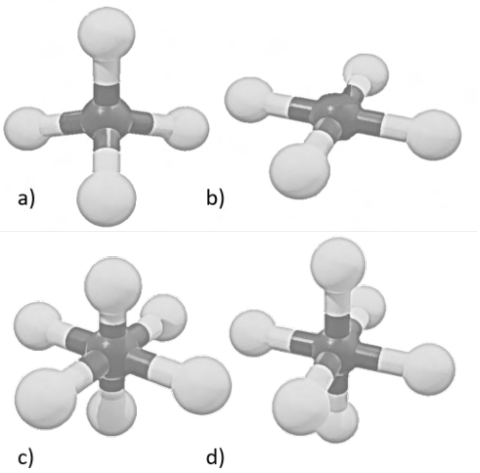

Fig. 2. Examples of possible metal coordination: a) tetrahedral b) square planar c) octahedral d) distorted square pyramidal

Metal ions have predictable geometric coordination preferences; octahedral, square planar or tetrahedral (Fig.2).[15] These control not only the overall architecture of a complex, but also subtle changes within one type of structure.

In 2002, an example of a simple bimetallic double stranded [M_2L_2] helicate (Fig. 1) with a larger than average twist was made by Sumby and Steel at Canterbury,[13] investigating metal ion control in the construction of helicates. Sumby and Steel found that changing coordination of metal ions resulted in a difference in torsion of the helix of the ligands, and therefore also changed the distance between the metal atoms. With octahedral nickel, the ligand adopts a large twist and brought the metals closer, while the distorted square pyramidal shape of copper atoms (Fig.2) meant that the ligand did not twist as much, and so extended further in length, increasing the metal-metal distance.

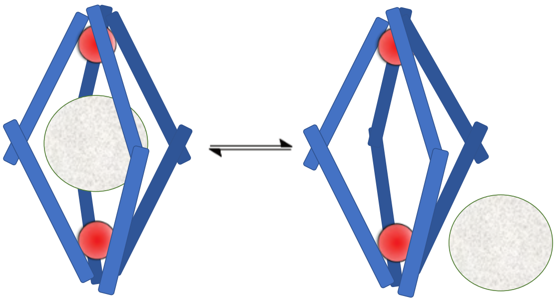

Fig. 3. Diagram showing a helicate cage made of four rigid ligands bound to two metal ions, [M_2L_4], encapsulating and releasing a molecule, the large circle, through the replacement of ligands

Helicate cages

In bimetallic quadruple stranded helicates [M_2L_4] (Fig. 3), the extra ligand means the twist of the helicate relaxes, creating a larger cavity between the ligand strands - a feature that has a greater capacity for function compared to the previous smaller helicates. With this, investigations have moved on from if it can be synthesised to the purposeful design of more complex function. These cavities are able to encapsulate small molecules, leading to helicates being investigated for their potential in medical fields such as attaching biological detectors, being the basis for future drug delivery vectors and other host guest or catalytic applications.[16]

Regarding SCCs with biological properties, Crowley *et al.* in Otago made [Pd_2L_4] cages capable of encapsulating two molecules of cisplatin, a chemotherapy medicine.[17] This helicate can be 'opened' and the cisplatin released when more competitive ligands are introduced, which then compete for placement in the helicate cage. This reversible encapsulation and release is what future drug delivery vectors could be developed from.

Crowley *et al.* expanded on their research with tripyridyl (tripy) $[Pd_2L_4]^{4+}$ cages capable of binding cisplatin.[17] One of the main obstacles that needs to be overcome is the decomposition of the helicate cage in the presence of chloride, histidine, and cysteine; all common nucleophiles found in biological systems. To increase the kinetic stability of these helicate cages, there were two possibilities; assemble the cage using more kinetically inert metal ions, proving difficult due to the formation of too stable intermediates, or sterically and electronically tuning the tripy ligand. Two new, amino substituted, tripyridyl ligands, and their complementing cages were generated and exposed to biological nucleophiles. However, the most robust cage created then failed to encapsulate the cisplatin. Development of functional cages for real world application requires a careful balance of features and rigorous testing.

Ligand geometry

The self-assembling directional-bonding approach of SCC is provided by the well-defined shapes, sizes, rigidity and geometries of the organic components. The shape of the building block components is dominated by the angle formed between the two open coordination sites, called the turning angle.

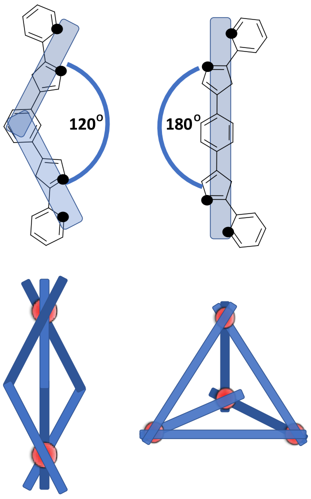

Fig. 4. Generic ligands with coordination sites positioned away from each other at angles of 120° (upper left) and 180° (upper right), leading to preferred structures of helicates (bottom left) and tetrahedrons (bottom right) respectively.

While Brooker *et al.* in Otago were exploring dipyridyltriazole based ligands for their electronic communication potential,[4] these investigations provided a practical demonstration of how the turning angle determines the final SCC. As illustrated in Fig. 4, the ligand with a 180° turning angle arranged into a tetrahedral $[M_4L_4]$, while the ligand held at a 120° angle meant that the ligands converged together again, forming a dinuclear triple stranded helicate.

Tetrahedral cages

Tetrahedral cages are discrete $[M_4L_6]$ polygons with internal cavities. Like the previous helicate cages, one of the main interests in these structures is the selective encapsulation of guests within the cages. Tetrahedrals can also contribute to reaction specificity, or to isolation and protection of volatile components from outside interactions, leading to a potential future in host-guest chemistry and drug delivery. Tetrahedral complexes are functionalised with ligands to provide non-bonding interactions complimentary to specific guests. These cavities are incredibly versatile, with changeable volume, topography and internal chemistry that create complementary environments capable of encapsulating a variety of size, shape and types of guests.[4]

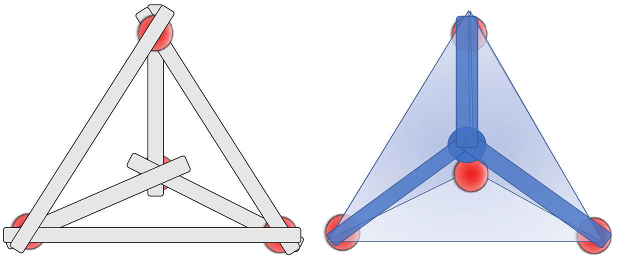

Fig. 5. Schematic showing tetrahedral cage geometries; when the ligands construct the edges of the pyramid $[M_4L_6]$ (left), and when the ligand forms the face of the tetrahedral $[M_4L_4]$ (right)

Ward, *et al.* in Canterbury were recently inspired by work on phosphorus-based porous organic cages (POCs) to create cages to incorporate sulfur and selenium functionalised phosphates.[18] This tetrahedral is structured so that the ligand formed the 'face' of the tetrahedral pyramid, where the ligand has three 'binding sites' diverging 60° away from each other to coordinate with metal ions to form a tetrahedral $[M_4L_4]$, illustrated in Fig. 5. This version of a tetrahedral cage is more enclosed, with the ligand more firmly covering the entrance to the cavity, compared with the ligand edged tetrahedral in Fig. 3.

Cyclohelicate squares

Cyclohelicate grid structures are made of parallel and perpendicular coordination of ligands that 'paddle wheel' around the metal atoms.[14] This is done either with bidentate ligands and tetrahedral metal atoms or with tridentate ligands and octahedral metal atoms. The constraints on the ligands in these structures create large rigidity between ligands and remarkable stability in the SCC.[19] These are popular target architectures due to the close proximity of the metal atoms, which often allow electronic or magnetic communication between appropriate centres.[20] This feature makes these structures probable candidates for the future design of novel materials in crystal engineering, nanoscale devices, information storage and processing technology.[21]

The first copper based [2x2] square grid was characterised by Youinou *et al.*[22] with 3,6-bis(T-pyridyl)pyridazine (dppn) (Fig. 6a). Many other ligand designs have been built around and upon this first square. In 2003, Brooker (Otago) and Jameson (Massey) *et al.*[23] provided a look into a 3,6-diformylpyridazine based ligand, complexed with a range of metal ions, that either preferred tetrahedral (Cu I) or octahedral (Zn, Ni, Co) geometry. The copper(I) complex self-assembled into a [2x2] grid $[M_4L_4]$, while the zinc(II) and cobalt(II) complexes assembled into side-by-side architectures $[M_2L_2]$ (Fig. 6d). This demonstrates again how the angles of coordination sites have to match those available on the metal to achieve desired shapes.

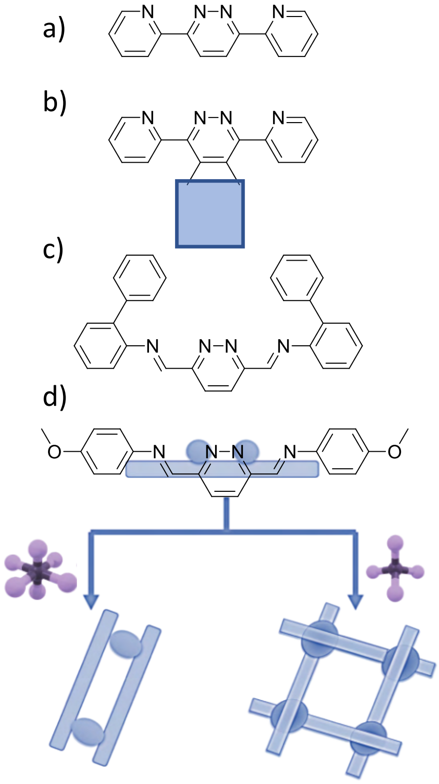

Fig. 6. a) 3,6-bis(T-pyridyl)pyridazine (dppn) ligand, b) dppn based ligands with varying steric bulks attached, c) 3,6-diformylpyridazine based ligand with sterically hindering benzenes, d) diagram showing Brooker and Jameson et al.'s example of SCC formation with octahedral metals forming a side by side structure in combination with tetrahedral metal ions forming a square grid. [23]

This work led onto further work[24] which extrapolated from this finding into a breadth of related ligands, derived from the same 3,6- diformylpyridazine. This expanded investigation further confirmed the tendency of copper(I) ions to cause a preference to be $[M_2L_2]$. This family of ligands even formed [2x2] squares with silver(I) ions, which was only the second time that silver grids have been successfully created and characterised; the first being Lehn *et al.*'s work in Poland in 2005.[25]

One ligand that was an exception to this was the ligand shown in Fig. 6c which produced a side-by-side architecture with copper(I) ions. The 'twist' of this ligand meant a grid architecture would be too sterically demanding, and it would be hard for metal ions to approach. Ligand design is still a vital part of creating the desired SCC.

In 2014, Canterbury's Fichett *et al.* provided another example of a [2x2] square grid with silver atoms and dppn based ligands.[14] This system had previously been investigated by other groups with a variety of other metal nuclei, previously showing less symmetric substitution patterns led to unsymmetrical coordination sites. Fichett *et al.* used silver, which is more forgiving of unusual coordination geometries in ligands, to then focus on the effect of the addition of increasing steric bulk remote from the coordinating system. A series of dppn derivatives (Fig. 6b) were investigated. It was found that the different fused bulks affected how much the pyridine rings were able to remain coplanar with the pyridazine, controlling whether the ligands are able to simultaneously chelate two or bridge four silver atoms as monodentate donors. As expected, the least bulky groups interfered the least, with the ligand successfully assembling into squares.

Even if a ligand should favourably form cyclohelicate squares, in that the angles and rigidity of the ligands and metal coordination have been picked well, other factors still need to be kept in mind. One of these factors is stoichiometry. In 2011, Moratti *et al.* in Otago[26] investigated a different backbone of ligand, with an interest in a pyrimidine-hydrazone (pym-hyz) motif.[26] This structure was of initial interest in the stabilising effects between the rings of a helical ligand strand. With an appropriate choice of metal ion and stoichiometry [1:1 ligand:metal] square-grids could be successfully made. However, if complexation was done with the metal in excess, [1:2 ligand:metal] squares would be unfavourable enthalpically, and the ends of the ligand would rotate in a way that prevented full coordination of each coordination site and metal, leading to the ligand 'uncoiling' and leaving a linear complex.

Cyclohelicate triangles

Cyclohelicate triangles are trinuclear metallacycles [M_3L_3], with three metal atoms most often equidistant, arranged at 60^o angles, in equilateral triangle geometries (Fig.7). Three structural ligands coordinate in the same above and below arrangement as squares, in an anti-parallel fashion. However, cyclohelicate triangles are much less common than cyclohelicate squares.[27] Cyclohelicate triangles are double stranded like squares, but have a more compressed internal angle geometry. Triangles are more entropically favourable than a square geometry, creating more molecules than squares. However, squares are usually favoured due to the reduced angular strain on the ligands being held close together. Triangle formation requires an alteration in this balance, which can be done through an increase in the flexibility of the ligand. However, most often trinuclear metallacycles are obtained serendipitously.

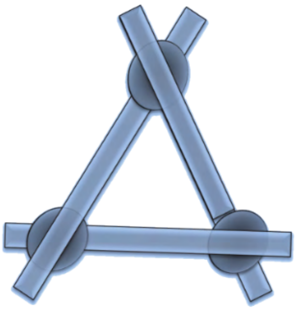

Fig. 7. Schematic diagram of a cyclohelicate triangle

One of the more recent polygons developed in New Zealand is a novel cyclohelicate [M_3L_3] triangle, rather than a metal edged or capped triangle. A pyrazine based ligand has been made and explored by the Brooker group at Otago[28] and the Plieger group at Massey.[29] The flexibility of the ligand allowed it to bend and bow outwards to reduce the strain at the triangular angles, so that the bite angles of the complexes ranged from 80 – 85^o, as opposed to the expected 60^o. This meant that these triangles were able to be more favoured over the usually expected square outcome.

Other polygons

An interesting example of how SCCs can be expanded on from these simple structures is how Kruger *et al.* in Canterbury demonstrated the transformation between three discrete complexes of a Pd_xL_y system.[30] This investigation reinforced the point that stoichiometry plays a vital role in the final architecture of a system, due to its involvement in determining the entropic favourability for each synthesis. Here a very simple ligand, with mono- and bidentate ends, was introduced to Pd^{II} in different ratios of [ligand to metal] to go from a mono-nuclear complex [2:1], to a dimer [2:2], and to a nona-nuclear cage [4:3].

Conclusions

There is an ever-increasing interest in supramolecular chemistry and its wide range of applications, from catalysis or electronics to biology and medicine. Numerous discrete SCCs of different shapes and sizes have been synthesised, with New Zealand chemists having contributed their own additions to this growing library of structures. While much is known about their design principles, and a high degree of synthetic control is now achievable, more information and application potential remains to be uncovered.

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Recent developments in visible light activatable photolabile caging groups

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Photopharmacology– optical control of biorelevant mechanisms

Traditional pharmacology often encounters the fundamental issue of poor drug selectivity.[1,2] Although poor selectivity leads to a host of issues including undesired side-effects, in early stages of drug development more basic issues of accurately identifying targets is of concern. The ability to precisely control when and where drug activation occurs enables one to overcome many problems associated with poor selectivity. Photopharmacology focusses on the utilisation of light to externally control the pharmacological activity of drugs in diseased cells and tissues.[3-6] In this context, light serves as a valuable external stimulus as it is non-invasive and offers a high degree of orthogonality, its wavelength and intensity can be controlled with ease, and it can be delivered with high spatial and temporal resolution. These features make light an ideal input stimulus for applications in biological settings, and when combined with light-responsive therapeutics, enables one to probe and regulate bio-relevant mechanisms with superior precision, addressing some of the underlying challenges associated with poor selectivity.

The photoresponsive molecular tools developed in photopharmacology are typically categorised into two classes: photoswitches and photolabile protecting groups (more commonly referred to as photocaging groups).

Photoswitches

Photoswitchable groups can be merged into the pharmacophore of a bioactive where exposure to light induces reversible conformational changes and the ability to toggle between pharmacologically active and inactive states using distinct wavelengths of light (Fig. 1, top).[7] Azobenzenes, diarylethenes, and spiropyrans are examples of molecular photoswitches that are frequently incorporated into bioactive molecules.[4,5,7]

Photocaging Groups

Photocaging involves installing bulky groups that block or hinder important binding regions of drugs, thereby rendering them inactive until light induced bond cleavage removes the caging group and restores activity (Fig. 1, bottom).[8,9] In contrast to reversible photoswitching, the cleavage of photolabile caging groups is irreversible, and as light-induced activation of a photocaged drug can only occur at a single predetermined time point this approach does not allow for reversible optical control over the biological function of the molecule. Despite this, photocaging serves as a valuable molecular tool since differentiation between the 'active' and 'inactive' states is generally much better compared with the photoswitching strategy. Additionally, the simplicity of photocaging is appealing as superficial modifications to known bioactive compounds are generally less demanding than redesigning molecules to incorporate photoswitches.

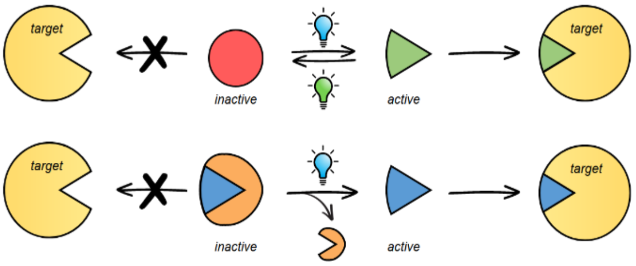

Fig. 1. A comparison of photoswitching (top) and photocaging (bottom) approaches for light-responsive bioactives

To date, much effort has been devoted to the development of light-responsive tools to study complex cellular pathways. Despite the numerous reports on photoresponsive molecules that can modulate biological processes with high spatiotemporal resolution, the majority of these have required UV light to achieve photoactivation.[5,6,9] The harmful effects of UV light on biological samples as well as poor tissue penetration impedes the utility of such probes in advanced biological settings.[10-14] As such, there is a need to develop new entities in which the wavelength of light used for photoactivation falls within the phototherapeutic window (650–900 nm).

Given the need to move away from this reliance on UV light, more research groups are focussing on the development of photoresponsive systems that strongly absorb visible / near-IR light, as well as the use of two photon methods.[3] This minireview serves to provide an overview of the progress made in the development of red-shifted photolabile caging groups. This is by no means an extensive review of the literature, but instead aims to highlight the significant advances made within the field over recent years.

Coumarin-derived caging groups

Coumarin-derived caging groups have been documented in the literature dating back from the 1980s[15] and have become a popular choice of caging group as they present a number of favourable properties, including strong absorption above 350 nm, efficient decaging reactions, good stability in the absence of light, and suitability for two photon decaging. As much work has gone towards optimising their photophysical properties, it is well known that coumarin-derived fluorophores and caging groups can be readily tuned via the inclusion of electron-donating and -withdrawing substituents in appropriate positions (3-, 6- and 7-positions), as well as the inclusion of a thio-carbonyl in place of the carbonyl group at the 2-position.[16] Coumarin caging groups typically contain electron donating amines at the 7-position and the cargo is caged via an ester or carbonate moiety connected to the coumarin at the 4-position.

The mechanism of photocleavage of coumarin derived caging groups has been thoroughly investigated.[17-19] In brief, photoexcitation results in heterolytic cleavage of the C–O bond in **1** (Fig. 2). The 4-methylcoumarin cation **2** then directly reacts with the solvent to form the corresponding 4-methylcoumain product **4**, and decarboxylation of **5** releases the bioactive component **6**.

Modification at the 7-position

Many examples of coumarins contain a dialkylamino-substituent at the 7-position, simply to enhance conjugation with the push-pull arrangement.[8] Similarly, extending the coumarin π-system by inclusion of an electron donating styryl group at the 7-position (Fig. 2, compound **7**) has been shown to retain good photophysical properties while significantly red-shifting its absorption profile compared to standard coumarin derivatives.[20] The resulting red-shifted coumarins have been employed as photocages for alcohol groups *via* attachment at the 4-position with a methylene carbonate and photocleavage of the 7-styryl-coumarin was achieved with 475 nm or two-photon excitation using 800 nm.

Modification at the 6-position

A number of examples of caging groups containing electron donating groups at the 6-position of coumarin have been reported (bromo, chloro, hydroxy, alkoxy, or 6,7-dialkoxy).[8] Examples of modification at the 6-position alone are relatively sparse, and they are most commonly seen in combination with 6,7-disubstituted derivates as electron donating groups (EDGs) at the 7-position result in more dramatic changes to their absorption spectra, and often improve their decaging quantum yields.

More recently, a caged 6-nitro-7-amino coumarin **8** was used for the detection of hypoxia and nitric oxide (NO) as the *in situ* reduction of the nitro group converted the non-fluorescent compound **8** to the corresponding 6,7-diamino compound **9** (Fig. 2).[21] The resulting diamino-coumarin displayed green fluorescence, and when in the presence of NO forms the corresponding triazolocoumarin **10** that displays blue fluorescence. All three derivatives were shown to be efficiently decaged with > 410 nm light, to release the anticancer agent chlorambucil.

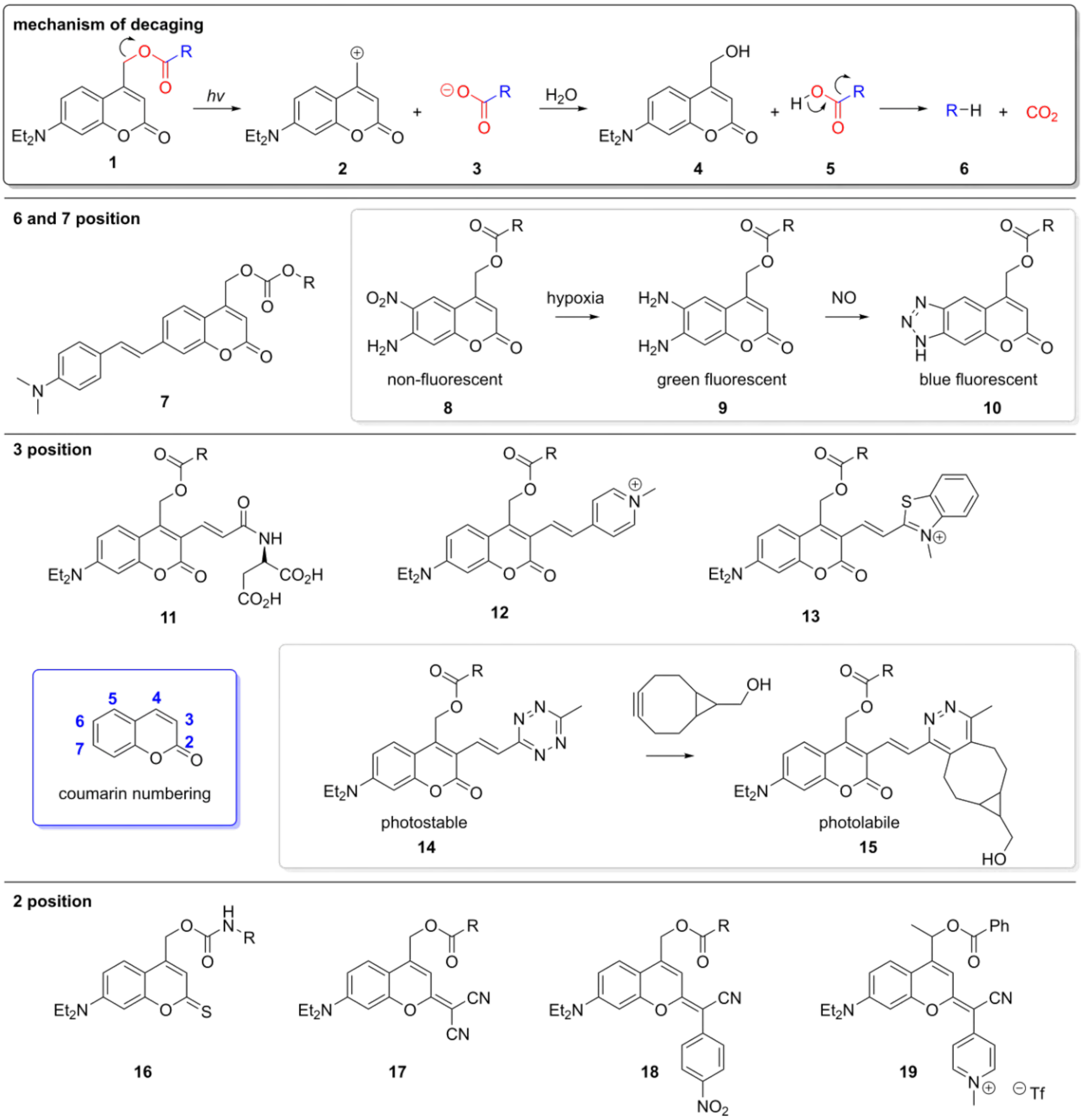

Fig. 2. General mechanism of coumarin photocage photolysis and examples of coumarin caging groups

Modification at the 3-position

Red-shifted coumarin caging groups *via* the extension of the π-conjugation at the 3-position has also been demonstrated by Ellis-Davies and co-workers by introduction of vinyl amides (attaching L-glutamate **11** and polyethylene glycol, Fig. 2).[22-24] This modification resulted in compounds suitable for both single photon decaging using 450 nm, or two-photon decaging with 900 nm light, and were applicable for orthogonal decaging experiments as they are relatively stable toward two-photon irradiation at 720 nm. Additionally, these modifications have afforded compounds with good water solubility and display good stability towards hydrolysis of the cargo in physiological buffer.

More recently, other red-shifted coumarin based caging groups with absorption maxima of 490–540 nm were achieved by functionalising with vinyl-heteroaromatic (pyridinium **12** and benzothiazolium **13**) groups at the 3-position (Fig. 2).[25] These modifications resulted in water soluble caging groups that were photocleavable with green light (λ_{irr} ~500 nm).

More complex systems have been developed by Kele and co-workers using the conditionally activatable photocage **14** (Fig. 2).[26] Coumarin protecting groups appended with a tetrazine were deactivated towards photolysis. However, upon bioorthogonal click reactions involving the tetrazine group, the sensitivity of **15** towards light induced decaging reactions was restored. Such conditional release systems enable additional means to improve spatial and temporal control for release of the active compound. This proof of concept work was performed in live cells and demonstrated a bioorthogonal approach for the release of three amino acids from the 'armed' photolabile coumarins.

Modification at the 2-position

Red-shifting the absorption maxima of coumarins can also be achieved by converting the carbonyl to a thiocarbonyl. This simple modification was used for the development of a photocaged ERT2 receptor, in which the 2-thiocoumarin **16** was readily cleaved when irradiated with blue light (λ_{irr} = 470–500 nm).[27] The caging group showed good applicability to biological systems as the decaging experiments were performed *in vivo* using zebrafish embryos and also exhibited good stability towards 350–400 nm light making it potentially useful for use with orthogonal photorelease systems.

In addition to 2-thiocoumarins, similar red-shifted analogues were also produced by addition of conjugated electron withdrawing groups at the 2-position, via dicyanomethylene[28] (**17**), or arylcyanomethylene[29] (**18**), although poor decaging yields after extended irradiation times were observed for some derivatives (< 5% after 10 h irradiation).

Similarly, arylcyanomethylene derivatives containing *N*-alkylpyridinium groups, dubbed COUPY (such as compound **19**), are green light activated (wavelengths of 505–620 nm), and exhibited good properties for biological applications including water solubility, efficient light-induced deprotection, and are stable towards hydrolysis (Fig. 2).[30] Caged model compounds have also demonstrated high cellular uptake into the mitochondria, adding another desirable property that aids their localisation prior to light induced activation.

BODIPY-derived caging groups

An array of BODIPY-derived caging groups has more recently appeared in the literature as valuable photolabile caging groups that are readily cleaved at wavelengths > 500 nm.[8,31] Such caging groups present a number of advantages in that the BODIPY core is often resistant to photobleaching, exhibit good biocompatibility, and the spectroscopic properties can be readily tuned via structural modifications. Due to the reactivity of the unsubstituted dipyrromethene core, 1,3,5,7-alkyl substituted derivatives are rather common, while the bioactive molecule is often introduced at the 8 (*meso*) position. Examples where the cargo is introduced at either the 4- or 2,6-position of the BODIPY core have also dotted the literature.

Inclusion of bioactive at the 4-position

In 2014, Uran and co-workers observed that 4-aryloxy BODIPY derivatives underwent a photoelimination reaction at the 4-position (cleavage of the boron-aryloxy bond) when irradiated with 500 nm, to afford BODIPY **21** and hydroxy aryl **22** as the corresponding photo-products (Fig. 3).[32] Photo-induced electron transfer between the BODIPY core and the adjacent aryl group was found to be the driving force behind the decaging reaction.[33] Interestingly, the decaging quantum yield was shown to be dependent on the polarity of the solvent system that the photolysis reaction was performed in, with higher decaging quantum yields observed in non-polar solvents, such as hexane.[33] The utility and biocompatibility of this new class of caging groups was further demonstrated when **24** was introduced onto the terminal amine of histamine *via* a self-immolating linker (Fig. 3). This probe was used to stimulate cultured HeLa cells in a light-dependent manner when exposed to blue-green visible light.[32]

While these were the first examples of BODIPY-derived caging groups, these new caging groups suffered from poor decaging quantum yields when compared to those caging groups that employ shorter wavelengths for the photolysis reaction.

Meso-methyl BODIPY caging groups

Shortly after the early reports of the 4-aryloxy BODIPY-based caging groups, in 2015, Weinstain and Winter simultaneously proposed that the installation of a methylhydroxy moiety at the *meso*-position of the BODIPY scaffold would also give rise to visible light absorbing caging groups (Fig. 3).[34,35] This design is analogous to that of coumarin- and xanthene-derived caging groups, and affords the added advantage in that the hydroxy group can be readily coupled to amino,

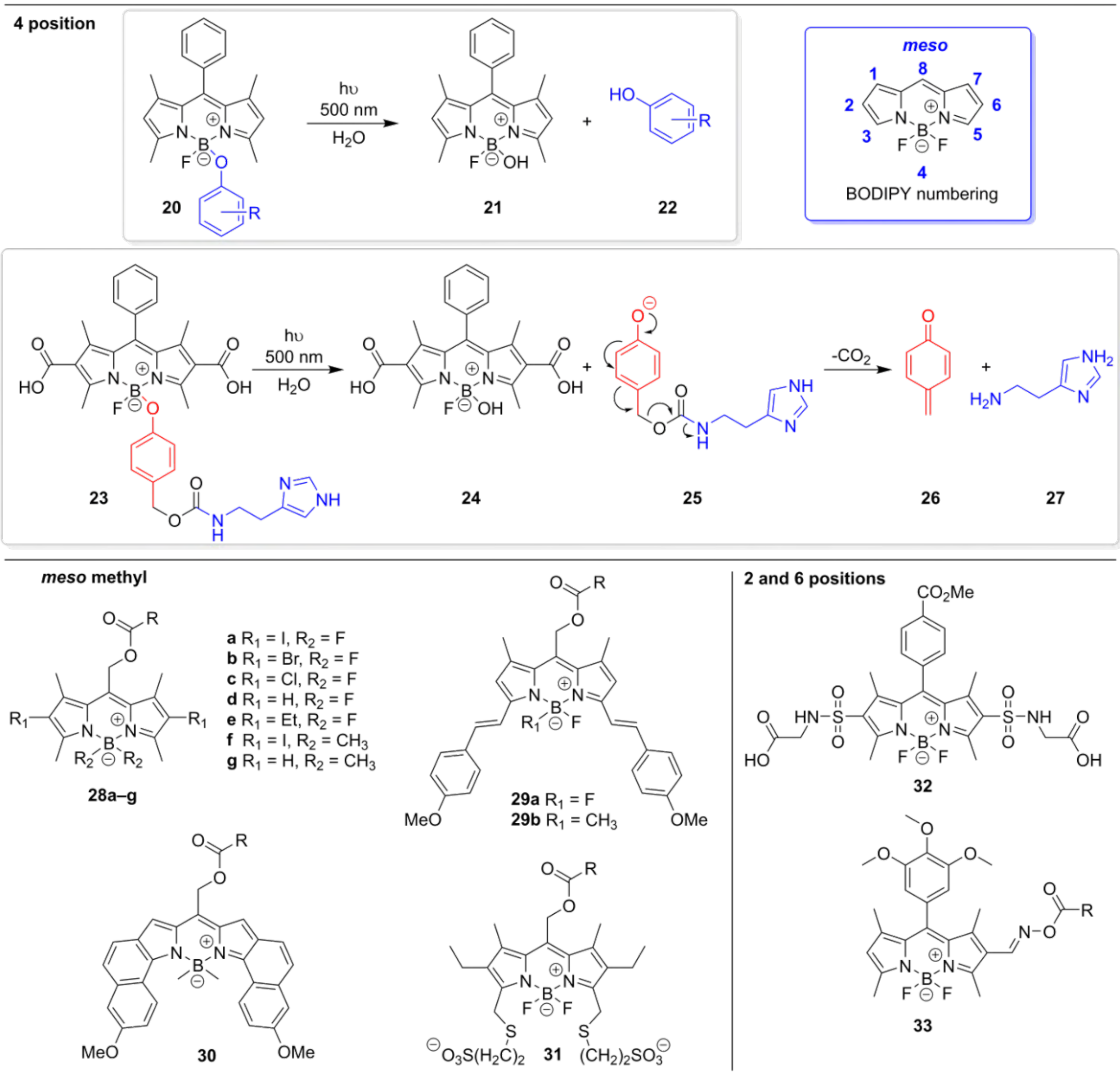

Fig. 3. Examples of BODIPY caging groups and decaging mechanism of 4-aryloxy BODIPY derivatives

hydroxy and carboxylic acid functionalities through the formation of carbamate, carbonate and ester groups, respectively.

Winter and co-workers studied the photorelease of carboxylic acids of 1,3,5,7-tetramethyl BODIPY-derived caging groups with varying substituents at the 2,6-position (compounds **28a–d**).[34] It was observed that the inclusion of halogen-substituents at these positions resulted in red-shifted absorption maxima, and that the 2,6-diiodo BODIPY **28a** exhibited the highest decaging efficiency. This increase in decaging efficiency is attributed to increased intersystem crossing (ISC) to a triplet excited state, which in turn, affords more time for the photoinduced reaction to occur. Unfortunately, these photocaged carboxylic acids still required long irradiation time, which is not ideal in biological applications.

The caged substrates bearing the *meso*-methyl BODIPY **28e** described by Weinstain, absorbed strongly around 545 nm and were readily decaged when irradiated with 540 nm.[35] In this study, the caging group was introduced onto a handful of amino (primary and aromatic amines) and phenol groups. The nature of the leaving group appeared to influence the rate of the decaging reaction as well as the decaging quantum yields. For example, the authors observed that the photorelease of aromatic amines occurred approximately 5-times faster than that of primary amines. Rapid decaging was also observed in aqueous media, and importantly these caged substrates exhibited good stability in the absence of light. Good cell compatibility was also observed when the *meso*-methyl BODIPY **28e** was introduced onto both histamine and dopamine. The bioactivity of these biogenic amines was readily photoregulated when exposed to visible light in cultured cells and neurons respectively.

The direct attachment of methylhydroxy caging groups to amines does not result in the efficient photoactivation of the caged bioactive.[8,9] Sitkowska *et al*. investigated a small series of BODIPY caging groups (compounds **28a–d**) deemed suitable for the photocaging of primary and secondary amines *via* a carbamate linker.[36] Rapid photorelease of 4-fluorobenzylamino moieties were observed when irradiated with λ_{irr} = 530 nm, albeit these caging groups exhibited poor solubility in aqueous media.

These early reports have sparked much interest in the community with detailed structure-property relationship studies being performed to aid the development of BODIPY caging groups with improved decaging efficiencies. Slanina *et al*. investigated, in detail, the 'heavy atom effect' on BODIPY derived caging groups.[37] The fluorescence quantum yields of the 2,6-dihalogenated BODIPYs decreased in the order of H>Cl>Br>I (due to increased ISC efficiency), while the decaging efficiencies were inversely proportional to the fluorescence quantum yields. The authors also demonstrated that increasing the electron density of the BODIPY core stabilises the carbocation intermediate, which in turn improves the decaging efficiency. The replacement of the two fluorides on the boron atom with methyl groups resulted in up to 30-fold improved decaging efficiencies when compared to the corresponding BF_2 derivatives. Diethyl- and diphenyl boron derivatives were also synthesised, however the increased steric bulk introduced by these substituents resulted in a decrease in the decaging quantum yield. Furthermore, the combination of 2,6-diiodo substituents with boron methylalkylation (BODIPY **28f**) dramatically improved the decaging efficiencies.

In 2018, Smith and Winter showed that extending the π-conjugation of the BODIPY core by installing styryl groups at the 3,5-positions afforded caging groups that strongly absorbed in the far-red region (*ca* 700 nm).[38] Whilst compounds **29a** and **29b** could be used for the photoinduced decaging reaction, unfortunately these BODIPY derivatives exhibited poor photorelease quantum yields ($\varphi \sim 0.1\%$). The flexibility around the C–C single bonds at 3,5-position was thought to result in unproductive radiationless decay processes. Therefore, in efforts to improve decaging efficiencies, the same authors synthesised conformationally restrained derivatives containing a fused polycyclic scaffold (Fig. 3, compound **30**).[39] The introduction of added rigidity into the design was highly successful, with significantly improved decaging efficiencies that were > 50 times greater than traditional BODIPYs. These properties are highly attractive as the BODIPYs absorb strongly in the biological window and are suitable for wavelengths that are capable of deeper tissue penetration.

In 2020, Weinstain and Miller reported water soluble BODIPY photocages by the installation of two sulfonated side chains at the 3- and 5- positions (Fig. 3, compound **31**).[40] Although sulfonation of the 2,6-positions and 3-morpholine substitution resulted in low decaging quantum yields, the addition of sulfonated sidechains at the 3,5-positions maintained high photorelease efficiency using λ_{irr} = 545 nm. The degree of sulfonation can be used to improve as well as modulate cellular permeability and localisation, as observed using caged sphingosine, serotonin, dopamine, and histamine derivatives.

Inclusion of the bioactive at the 2,6-position

In contrast to the BODIPY-derived caging groups previously described, Urano and co-workers discovered that 2,6-disulfonamide BODIPY derivatives (Fig. 3, compound **32**) underwent a photoinduced reaction when irradiated with visible light (λ_{irr} = 490 nm).[41] The inclusion of **32** onto the amino moiety of the neurotransmitter, γ-aminobutyric acid (GABA), masked GABA's cellular activity. Exposure to visible light released the active form of GABA to stimulate neuronal cells.

In 2019, Sambath *et al*. reported a new BODIPY caging group bearing a photoreactive oxime ester at the 2-position (Fig. 3, compound **33**).[42] Exposure to green light cleaves the N–O bond to release either an aromatic or aliphatic carboxylic acid. The known histone deacetylase inhibitor, valproic acid, was rendered inactive with introduction of the BODIPY oxime ester **33**. Inhibitory properties were restored when irradiated with 503 nm in HeLa cells.

Conclusions

Caging groups enable precise control over the release of bioactive molecules, and the development of red-shifted photocages have only expanded the molecular toolbox of caging groups that are necessary for practical use in biological systems. As lower energy visible to near-IR light can be utilised for photoactivation, high energy light can be avoided and the effects of phototoxicity minimised. Although a growing number of visible light photocages are available, they often suffer from poor solubility in aqueous solutions and undesirable cell permeability properties. The poor solubility of caging groups in aqueous environments remains an issue as they are highly lipophilic in nature, limiting their applications in cells. Additionally, due to poor water solubility, organic solvent/water mixtures are often needed for photophysical characterisation, which does not accurately reflect the intracellular environment in which such probes are to be used. As such, caging groups that are highly water soluble are of great interest and this challenge is currently being addressed with the development of water-soluble caging groups that are starting to appear in the literature.[25,40,43]

Future work may focus on further developing caging groups with narrow absorption bands for multicomponent systems involving orthogonal activation, as well as conditionally activatable systems to further enhance the level of spatiotemporal precision. As this fascinating field of research continues to evolve, so does the possibility to progress from simple 'proof-of-concept' studies to the development of new molecular tools suitable for advanced multicellular systems. The ability to choose when and where small molecular bioactives exhibit their therapeutic properties will afford one with the opportunity to perform detailed studies on the mode of action of drugs and further understand the intricacies involved in complex systems.

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Disinfectants and sanitisers for decontamination of fresh produce

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Introduction

Fresh produce is one of the most important categories of the daily diet, providing us with necessary essential components including vitamins, minerals, carbohydrate, and dietary fibre. The Food and Drug Administration (FDA) experts suggest that we eat 5-9 servings of fruits and vegetables every day.[1] Despite the high nutritional values, ensuring the safety of fruits and vegetables for consumption is a significant challenge. This challenge is reflected by several food safety breaches in recent years, where consumption of contaminated fruits and vegetables has caused over 50% of the foodborne illnesses in the world.[2] The National Institutes of Health (NIH) estimates that around 5.2 million cases of foodborne disease are due to bacterial infections from the 1980s through to 1999 in the United States.

Among all the foodborne outbreaks and illnesses, the number of illnesses linked to fresh produce is higher than any other single food category.[3] There have been more than 40 outbreaks of foodborne illness related to fresh produce in North America from 2013 to 2020.[4] In New Zealand, the number of foodborne illness outbreaks increased overall in the last ten years, although the number of illnesses per 100,000 population was less than most other countries in the world.[5] These statistics reflect food safety challenges for raw and minimally processed products and represent a significant number of human illnesses and deaths. There is also a large economic impact. Therefore, addressing microbial contamination is of great importance for the fresh produce industry.

The foodborne diseases related to fresh produce are caused by both bacterial and viral pathogens such as pathogenic *Escherichia coli* O157:H7, *Listeria monocytogenes*, *Salmonella* spp., *Campylobacter* spp., *Enterobacter* spp., human norovirus, and hepatitis A virus, as recorded by the Centre for Disease Control and Prevention (CDC).[4] Moreover, the novel coronavirus (COVID-19) may be able to survive on food, especially on the skins of fresh produce.

It has been identified that the naturally occurring microbial populations found in minimally processed fresh produce can range from 10^3 to 10^8 CFU/g (where CFU is a colony forming unit).[6] Microbial contamination can arise from animal manure, irrigation and surface water runoff, improper handling by workers and consumers, transport containers, and improper storage.[2,7] The risk of cross-contamination increases as the food products move at any point on its journey from farm to table. And because it is often served uncooked, there is no single, sure-fire step people can take to mitigate the risk of produce-related foodborne illness. The limitation on reducing pathogenic load on minimally processed fruits and vegetables is a key consideration for ensuring the safety of food products. Sanitation and washing procedures of minimally processed food such as fresh produce are vital steps for improving safety of these food products by inactivating bacteria and viruses on the surface of food products. Unfortunately, the current washing and sanitation approaches may not be effective. This introduces a significant risk as fresh produce can be naturally contaminated with bacterial and viral pathogens.

This article provides an overview of current chemical sanitisers used in the fresh produce industry. It also summarises the novel approaches developed in the last two decades that aim to enhance the sanitation efficacy of fresh produce.

Factors affecting sanitation efficacy of fresh produce

The washing of raw or minimally processed foods is a critical processing step that impacts significantly on product quality, shelf-life and food safety. Several processing factors can influence the efficacy of sanitisers in reducing both indigenous microflora and pathogens on the produce surface, including temperature,[8] pH,[9] contact time, organic load,[10,11] total dissolved solids, oxidation-reduction potential, microbial attachment and biofilms.[7,12,13]. Considering all these factors enables selection of the appropriate sanitiser or disinfectant to use on fresh produce and effectively reduce the microbial population on their surfaces.

Many studies have suggested that microbes can attach to the surface of fresh produce by specific adhesin-ligand interactions, highlighting the roles of surface chemistry and roughness on the interaction between produce surface, microbes, and sanitisers. In particular, the surface chemistry and surface topology of fresh produce such as leafy greens can limit the access of sanitisers to bacteria.

The varied surface topographies of produce provide numerous sites for the formation of biofilms. Biofilms that harbour a combination of microbial cells from different species and their secreted extracellular polymeric substance (EPS) are more resistant to sanitisers than planktonic cells, causing major problems for the food industry.[14] In order to remove these biofilms, sanitisers must penetrate the EPS matrix and reach microbial cells, therefore enabling inactivation.[15] However, many of the current sanitisers cannot diffuse sufficiently through biofilm matrix, because the dispersion of solutes and cells in the biofilm matrix behaves similarly in glycoprotein or polysaccharide gels, that is, the diffusion coefficient of sanitisers in biofilm is rather low, and thus it is not guaranteed that antimicrobial molecules can reach the sites where microbes locate.[14] Therefore, the location of microbes on produce surfaces and the formation of their biofilms significantly affect the sanitation efficacy.

Current chemical sanitisers

Chlorine / hypochlorite

Chlorine is the most commonly used disinfectant chemical in the food industry, because of its documented efficacy and low cost. It acts on the bacterial membrane to initiate leakage of proteins and RNA, leading to cellular disruption. Since oxidative phosphorylation in bacteria is highly sensitive to chlorine content, adenosine triphosphate (ATP) is no longer produced, and thus the bacterial membrane is impossible to repair without any macromolecules being formed due to lack of energy input. The antimicrobial activity of chlorine highly depends on the concentration of free chlorine that can come into direct contact with microorganisms. Free chlorine is effective and efficient in inactivating a diversity of pathogens such as *E. coli*, *Salmonella* and *Listeria*, when an effective concentration is maintained during disinfection. Furthermore, chlorine is known for having minimal impact on the quality of processed fresh produce both physically and nutritionally and it is low in cost.

Although chlorine is very effective for inactivating pathogens in water, both laboratory and industry data show that chlorine-based sanitisers are only capable of a 1-2 log CFU/g reduction of bacteria on the surface of food materials such as fresh produce.[16] The limitation of using chlorine alone in any sanitation process is due to its nonspecific consumption by reactions with the organic load in food matrices and the shielding of pathogens because of biofilm formation on plant tissues as well as the specific structures and features of the plant that leads to limited contact of chlorine with microbes. The consumption of chlorine by high organic load is problematic because the reduced concentration of hypochlorous acid is not sufficient to kill microbes. In addition, environmental and health concerns with the use of chlorine have been raised and the food industry is worried about the possibility of regulatory constraints in the future.

The FDA has permitted use of chlorine for disinfection of fresh produce with a concentration limit of 200 ppm and a contact time of 1-2 min. In contrast, the use of chlorine for washing fresh produce has been restricted by the European Union because of possible formation of carcinogenic chloroform and organochlorine compounds when chlorine reacts with organic load such as plant tissues in wash water.[17] It can be foreseen that chlorine will be gradually phased out and alternative chemical disinfectants will be used to improve the microbial safety of fruits and vegetables in the near future.[18]

Chlorine dioxide

Chlorine dioxide (ClO_2) is a yellow to red gas that has been used for water disinfection since the beginning of the 20th century.[19] It has attracted increased interest over the last ten years in the produce industry.[20, 21]The advantages of using chlorine dioxide for the decontamination of fresh produce is mainly due to its high antimicrobial activity and the ability to overcome the constraints of low pH and the presence of organic load in foods.[22] It has been demonstrated that both gaseous or aqueous forms of ClO_2 are effective in killing pathogenic bacteria and their spores on the surface of fresh produce.[23-26] However, several studies suggest that ClO_2 gas treatment is more effective in reducing microbes on rough produce surfaces than aqueous ClO_2 treatment, due to its high accessibility.

In 2008, the FDA granted an approval for ClO_2 to wash fruits and vegetables and to be used as an ingredient in meat and poultry products.[27] The maximum concentration of ClO_2 permitted for sanitising food-contact surfaces is 200 mg/ml.[20] For treating whole produce using ClO_2, the highest allowable concentration is 3 mg/l, and is followed by thermal processing such as blanching, cooking, or canning.[28]

Hydrogen peroxide

Hydrogen peroxide (H_2O_2) inactivates microbial cells due to its properties as an oxidant, generating cytotoxic oxidising species such as hydroxyl radicals. Using H_2O_2 for washing fresh fruits and vegetables has been investigated for 20 years. This cost-effective and easily handled compound can kill both vegetative cells and spores, and is fast acting without producing toxic products. For example, treatment with 2% H_2O_2 for 2 min has shown an approximately 2 log CFU/g reduction of *Salmonella* populations on alfalfa sprouts.[29]

Compared to hypochlorite and peroxyacetic acid (see next section), H_2O_2 is generally less effective at reducing levels of pathogens on the surface of produce.[30] Thus, several studies have been conducted to explore the possibility of combining H_2O_2 with other chemical or physical approaches for improving the inactivation efficacy of microbes. For example, washing baby spinach with a combination of 1% H_2O_2 and 1% lactic acid at 40°C for 5 min resulted in an approximately 2.7 log CFU/g reduction of *E. coli* O157:H7.[31]

Hydrogen peroxide is classified as one of the generally recognised as safe (GRAS) compounds approved by the FDA. However, the FDA has not approved the use of H_2O_2 for the washing of fresh produce.[32] Its limited use in the produce industry is because it can cause severe browning and bleaching due to its strong oxidative activity.[33]

Peroxyacetic acid

Peroxyacetic acid (PAA, also known as peracetic acid) is another chemical sanitiser that is currently widely used throughout the fresh produce industry.[34] PAA used for sanitation is an equilibrium mixture of peroxyacetic acid, acetic acid and hydrogen peroxide. Solutions of PAA are produced by reacting glacial acetic acid with a hydrogen peroxide solution, as shown in Fig. 1. PAA is effective in reducing the microbial load in wash water by causing disorganisation of cell structure and cell lysis. The oxidative stress caused by PAA can damage all types of macromolecules associated with a microbial cell, e.g., lipids, proteins and carbohydrates.[35] Despite its high effectiveness and noncorrosive properties, PAA has an undesirable aroma, which can be a concern for food applications. In addition, its effectiveness can be significantly affected by the presence of metals.

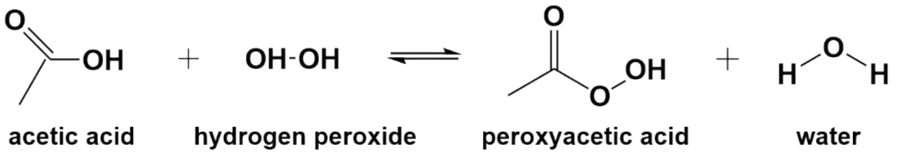

Fig. 1. Production of peroxyacetic acid

PAA is more expensive to use than chlorine but it is more active in the presence of high organic content, unlike chlorine and ozone (see next section). Furthermore, the effective pH range for PAA is very broad, enabling the produce industry to recycle wash water for multiple batches of processing. The FDA permitted PAA concentration for use in produce wash water is 90 ppm, while 500 ppm is allowed in solution for sanitising purposes.

Aqueous ozone

Ozone (O_3) has exhibited excellent antimicrobial activity against a broad spectrum of microbes including bacteria, moulds, protozoa, viruses and spore cells.[36] It can be used in either the gaseous or aqueous phase. The unique feature of ozone is that it decomposes rapidly in air producing oxygen and leaves no residues. This enables ozone to be a greener alternative to traditional chemicals for various food-related applications.

While gaseous ozone has been widely used in cold storage environments to prevent airborne moulds,[37] aqueous ozone has been demonstrated to show an even higher oxidation potential than gaseous ozone.[38] Aqueous ozone can decompose in water into free radicals such as hydroxyl, hydroperoxyl and superoxide radicals. The antimicrobial mechanism of ozone is that it causes damage to cell walls and membrane constituents. This action does not require a high concentration and so the use of ozone for sanitising food products is extremely environmentally friendly. Kim and Yousef have reported a 5 log CFU/g reduction of *Pseudomonas fluorescens* and *L. monocytogenes* after exposure to 2.5 ppm ozone for 40s.[39] Furthermore, ozone has shown to be effective on many varieties of fruits and vegetables and many research and industrial trials are underway to validate the feasibility of transforming this technology into industry applications.

Ozone has been legally permitted to be used in food applications in North America, Australia, New Zealand, Japan and several European countries.[40] No evidence has shown that low dose ozone treatment causes destruction of nutritional or sensory qualities in the food materials.[18] However, high dose ozone treatment can significantly degrade the sensory qualities in fresh produce.[41] Another limitation of using ozone for food applications is its instability at higher pH. This is because more OH^- ions that are available at higher pH can decompose ozone.[41] In this sense, the efficacy of ozone treatment may be dependent on the type of fresh produce being considered.

Novel sanitation approaches

Synergistic antimicrobial effects of natural food-grade compounds

One novel sanitation strategy is to utilise synergistic antimicrobial effects generated by a combination of multiple treatments. While the concept of "synergistic effects" has some similarities with the "hurdle technology" term that is used in food processing, synergistic effects focus on intensified antimicrobial effects caused by the combined hurdles.[42] Compared to traditional processing, synergistic antimicrobial treatments can lower the processing intensity while reducing the use of chemicals. Subsequently we can achieve the same level of microbial inactivation while maintaining the high quality attributes of food products.

Diverse natural compounds such as essential oils, spices and fruit and vegetable extracts have been explored for their antibacterial and antiviral potential in fresh produce. The unique advantages of natural food-grade compounds compared to conventional chemical sanitisers such as chlorine include higher consumer acceptance, low risk of chemical residues, reduced environmental concerns and minimal impact on food quality. However, their translation to practice has been limited because they have limited efficacy and need unrealistically long exposure times before substantial microbial inactivation can be achieved. High concentrations of natural compounds have been utilised to mitigate the efficacy issue, only to find unacceptable changes in product flavour and colour.[43]

The synergistic antimicrobial treatments that can address the issue of quality degradation are based on the use of natural food-grade compounds combined with light, ultrasound, cold plasma technology, irradiation and so on.[44-47] General antimicrobial mechanisms can be divided into two types. The first type is a combination of two treatments which intensify individual stresses on cells, resulting in accelerated cell death. For example, antimicrobials such as essential oils and PAA that can mechanically disrupt cell membranes[48,49] are used together with ultrasound, leading to irreversible damage to the bacterial cellular structure and enhanced inactivation efficacy. The second type is incorporation of another treatment to generate a new antimicrobial effect that is not observed by the individual treatments. For example, UV or visible light combined with photosensitisers can enhance the antimicrobial effect by generating free radicals.[45,50,51] These reactive oxygen species (ROS) directly attack cellular targets resulting in increased intracellular oxidative stress. Overall, these approaches have been demonstrated to be an alternative to traditional chemical sanitisers by lowering processing intensity and reducing the use of chemicals.

Novel biobased antimicrobial delivery systems

In addition to synergistic antimicrobial effects, using biobased antimicrobial delivery systems is another novel strategy to enhance the sanitation efficacy of fresh produce. Several biobased micro- or nano-carriers have been investigated such as yeast-derived carriers, microbubbles, lipid-based carriers, micelles and liposomes. These carriers can not only assist the delivery of a localised high concentration of sanitisers to the target sites on the surface of fresh produce, but can also improve the stability of chemical sanitisers against organic matter in the wash water.[52] Furthermore, the enhanced shear force generated by the movement of micro-particles also improves the contact between chemicals and bacteria attached on the produce surface.[52]

For instance, to address the issue of limited efficiency of free chlorine in sanitising leafy greens, microcarriers to deliver high concentrations of localised chlorine were developed. One study was generated to immobilise chlorine onto micron-scale silica particles using *N*-halamine chemistry, and the sanitiser achieved more than a 5-log CFU/g reduction of *E. coli* O157:H7, *Listeria* and *Pseudomonas* spp. without any quality change of fresh lettuce.[52] In contrast, conventional chlorination can only achieve 0.5 a log CFU/g reduction of microbials with an organic load between 500 and 1000 mg/L, as the majority of the chlorine is consumed by the organic matter in the wash water.

Another study was carried out by encapsulating chlorine-binding polymer into a biobased yeast cell wall particle to enhance the efficiency of the sanitiser developed in the previous study to target biofilm. The result showed more than a 7 log CFU/g reduction of bacterial biofilm after one hour of treatment.[16] In contrast, after treating the bacterial biofilm for one hour, there was only a 2-3 log CFU/g reduction achieved using free chlorine in wash water in the same experiment.[16] These two studies provide insight into how the use of microcarriers can achieve more efficient sanitisation using inexpensive chemicals like chlorine.

Conclusions

In summary, washing or sanitation is essential in the post-harvest processing of fresh produce to minimise the microbial cross-contamination risk of fresh fruit and vegetable products. This article has discussed the advantages and limitations of chemical sanitisers currently used in the fresh produce industry. Chlorine is still the most commonly used sanitiser due to its high effectiveness and low cost. However, the efficacy of chlorine in inactivating microbes on the produce surface is limited due to the high organic matter load in the wash water and on the produce surface. Novel synergistic antimicrobial effects and biobased antimicrobial delivery systems were also discussed in this article. Future work should focus on building strong collaboration between the food industry and research institutions to facilitate effective implementation of these solutions within the food processing and food service sectors.

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