NZIC Chemistry IN NEW ZEALAND

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Metal-organic frameworks as a platform for transition metal catalysis

A review of the impact of anthelmintic resistance on the New Zealand sheep industry: current scenario and potential solution

Sentiment analysis: a lens for viewing chemistry narratives

Oligonucleotide-based therapeutic agents: challenges and advances

Something old, something new: foldamers as catalysts

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The New Zealand Institute of Chemistry Incorporated
PO Box 13798
Johnsonville
Wellington 6440
Email: nzic.office@gmail.com

Editor
Dr Catherine Nicholson
C/- BRANZ, Private Bag 50 908
Porirua 5240
Phone: 04 238 1329
Email: catherine.nicholson@branz.co.nz

Publishing Editor
Raoul Solomon
Email: r.solomon@massey.ac.nz

Advertising Sales
Email: nzic.office@gmail.com

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NZIC Chemistry IN NEW ZEALAND

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Articles and features

Other Columns

A word from the President

Welcome to the October edition of *Chemistry in New Zealand*. As there was no July issue, this edition is a bumper one with lots of articles. Our new publishing editor **Raoul Solomon** has been working hard on the new look for the publication and we hope you like it.

With great sadness Council has accepted the resignation of our administrator **Joanna Dowle**. Joanna has worked closely and tirelessly with the NZIC Council since 2018 and has recently accepted a full time position elsewhere utilising her chemistry skills. We are recruiting a replacement and hope to make an announcement soon. In the meantime I want to thank Joanna for all her incredible work for NZIC and her support of institute, she will be very hard to replace!

I recently presided over my last Council meeting before handing the reins over to **Michael Mucalo**. It was a full meeting and one of the great jobs we had to do was decide our 2020 NZIC prize winners. Many congratulations to **Geoffrey Waterhouse** (Maurice Wilkins Centre Prize for Chemical Science), **Justin Hodgkiss** and **Kai Chen** (Industrial and Applied Chemistry Prize) and **Murray Thompson** (sciPAD Denis Hogan Chemical Education Award). This year saw applications for the inaugural JEOL Brian Halton Award. This was very well subscribed and I'm delighted to announce that **Lynn Lisboa** is the recipient. It is very pleasing that the field for these awards was strong and the decisions took a lot of discussion. This is a reflection of the strength and depth of talent in chemistry in New Zealand from the established to early career researchers. Congratulations to all of you. I hope to be able to connect with you all to present your awards this year.

The NZIC AGM will be held on 30 November at 4.30pm, and this will be held online for the first time ever. The aim is to enable everyone to attend regardless of location and make the event inclusive for all members. More details will be circulated to the membership nearer the time.

The inaugural online poster conference for Commonwealth Chemistry is taking place as this column is typed. This has been a fantastic event held online using poster conference technology. Posters are created *in situ* and are very interactive with the ability to include animation, videos and narration. I have been very impressed with the standard of presentation and the work that is going on across the Commonwealth in support of the UN Sustainable Development Goals. It is wonderful to see the links being made and to hear feedback about the networking that is taking place. I am delighted that our original representatives from New Zealand, **Anna Garden** (Otago), **Catherine Whitby** (Manawatu) and **Sangata Kaufononga** (Waikato) are all taking part and their posters look awesome! Many congratulations to **Anna Garden** who was one of the poster prize winners. One of the things we were not sure about was the difference in time zones but the multiple 2 hr poster sessions are working well and I have been able to connect with so many amazing researchers. I look forward to another event like this in the not too distant future and to being able to open up participation to a broader audience.

Finally this is my last column before stepping down as president of NZIC. I have been very privileged to hold the term for two years and believe that we have achieved a great deal in that time. I am very grateful to those with whom I have worked closely, and thank everyone on Council and the *Chemistry in New Zealand* editorial and publishing team for their collegiality and kindness. I look forward to remaining on Council next year in the Past President role to support Michael and to seeing NZIC continue to progress and modernise, all the while supporting our members.

Sarah Masters
NZIC President

October News

Notice of NZIC AGM

Date: Monday 30 November 2020

Venue: Via Zoom video conference. Zoom details will be sent out to members closer to the time.

Time: 4:30pm

AUCKLAND

The University of Auckland

QS Rankings

Chemistry at the University of Auckland is back in the 101-150 range in the latest QS rankings after briefly being ranked in the 151-200 range last year. The QS ranking includes research productivity and citations, as well as external perceptions from peers and employers.

Our Changing World

James ***Wright*** and *Cameron* ***Weber*** were interviewed by Alison Ballance for an episode of Our Changing World on the topic of Green Chemistry:
https://www.rnz.co.nz/national/programmes/ourchangingworld/audio/2018760034/green-chemistry-better-safer-more-sustainable

Nature article

The School of Chemical Sciences at the University of Auckland featured in an article in Nature on how university research is restarting after COVID-19 lockdowns:
https://www.nature.com/articles/d41586-020-01587-z

School of Chemical Sciences Seminars

The School of Chemical Sciences at the University of Auckland has continued to host several seminars this year:

Dr Bhuvana Kannan (Revolution Fibres Ltd): *Commercialization is real science. Commercializing science is real art.*

Professor Edwin Charles Constable (University of Basel, Switzerland): *Sustainable materials chemistry – light-emitting electrochemical cells.*

Dr *Ben* ***Mallett*** (The University ofAuckland): *Superconductivity and magnetism, and other acquaintances, in superconductor sandwiches.*

Professor *David E* ***Williams*** (The University of Auckland): *The challenge for sensors in the "Internet of Things": how do you know that the data are reliable?*

NZIC Auckland Branch Seminars

The University of Auckland hosted the following NZIC Auckland Branch Seminars:

Dr *Courtney* ***Ennis*** (University of Otago): *Laboratory simulations of Titan's cyanide aerosols*.

Dr Love-Ese Chile (Regenerative Waste Labs, Vancouver, Canada): *Advocacy, education and research to build a circular bioeconomy for plastics.*

Staff Successes

Congratulations to Dr *Bruno* ***Fedrizzi*** on his Young Scientist 2020 award from the Agricultural and Food chemistry Division of the American Chemical Society. Bruno's research in wine extends from studying aroma in New Zealand's flagship wines to investigating ways to decrease the alcohol content in wine, developing methods to measure and modulate the concentrations of sulfur-containing flavour compounds in wine, and developing methods to extract valuable chemicals from grape waste (marc).

Bruno Fedrizzi's award from the American Chemical Society

Funding

Dr *Bicheng (Amy)* ***Zhu***,successfully secured funds in the 2020 National Science Challenge Science in the Technological Innovation Seed Projects round for the project, *Stretchable and self-healable energy storage for epidermal and implantable bioelectronics*. Dr *Bicheng* ***Zhu*** is the PI and a research scientist on the project under the mentorship of Professor *Jadranka* ***Travas-Sejdic*** and Macdiarmid Institute commercialisation manager Kevin Sheehy.

Dr *Hannah* ***Holtkamp*** was awarded the Kelliher Charitable Trust Emerging Research Start-up Award, receiving $30,000 towards her research costs for her Auckland Medical Research Foundation (AMRF) research project.

Dr *Muhammad* ***Hanif*** received an AMRF grant to attend the Metals in Medicine Gordon Research Conference in Andover, USA.

Dr *Daniel* ***Furkert*** and Dame *Margaret* ***Brimble*** received AMRF funding for the project, *Antiviral therapeutics and development platform for COVID-19.*

In July, Neuren Pharmaceuticals announced that they had raised AUS$20 million to fund clinical trials of NNZ-2591, the second drug candidate developed by the ***Brimble*** group to have reached this stage. NNZ-2591 is being tested as a treatment for Phelan-McDermid syndrome, Angelman syndrome and Pitt Hopkins syndrome, each of which has orphan drug designation in the United States.

Student Successes

PhD Completions

Congratulations to the following students on their successful PhD defences:

Jinal ***Patel*** defended her PhD thesis, *Structural and inhibitor binding studies of tyrosyl-DNA phosphodiesterase 1*. Jinal was supervised by Dr *Ivanhoe* ***Leung*** and co-supervised by Dr *Jóhannes* ***Reynisson*** and Associate Professor *Chris* ***Squire***. During her PhD, Jinal worked tirelessly to study the interactions between TDP1, a DNA repair enzyme, and its inhibitors. Jinal co-authored six publications during her PhD.

Deepika ***Kanyan*** defended her PhD thesis entitled, *Exploring applications of O-BODIPY complexes: sugars and cobaloximes.* Her investigations used the fluorescent O-BODIPY molecule for tagging mono- and disaccharides, and also inserting it into the cobaloxime ligand framework as the photosensitiser for catalytic hydrogen production. Deepika's PhD was supported by a Marsden Fund PhD scholarship and supervised by *Penny* ***Brothers*** and *David* ***Ware***.

Dona ***Gunawardana*** defended her PhD thesis, *Structural and mechanistic studies of 1-aminocyclopropane-1-carboxylic acid oxidase*. Dona was supervised by Dr *Ivanhoe* ***Leung*** and co-supervised by Associate Professor *Chris* ***Squire***. Dona will be moving to the UK for her postdoctoral research.

Michael Ziqi ***Lu*** defended his PhD theses entitled, *Metalloporphyrin-decorated semiconducting oxides for gas sensing applications*. He was supervised by *David* ***Williams***, *Penny* ***Brothers*** and *David* ***Ware*** and was funded by the MacDiarmid Institute.

Cherie ***Tollemache*** defended her PhD entitled, *Evaluation of mixed alkanethiolate self-assembled monolayers on gold electrodes for biosensor applications*, supervised by *Penny* ***Brothers*** and *David* ***Ware***, and funded by MBIE.

Victor ***Yim*** defended his PhD thesis entitled, *Structure-activity relationship studies and syntheses towards antimicrobial lipopeptides*. He was supervised by Distinguished Professor *Margaret* ***Brimble***, Associate Professor *Paul* ***Harris*** and Dr *Alan* ***Cameron***. Several papers have been published from his thesis including a front page article in *Organic and Biomolecular Chemistry*, a paper in *Chemical Science* and a paper in *Frontiers in Chemistry*. Victor received a PhD scholarship from the Biocide Toolbox and he is now working for the cosmetic company Snowberry in Warkworth.

Phil ***Grant*** defended his PhD thesis entitled, *Synthetic studies towards leonuketal*. Phil was supervised by Dame *Margaret* ***Brimble*** and Dr *Dan* ***Furkert***. The thesis reports a substantial volume of creative and original chemistry directed towards the total synthesis of leonuketal, a complex terpene natural product. The examiners noted that it was hard to determine who was the student in the oral exam given Phil's demonstration of his extensive knowledge of the broad field of organic synthesis. Phil is taking up a postdoctoral fellowship with Professor Nuno Maulide at the University of Vienna. Phil was also added to the Dean's List; this recognition by the School of Graduate Studies is only awarded to the very best PhD theses.

Kristel ***Castillo*** successfully defended her PhD thesis, *New routes toward structured silane and siloxane compounds*. Kristel was supervised by Dr *Erin* ***Leitao*** and has published 1 review article and 2 research articles from her PhD.

Min ***Wang*** defended her PhD thesis entitled, *Photo-patternable stretchable electroactive conjugated polymers*. She was supervised by Professor *Jadranka* ***Travas-Sejdic*** and co-supervised by Professor *David* ***Barker***.

Danielle ***Paterson*** (*supervisors:* Distinguished Professor *Margaret* ***Brimble*** and Dr *Paul* ***Harris***) successfully defended her PhD thesis, *New chemistry for probing the interface of GPCR and PI3K signalling systems and design of inhibitors*.

Jason Ko (supervisors: Distinguished Professor *Margaret* ***Brimble*** and Dr *Dan* ***Furkert***) successfully defended his PhD thesis, *Formal synthesis of the cytotoxic macrolide callyspongiolide*.

Pekai ***Zhang*** defended his PhD thesis entitled, *Direct writing of 3D conducting polymer microarrays for biological sensing and cell stimulation*. He was under the supervision of Professor *Jadranka* ***Travas-Sejdic*** and co-supervised by Professor *David* ***Williams*** and Professor Maan Alkaisi (Canterbury). Peikai's PhD was funded by the MacDiarmid Institute. Peiaki's PhD oral exam was the first School of Chemical Sciences PhD exam conducted fully via videoconference and under the COVID-19 lockdown.

Jared ***Freeman*** (supervisors: Distinguished Professor *Margaret* ***Brimble*** and Dr *Dan* ***Furkert***) defended his PhD thesis entitled, *Synthetic studies towards anthracimycin*. Jared published 3 papers from his doctoral work and laid the foundation for final completion of this significant synthetic project by the group. Following the submission of his PhD thesis, Jared moved to Germany (along with Hans Choi and Danielle Paterson) to take up a chemistry position with the pharmaceutical company Bayer in Frankfurt.

Hans ***Choi*** (supervisors: Distinguished Professor *Margaret* ***Brimble*** and Dr *Dan* ***Furkert***) defended his PhD thesis entitled, *Synthetic study towards the spiroimine unit of portimines*. Hans' PhD work is also reported in 2 papers. His paper in *Organic Letters* (2020, *22*, 1022-1027; 10.1021/acs.orglett.9b04567) was also featured on the *Chem Help ASAP* YouTube channel run by Davidson College, North Carolina. A great example of how research can inform teaching. For more see:
https://www.youtube.com/watch?v=2Si4Gel3H8E

Rebecca ***Jelley*** defended her PhD thesis entitled, *Extraction and novel applications of grape marc-derived materials*. Rebecca completed her PhD with Associate Professor *Bruno* ***Fedrizzi*** and Professor *David* ***Barker***. Her project was supported by Bioresource Processing Alliance. She is now working as a postdoctoral fellow on a number of research projects in wine science funded by NZ Winegrowers and MBIE.

Piao ***Ye*** defended her PhD thesis entitled, *Plasmonic enhanced photocatalytic water splitting under UV and visiblelLight*. Piao's thesis research was supervised by *Geoff* ***Waterhouse*** and *Dongxiao* ***Sun-Waterhouse.***

PhD Student Prizes
L H Briggs Prize
The School of Chemical Science awards the L H Briggs Prize to the most notable PhD thesis awarded in the areas of chemistry, food science or forensic science. The prize arises from a fund raised by subscriptions among past and present students, colleagues and friends of the late Professor Heathcote Briggs, Emeritus Professor of Chemistry and a member of staff of the Chemistry Department from 1933 to 1975.

Dr *Danilo* ***Correddu*** won the 2019 L H Briggs Prize. Danilo worked with Dr *Ivan* ***Leung*** on his thesis entitled, *Studies on human proteins involved in deregulated translation in Parkinson's disease*. His project involved the successful design and development of experiments to study the effect of rare codons in protein translation in bacteria. The selection panel commented that "Danilo took on something very tough, and cracked it!" Danilo is now working as a postdoctoral researcher in the group of Professor Gianfranco Gilardi at the Università di Torino, one of the top five universities in Italy.

The selection panel stated that there was an excellent field of applicants this year, and when asked for a runner-up could not differentiate between *Shengping* ***Zhang*** and *Matt* ***Sullivan***, so congratulations to Shengping (Allan) and Matt too.

Auckland University of Technology

New Faces
Roisin ***Mooney*** joins us for a PhD under the supervision of Dr *Marcus* ***Jones***. Roisin was awarded an AUT Vice Chancellor's Doctoral Scholarship and is working on the fabrication of plasmonic silver nanoparticle films to investigate the enhancement of photophysical phenomena in light-harvesting materials.

Bhanumathi ***Bandhi*** was also awarded an AUT Vice Chancellor's Doctoral Scholarship and will be working with Dr *Jack* ***Chen*** and Dr *Cassandra* ***Fleming***. Bhanu's research is on the design of anion sensors built by the modular self-assembly of amphiphiles.

Stephen ***Lo*** joins as a research assistant working with Dr *Jack* ***Chen*** and Dr *Ebubekir* ***Avci*** from Massey University, funded by the MacDiarmid Institute. Stephen is working on the project, *Communication in chemical systems for adaptive, intelligent behaviours*.

Ema ***Maretic*** is carrying out a 3rd year research project with Professor *Nicola* ***Brasch***. Ema's research involves synthesising fluorescent conjugates of vitamin B12 which will be used to assess the selectivity of uptake of vitamin B12 analogues into bacterial versus mammalian cells.

Events
Dr *Jack* ***Chen*** and PhD students *Pablo* ***Solis Munana*** and *Chloe* ***Zhijun Ren*** travelled to Sydney, Australia in early March to perform experiments at the Australian Centre for Neutron Scattering, ANSTO (just before covid-19 hit our shores!). This was conducted in collaboration with Professor Gregory Warr from the University of Sydney and supported by a Catalyst Seeding Grant (Royal Society of New Zealand) and a grant from the Australian Centre for Neutron Scattering, ANSTO.

Professor *Allan* ***Blackman*** organised a nationwide Zoominar titled, *The Nature of Chemistry Publishing* by Dr Stuart Cantrill, Editor of *Nature Chemistry* on 26 May.

Congratulations
Dr *Marcus* ***Jones*** has been appointed Head of Chemistry and Professor *Nicola* ***Brasch*** has been appointed Head of Postgraduate Studies for the School of Science. Congratulations both!

Professor *Nicola* ***Brasch***, Dr *Cassandra* ***Fleming*** and AUT microbiologist Brent Seale were awarded a Maurice Wilkins Centre Category 2 grant to develop vitamin B12 analogues for targeted uptake of antimicrobial agents, together with collaborators in the Department of Microbiology & Immunology at the University of Otago.

With several colleagues in the US, Dr *Marcus* ***Jones*** was awarded two patents in the last six months. The first entitled, *Quantum dot light emitting devices*, is about a way to use electroluminescent colloidal quantum dots in LEDs. The second entitled, *Methods and compositions for biosensing,* describes a quantum dot based biosensing method.

Pablo ***Solís-Muñana*** and Dr *Jack* ***Chen*** published a *News & Views* article in *Nature Chemistry* entitled, *Combining catalysis and replication* that describes recent work on how a self-replicating system can spontaneously incorporate metabolic processes.

Dr *Jack* ***Chen*** published an article in *ACS Catalysis* entitled, *Dynamic and modular formation of a synergistic transphosphorylation catalyst*, together with students *Chloe* ***Zhijun Ren*** and *Pablo* ***Solís-Muñana***. This work describes how self-assembly can be used to produce catalysts that are modular and dynamic, allowing for triggered up - and down-regulation of catalytic activity.

CANTERBURY

NZIC held a "Winter Warmer" on 9 July which 47 people attended and enjoyed. Unfortunately, thanks to Covid-19, many other events have been cancelled or postponed.

The University of Canterbury

Mexican Ambassador's visit to the School of Physical and Chemical Sciences
The School hosted The Right Honourable Ambassador of Mexico, Alfred Perez Bravo from 17-20 July. The Ambassador is a Mexican career diplomat with 44 years of experience at the Mexican Ministry of Foreign Affairs. He was promoted to the rank of Ambassador at 33 years of age. For the last 30 years, he served as Ambassador of Mexico, and the President of the United Mexican States appointed him Ambassador Extraordinary and Plenipotentiary of Mexico to New Zealand in May 2019.

During his stay, he was able to visit the main campus, met with both the VC and PVC in addition to visiting the Mt John Observatory with his wife Dr Julieta Cervantes. The Ambassador was able to celebrate Matariki with the School and hear first-hand about some of the research going on in the School and wider University.

He held a research symposium on 18 August to showcase the large number of scientific interactions and exchanges between the two countries and gave a lecture entitled, *Mexico-New Zealand, New Partners*.

Kidsfest
On 10 July at Christchurch's library Turanga, Dr *Rodrigo Martinez* ***Gazoni***, *Graeme* ***Plank*** and their team (*Sarah* ***Masters***, *Imogen* ***Masters***, *Rosemary* ***Dorsey***, *Colm* ***Healy***, *Rhiannon* ***Hewett***, *Nicole Soriano* ***Ladino***, *Rian* ***Lee***, *Kim* ***Fowler***, *Caitlin* ***Wallis***, *Alex* ***Goodenbour*** *and Fuchsia* ***Moran***), organised the first ever School participation in Kidsfest (***https://www.kidsfest.co.nz***). Kidsfest is a programme organised by the council every year for kids in the Canterbury area. Presentations by Sarah and Graeme were well received by the children who enjoyed the hands-on activities. Feedback from the event has been overwhelmingly positive.

Associate Professor Sally Gaw radio broadcast
Sally ***Gaw*** gave a radio interview in early June entitled, *Ending our love affair with plastic*, which can be found at: ***https://www.canterbury.ac.nz/science/outreach/uc-science-radio/episode-5/***

MANAWATU

The School of Fundamental Sciences Student Research Symposium took place on 16 July and several of our chemistry students took part. The quality of the presentations was high, making it highly rewarding for all those involved. *Aaron* ***Whitehead***, of the ***Rowlands*** group, was awarded the NZIC prize for the best chemistry presentation for his talk titled, *Synthesis of an azo-driven molecular photoswitch*.

The NZIC student event was held on 6 August. 36 people attended the event, which was organised by *Suraj* ***Patel***. Associate Professor *Mark* ***Waterland*** was the Master

of Ceremonies. *Taichi* ***Takeuchi*** won the NZIC prize for the top Level 6 chemistry student at UCOL 2019. *Vitoria-Jayne* ***Reid*** of the ***Telfer*** group and Jack ***Francois*** of the ***Leitao*** group won the NZIC top 300 Level chemistry student at Massey University 2019.

A series of webinars between Massey and Victoria University have begun to temporarily replace our traditional in-person seminars. It was our great pleasure to have Professor Richard Payne from the University of Sydney as our first speaker giving a presentation titled, *Accelerated synthesis of modified proteins via novel peptide ligation technologies* on 5 June. Associate Professor *Robin* ***Fulton*** from Victoria University gave the second seminar on 3 July. Robin gave a very interesting talk titled, *The metallo Diels-Alder reaction: examining the metalloid behaviour of germanimines*. Dr *Kim* ***McKelvey*** has given the most recent talk on 6 August titled, *The wild west of nanoelectrochemistry*. The talk covered a diverse range of principles including 3D character animation, artificial intelligence software engineering, physical chemistry and electrochemistry.

Heather ***Jameson*** successfully defended her PhD thesis titled, *Interior decoration of metal-organic frameworks through a thermolabile protecting group strategy*. Heather was supervised by Professor *Shane* ***Telfer***. She has gained a postdoctoral position with *Bill* ***Williams*** and *Geoff* ***Jameson***, funded by the Marsden fund.

Brodie ***Matheson*** commenced his PhD with the ***Plieger*** group exploring *The utilisation of second sphere interactions for the enhancement of magnetism*.

Aaron Whitehead receives his NZIC award for best chemistry presentation from Catherine Whitby

Josiah ***Waldrom*** joined the ***Plieger*** group as part of a research course exploring new magnetic materials.

Zach ***MacDonald*** joined the ***Rowlands*** group as a BSc Honours student and will be exploring synthetic amino acids using [2.2]paracyclophane.

Jacob ***Scott*** joined the ***Rowlands*** group as a BSc Honours student and will be exploring [2.2]paracyclophane as an asymmetric catalyst.

Taichi Takeuchi receives his NZIC award for the top-level 6 chemistry student at UCOL 2019 from Vyacheslav Filichev (Photo credit: Jaired Photography)

Hannah ***Wykes*** has joined the ***Rowlands*** group as part of a research course exploring the synthesis of imidazoline [2.2]paracyclophane derivatives.

Shikeale ***Harris*** commenced her PhD with *Graeme* ***Gillies***, Principal Research Scientist at Fonterra Co-operative group limited, and *Catherine* ***Whitby***, exploring casein micelles under stress. The project is funded by Fonterra.

Sam ***Otter*** has joined the ***Waterland*** group as an MSc student and will be exploring silver nanostructures in optical trapping and SERS.

Andre ***Buzas Stowers-Hull*** has joined the ***Waterland*** group as a PGDipSci student and will be exploring SERS detection of organophosphorus compounds.

Nicole ***Park*** has joined the ***Harjes*** group as an MSc student and will be exploring the structure of APOBEC3BCTD DNA based inhibitor using X-ray crystallography.

Sarah ***Tallon*** has joined the ***Telfer*** group as part of a research course exploring mixed metal MUF16 MOFs.

Victoria-Jayne Reid receives her NZIC award for the top 300 level chemistry student at Massey University 2019 from Vyacheslav Filichev (Photo credit: Jaired Photography)

OTAGO

The Otago branch of the NZIC is proud to continue its sponsorship of the Aurora Energy Otago Science and Technology Fair, which was held at the Otago Museum in August. The event involved 262 students from around the Otago region and projects were of high calibre, especially considering the disruptions due to Covid-19. The NZIC prize winners were: Year 7: Bella McAnelly and Brea Schofield - *Melting down* from Dunedin North Intermediate; Joanne Mayyas and Lucy Kahn - *The power in the produce* from Dunedin North Intermediate; Max Bagley - *Electroplating a 20 cent coin* from Mount Aspiring College; Manon Tartonne - *Crystal clear*; Year 8: Liesel Tolson - *Juice judge* from St Hilda's Collegiate; Lucy Burke - *Deceiving drinks* from St Hilda's Collegiate; Year 9: Ryan Williams - *Weeding waterways* from South Otago High School; Year 10: Jomana Moharram - *The Ngaio tree: testing for anti-microbial activity* from Otago Girls High School; Year 11: Eddie Wright - *3,2,1 ... Blast Off!* from Otago Boys High School; Year 13: Thomas Grayson - *Have we cock(l) - ed up* from Otago Boys High School. Well done everyone – it is exciting to see the great chemistry coming from the next generation!

University of Otago, Department of Pharmacy

Jessica ***Fairhall*** graduated in August with a PhD for her Thesis project, *Bioorthogonal chemistry as a tool for prodrug activation and drug design*. Jess was supervised by *Allan* ***Gamble*** and *Sarah* ***Hook***. As part of her project Jess was a visiting intern at Novartis Institutes for Biomedical Research in California.

The ***Gamble*** group welcomes new PhD students Parul Rani and Thomi Brind who will be working on projects in the hydrogel and bioorthogonal chemistry fields.

Allan ***Gamble*** and collaborators from Chengdu University of Traditional Chinese Medicines (Professor Bo Han and Dr Xiang Li) recently published an article in *Tetrahedron Letters* titled, *Regiodivergent synthesis of aza-quaternary carbon derivatives from pyrazolinone ketimines and 1,2-dihydroquinolines* which was selected as part of the 2020 Editors' Choice Collection.

University of Otago, Department of Chemistry

A number of women from the department have been selected for the upcoming digital exhibition at the Otago Museum titled, *100 women, 100 words... infinite possibilities*. Over 300 nominations were received for women and girls in Otago and Southland who have inspired those around them to engage with science, technology, engineering, and mathematics. The exhibition is part of the Unlocking Curious Minds-funded project, *Full STE(a)M ahead* in partnership with the Dodd-Walls Centre and MacDiarmid Institute and is designed to help close the gender gap in STEM fields. The scientists in the exhibition are *Sally* ***Brooker***, *Anna* ***Garden***, *Sara* ***Miller***, *Samantha* ***McIntyre*** and *Jasmine* ***Hwang*** (pharmacy). We encourage all to view the exhibition and support our southern wāhine!

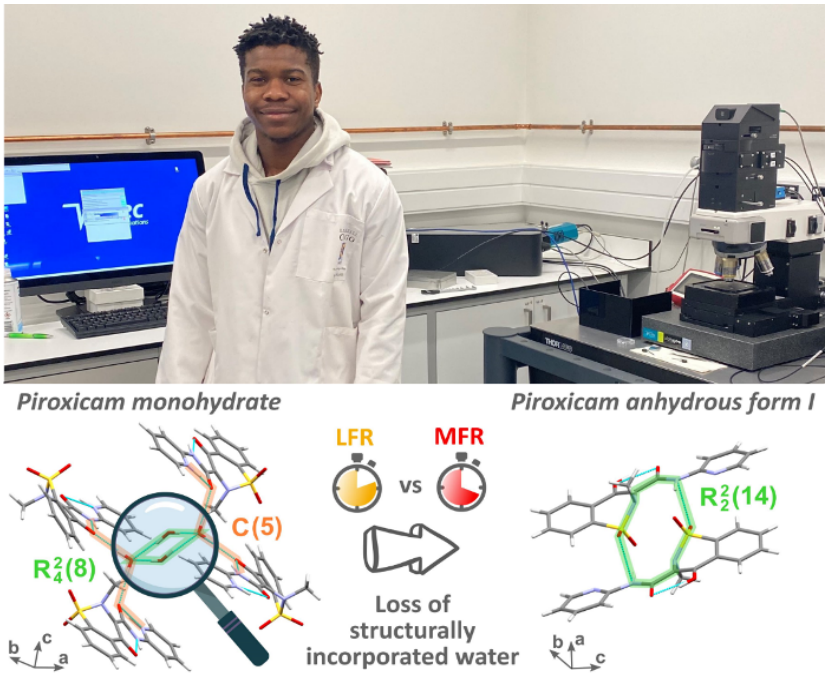
The Covid lockdown doesn't seem to have slowed progress in the group of *Keith* ***Gordon*** with a lot going on this quarter. *Joe* ***Mapley's*** paper on *Investigation of ferrocene linkers in β-substituted porphyrins* was published in the *Journal of Physical Chemistry A*. Kārlis ***Bērziņš*** and *Sara* ***Miller*** published a paper on *Co-amorphization of kanamycin with amino acids improves aerosolization* in collaboration with researchers from the School of Pharmacy, University of Otago. *Sara* ***Miller*** and *Sam* ***McIntyre*** published Sam's summer studentship work with the ***Gordon*** group in the paper, *Vibrational spectroscopy and chemometrics for quantifying key bioactive components of various plum cultivars grown in New Zealand*, in the *Journal of Raman Spectroscopy*.

Carla Meledandri (examiner), Joshua Sutton, Keith Gordon (supervisor), and Lyall Hanton (convenor) after Joshua's PhD defence

Joshua ***Sutton*** successfully defended his PhD thesis titled, *Donor-acceptor systems: a study using vibrational and electronic spectroscopies and computational modelling* in the middle of July and is working on finishing a few papers. *Elliot* ***Tay*** submitted his MSc thesis titled, *Investigating the vibrational and electronic states of various π-conjugated systems* and will be furthering his education by undertaking a PhD in Bochum, Germany.

ised alongside the International Conference of Raman Spectroscopy (ICORS2021). This was great science exposure to non-linear vibrational spectroscopy and its novel applications conducted by experts in the field.

Samantha ***Jarvis*** and *Peter* ***Remoto*** joined the ***Gordon*** group as CHEM390 students, completing projects in organic and inorganic donor acceptor systems, respectively, over the semester break.



Chima and the graphical abstract of his talk

Despite the Covid-19 pandemic, ***Gordon*** group members have been busy presenting and participating in different virtual conferences and workshops. *Chima* ***Robert*** and Kārlis ***Bērziņš*** gave talks titled, *Understanding the isothermal dehydration of crystalline hydrates in both the low and mid-frequency Raman regions* and *Solving the computational puzzle: towards a pragmatic pathway for modelling low-energy vibrational modes of pharmaceutical crystals*, respectively, at the annual Pharmaceutical Solid State Research Cluster (PSSRC) Zoom meeting at the end of the June. Chima's presentation was nominated as one of the 12 best presentations at the meeting. Chima's work highlighted the polymorphic transformation of some common drugs upon dehydration.

The majority of the ***Gordon*** group participated in the International School On Nonlinear Vibrational Spectro-microscopy (ICONS2020) virtual school, which was organ-

WAIKATO

The branch provided two cash prizes for the NIWA Waikato Science Fair. The prize for the best junior chemistry exhibit was won by Lani Jarrett of Southwell School, whose project *Nature's colours*, looked at making dyes from materials found in nature and their colour fastness after repeated washings. The prize for the best senior chemistry exhibit was won by Lance Jones of St. Peter's School for his project *On the nano scale*, which involved preparing colloids.

University of Waikato

Obinna Okpareke (supervisor *Bill* Henderson, second supervisor *Jo* Lane) has recently (during lockdown) completed his PhD oral defense, with a thesis titled, *Studies on the metallacyclic chemistry of thiourea monoanion and dianion ligands; synthesis, structures and theoretical investigations*.

Scion

Currently in development at Scion and funded through the National Science Challenge SfTI seed funding, *Angelique* ***Greene*** and *Helena* ***Quilter*** are tackling water remediation by merging the fields of stimuli-responsive chemistry and supramolecular chemistry to produce hydrogel actuators. These hydrogels act as "self-cleaning"

Chemistry prize winners Lance and Lani at the prize giving ceremony with compere Te Radar

Helena (left) and Angel (right) at work in the laboratory

molecular sponges to reversibly trap micro-pollutants in water. They contain particular monomers that use the principles of host-guest chemistry to entrap nonpolar pollutants, such as oestrogens and polycyclic aromatic hydrocarbons (PAHs), in the presence of water and then utilise thermal and electrochemical stimuli to eject the pollutant out of the gel via a de-solvating/actuation mechanism while in an external environment. The "cleaned" gel can then be reused by swelling in water.

Jamie ***Bridson*** has enrolled in a PhD as part of the Aotearoa Impacts and Mitigation of Microplastics (AIM²) research programme under the supervision of Associate Professor *Sally* ***Gaw*** (University of Canterbury), Dr *Grant* ***Northcott*** (Northcott Research Consultants Ltd) and Dr *Dawn* ***Smith*** (Scion). *Jamie* ***Bridson***, *Meeta* ***Patel*** and *Dawn* ***Smith*** have established a semi-automated method for the analysis of small microplastic particles (30-300 µm) using FTIR microscopy. Particles are first filtered onto an IR transparent membrane, which is then imaged using an array detector. Data is processed using polymer databases and image analysis to establish polymer counts, type and size.

Hill Laboratories

As part of their commitment to innovation and growth, Hill Laboratories has expanded their viticulture testing capability with the acquisition of the assets of Vine Testing Laboratory (VTL), a specialised ELISA laboratory able to diagnose Grapevine leafroll-associated virus 3 (GLRaV-3). An agreement to purchase the assets of VTL was reached earlier this year between Ormond Nurseries and Villa Maria Estate, as part of Ormond Nurseries' purchase of Villa Maria's nursery.

This new specialised service will be provided from Hill Labs' Blenheim laboratory that is already focused on providing testing services such as soil, petiole and residue testing in finished wines for the wine and viticulture industries. This service will provide fast, accurate reporting and industry-leading turnaround times to New Zealand grapevine nurseries and for any grape growers wanting to understand GLRaV-3 levels in their vineyards. With Hill laboratories' state-of-the-art instruments and the expertise available in the lab, they expect to offer virus testing results in just five working days.
The Grapevine leafroll virus (GLRaV-3) is one of the biggest threats to the wine industry globally, as vines infected with the virus show decreased ripening potential and yield. New Zealand grapevine nurseries all routinely test for this virus as part of the

Riaan Botha; Market Sector Manager, Food and Bioanalytics (left) and Hill Laboratories CEO, Jonno Hill (right)

certification process for the New Zealand Winegrowers Grafted Grapevine Standard.

As part of the VTL acquisition, Hill Laboratories also intend to invest in research and development of wine sector testing methodologies and are also looking at expanding their services to include testing for Grapevine leafroll-associated virus type 2 and 1, in addition to type 3. The laboratory will be up and running in time for the 2021 testing season.

WELLINGTON

As with other branches, 2020 is turning out to be an interesting time for the Wellington branch of the NZIC. Some of the bright spots were PhD completions for our students, including our own branch secretary *Emma* ***Wrigglesworth*** (PhD supervisor: Professor *Jim* ***Johnston***), *Loc* ***Tran*** (PhD supervisor: Associate Professor *Robin* ***Fulton***) and *Tao* ***Xu*** (PhD supervisor: Associate Professor *Joanne* ***Harvey***).

The annual NZIC quiz for secondary school kids was unfortunately cancelled; however, the planned quiz questions were put to good use as the NZIC student reps *Fraser* ***Hughson***, *Matthew* ***Brett***, *Damon* ***DeClerq*** and *Stephanie* ***Lockwood*** along with *Calum* ***Gordon*** and help from Wellington Chair Dr *Nate* ***Davis***, organised a welcome back chemistry quiz for the returning Victoria University of Wellington chemistry students. Over 50 students participated in teams of 4 – 5, with the first-place group winning School of Chemical and Physical Sciences (SCPS) tracksuits.

The NZIC Wellington branch would like to welcome four new academics to SCPS, including Dr *Mat* ***Anker***, Dr *Luke* ***Liu***, Dr *Kim* ***McKelvey*** and Professor *Tricia* ***Hunt***.

Dr *Mat* ***Anker*** joined SCPS as a lecturer at the end of 2019. Mat studied for his undergraduate and postgraduate degrees at the University of Bath, obtaining his PhD under the supervision of Professor Mike Hill in the area of main group chemistry. He then joined SCPS as a postdoctoral fellow with Professor Martyn Coles in 2017. He obviously fell for the charms of New Zealand and we were very happy that he secured a lectureship position at VUW.

Dr *Luke* ***Liu*** did his undergraduate studies at Shanghai Jiao Tong University in China. After working in the paint industry for a couple of years, he decided to pursue his PhD with Professor *Shane* ***Telfer*** at Massey University, focusing on the development of new metal organic frameworks (MOFs). This was followed by postdoctoral fellowship at Northwestern University in the USA. Fortunately, New Zealand had won him over and VUW was happy to welcome him as a lecturer at the beginning of 2020.

Dr *Kim* ***McKelvey*** is a native New Zealander, obtaining a BAppSc and MAppSc in computational modelling from the University of Otago, after which he worked as a software developer for NaturalMotion in Oxford, UK. He then decided to take up further study, obtaining an MSc and PhD from the University of Warwick, UK, with his PhD studies focusing on new approaches and applications in electrochemical scanning probe microscopy. After postdoctoral appointments in the USA (Universities of Notre Dame and Utah), he started as an academic at Trinity College Dublin, Ireland. Fortunately for VUW, he was able to be lured back to New Zealand as a senior lecturer. Although his job did not formally start until July, he managed to squeeze himself back into New Zealand just in time for the lockdown.

Professor *Tricia* ***Hunt*** is another native New Zealander, obtaining a variety of degrees from the University of Auckland including a BSc and MSc conjoint in chemistry and physics, a BA in philosophy and a PhD in theoretical chemistry under the guidance of Professor *Peter* ***Schwerdtfeger***. After completion of her studies, she continued her research in the UK, with research associate positions at Kings College London and Cambridge and then as a Royal Society University Research Fellow at Imperial College London. She continued her academic career at Imperial, obtaining her professorship in 2018. VUW is delighted to welcome her back to New Zealand!

The winning team. Top row (left to right): Fraser Hughson (quiz master), Nate Davis (NZIC Wellington branch chair). Bottom row: chemistry students showing off their newly acquired SCPS tracksuits.

Metal-organic frameworks as a platform for transition metal catalysis

Bernhard Auer* and Shane G. Telfer

MacDiarmid Institute for Advanced Materials and Nanotechnology and School of Fundamental Sciences, Massey University, Palmerston North

Email: b.auer@massey.ac.nz

Keywords: *catalysis, MOF, transition metal*

Introduction

Molecular transition metal complexes are a highly important class of homogeneous catalysts. C-C bond formation reactions like the Sonogashira,[1] Suzuki[2–4] or Heck[5] reactions are only some of the prominent examples that made it into chemistry laboratories around the globe. Today, the periodic table is widely exploited for different synthetic applications including earth-abundant catalysts for hydrosilylations and hydroborations,[6] nickel catalysts for asymmetric reactions[7,8] and heavy transition metals like gold for the activation of multiple C-C bonds[9–11] to name a few.

Often the improvement of those homogeneous catalysts relies heavily on the design of new functional ligands to create highly specialised coordination environments around the active metal centre. These ligands improve the catalytic activity and/or stabilise the catalyst (Fig. 1).[12–15]

Heterogeneous catalytic alternatives are rewarding targets, not only because their heterogeneous nature facilitates catalyst recovery, but more importantly it can extend the scope of catalysis. The following paragraphs give an illustration on how this can be achieved by designing hybrid materials that incorporate transition metal catalysts into coordination polymers. In addition, there are other promising heterogeneous transition metal catalysts as well, such as nanoparticle based catalytic systems as well as the emerging field of single-atom metal catalysts on supports.[16] Yet, those systems follow new pathways and come with their own challenges. Heterogenisation of homogeneous catalysts that already exist, however, allows us to use well-studied mechanisms while evolving the catalysts beyond the limits of homogeneous catalysis and is the focus of this article.

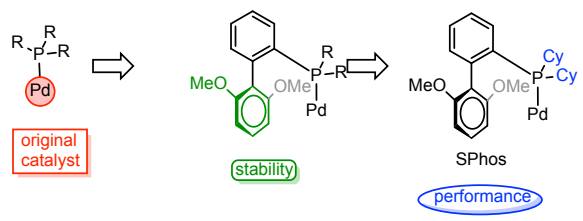


Fig. 1. **The evolution of ligand design for homogeneous catalysis, illustrated by the example of SPhos[15] (a commercially available Buchwald ligand). Depending on the steric and electronic properties of the ligand it is possible to stabilise the catalyst and improve its performance.**

Metal-organic frameworks

Catalysts that are known to work in homogenous form are a good target for incorporation into new materials. A potential heterogeneous platform should offer an accessible and large surface, as well as chemical and physical stability under the targeted reaction conditions. Further, in ideaal materials, the local environment of the catalyst is known (or can be predicted and characterised) to understand and to design the catalytic properties of this hybrid material. Metal-organic frameworks (MOFs) are promising materials for the integration of transition metal catalysts in this regard. The coordination networks with organic linkers and inorganic nodes are often crystalline and highly porous (Fig. 2).[17,18]

Since their advent in the early 1990s[2] MOFs were soon identified as potential hydrogen storage materials.[19,20] Today their applications are manifold and range from gas separation,[21] molecular sensing,[22] biomedical approaches,[23] molecular sensing[22] and protein encapsulation[24] to the adsorption of chemical warfare agents.[25] The versatility of MOFs arises from the unique combination of organic linkers and inorganic building blocks, offering a highly tunable class of materials. Isoreticu-

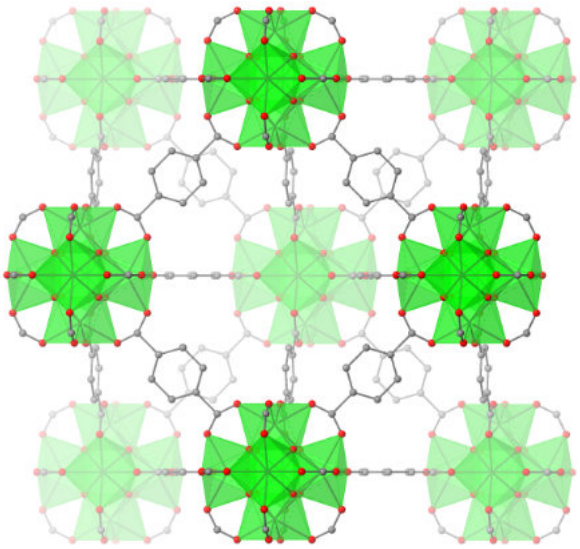


Fig. 2. **One of the archetypal MOFs, UiO-66 (Universitetet i Oslo), a framework built from terephthalic acid linkers and $Zr_6O_4(OH)_4(CO_2)_{12}$ node.[18] The zirconium-carboxylate bonds in this framework are extremely stable, giving the framework its chemical and thermal robustness. Carbon atoms are shown in black, oxygen is shown in red and zirconium in green. Hydrogen atoms are omitted for clarity.**

lar chemistry allows exchange of selected building blocks in MOFs without changing the framework topology. This was beautifully illustrated by the Yaghi group in 2002.[26] By functionalisation or extension of the orthogonal ligands in MOF-5/IRMOF-1, the framework properties could be systematically altered while maintaining the overall structure (Fig. 3).

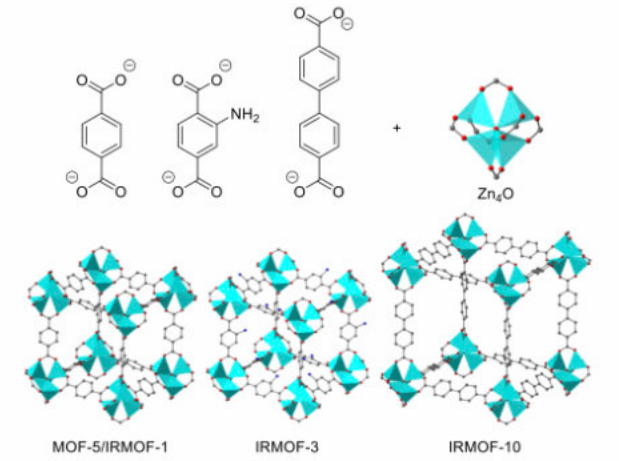


Fig. 3. **The isoreticular principle illustrated by the IRMOF-series. Structurally similar MOFs to MOF-5 can be synthesised by replacing terephthalic acid with functionalised or elongated orthogonal linkers.**

This concept also paved the way for incorporation of catalytically active linker into MOFs as discussed in the next paragraph. It is important to note that the design flexibility of MOFs is not limited to the organic building blocks but can also be applied to the inorganic nodes,[27] although a detailed discussion of this is outside the scope of this article.

Scope of molecular transition metal catalysts in MOFs

Zirconium-based MOFs, for example UiO-66, are popular platforms for catalysis due to the chemical and thermal stability of the zirconium-oxygen bonds, providing a robust framework for the integration of well-known homogeneous ligands like NacNacs (β-diketimines)[28] or salicylaldimines (salen).[29,30]

The beauty of MOF synthesis lies in the versatility of possible approaches.[31] In many cases MOFs can be synthesised directly from the linkers and the metal salts.[32,33] If this direct approach is not suitable, the organic linkers (or the inorganic nodes) can often be functionalised upon framework formation.[34] Sun *et al.* adapted this post-synthetic modification strategy for the design of UiO-66 and UiO-67 frameworks (in UiO-67 the ligand is a biphenyl dicarboxylic acid analogue instead of terephthalic acid).[35] The linkers were stepwise modified upon MOF synthesis to anchor the catalytically active palladium complex (Fig. 4a).

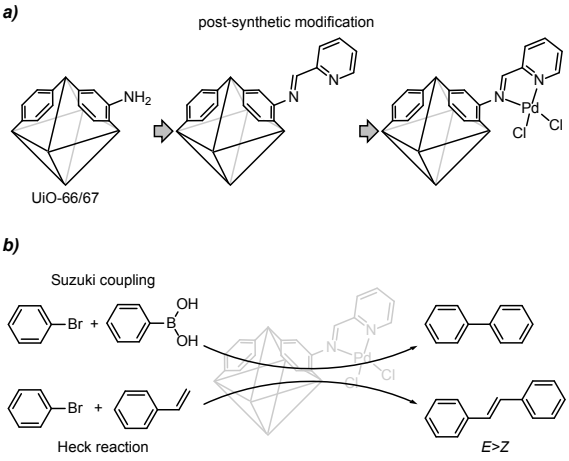


Fig. 4. **a) The catalytic unit can be introduced into the MOF by post-synthetic modification without altering the framework. b) The UiO-66 and UiO-67 analogues successfully promoted different C-C coupling reactions.**

The optimised UiO-67 catalyst with a Pd content of 0.27 mmol g^{-1} showed a conversion of up to 95% for Suzuki coupling and 93% for the Heck reaction with an *E*-selectivity of 100% (Fig. 4b). The heterogeneous catalyst showed superior activity and selectivity compared to the homogeneous controls.

CO_2 can be hydrogenated to formic acid/formate catalysed by Ir(III)-coordinated inside a Zr(IV) MOF.[36] To obtain this MOF the traditional biphenyl linker was replaced with a [2,2-bipyridine]-5,5'-dicarboxylic acid (Fig. 5).

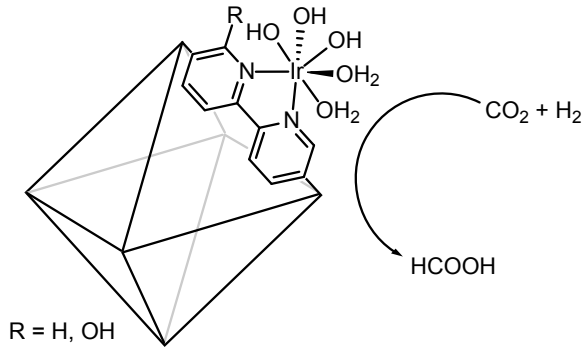


Fig. 5. **A Ir(III) based MOF catalyst for the hydrogenation of CO_2**

Upon coordination of the catalytically active iridium species the catalyst reached a turnover number of 6149±50 in 15 h and a turnover frequency of 410±3 h^{-1} under atmospheric pressure at 85°C. The heterogeneous nature of the catalyst allowed the creation of a dynamic gas/liquid interface at the catalytic site, enhancing the contact of CO_2, H_2 and H_2O.

A different approach was chosen for the synthesis of a phosphine-based MOF catalyst. Instead of depending on an existing structure, 4,4′,4′′-phosphinetriyltribenzoic acid was selected as a linker in combination with a zirconium metal source to form LSK-1 (German acronym of the Laboratory for Catalysis and Sustainable Chemistry) (Fig. 6).[37]

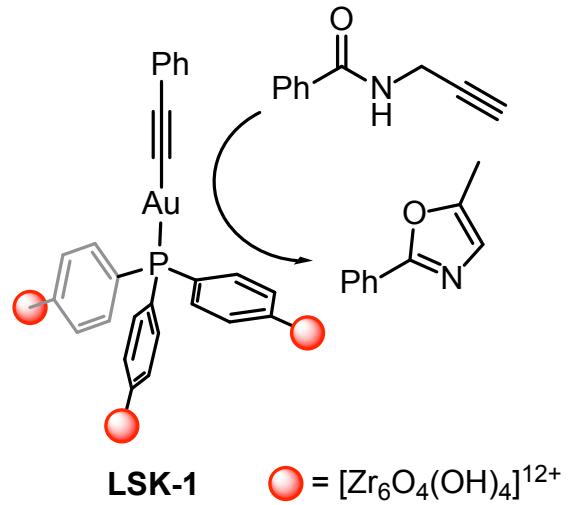


Fig. 6. **LSK-1, a MOF with triphenyl phosphine groups as organic linkers to anchor the catalytically active gold complex**

The LSK-1-Au-Cl pre-catalyst was obtained after post-synthetic addition of chloro(tetrahydrothiophene)gold(I). Activation of the catalyst was done by formation of the gold-alkyne species. This elegant method avoids activation with silver salts, commonly used in homogeneous catalysis,[38,39] which leads to the precipitation of AgCl and thus complicates the recovery of the heterogeneous catalyst from solution. This catalyst successfully promoted the hydration of phenylacetylene and cyclisation of *N*-(prop-2-yn-1-yl)benzamide exceeding homogeneous catalytic activity for the latter.

MOFs as a platform for synergistic catalysis

MOF synthesis is not limited to one organic linker or one metal centre but also allows incorporation of multiple linkers of different length and connectivity.[40] This opens the door for cooperative catalysis, where a combination of catalysts improves the catalytic performance. Utilising two linkers which promote different reactions allows sequential or stepwise reaction cascades to be targeted.

Recently, LIFM-28 (Lehn Institute of Functional Materials) was reported as a platform to install a variety of catalytically active linkers for Knoevenagel-condensation, alcohol-oxidation, acetal-, click- and Baylis-Hilll-mann reactions (Fig. 7).[41,42] The possibilities of multi-ligand MOFs were beautifully showcased by the simultaneous incorporation of multiple catalysts into the same framework for stepwise or sequential reactions. In this example, copper(I) sites promote the aerobic alcohol oxidation and the click reaction to form the triazole. Upon workup, the amine functionalised linker is utilised for Knoevenagel condensation.

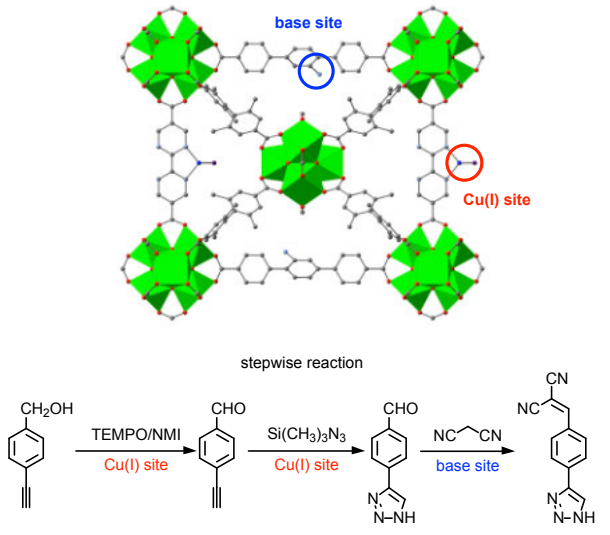


Fig. 7. **Synergistic catalysis in LIFM-28, a MOF incorporating multiple catalytic centres**

The Cui group reported the synthesis of isoreticular UiO-68 frameworks by post-synthetic introduction of metal-salen (Cr, Cu, Fe, Mn, V) linkers.[29] The MOFs were employed as enantioselective catalysts for the asymmetric cyanosilylation of aldehydes, ring-opening of epoxides, oxidative kinetic resolution of sec-

ondary alcohols and aminolysis of stilbene oxide. Combination of Mn- and Cr-coordinated ligands in the framework allowed subsequent promotion of epoxidation of 2,2-dimethyl-2H-chromene with sPhIO as oxidant followed by a ring-opening reaction with anilines in 80-85% yield and up to 99.5% ee.

Through framework design it is also possible to achieve cooperative effects by installing catalytically active metal centres in proximity to each other. For example, chiral salen-VO MOFs showed advanced stereoselectivity for the cyanation of aldehydes compared to the homogeneous counterpart while maintaining the catalytic activity.[33] Control experiments indicated that the improved selectivity of up to > 99% ee was due to the close proximity of VO units in the MOF pores, leading to cooperative activation of the substrates. In another example, copper coordinated Schiff base ligands were employed for Friedel–Crafts and Henry reactions.[32] The framework also showed increased activity in comparison to homogeneous catalysis, due to the cooperative effects of the bimetallic catalytic centres.

Architectural stabilisation of the catalyst

The true potential of MOFs, however, can only be reached by exploiting the entirety of the framework. The groups of Toste and Yaghi followed this multidisciplinary approach to improve the stability of a homogeneous gold(III) catalyst.[43] The homogeneous catalyst IprAu(III)(biphenyl)X (where Ipr is [1,3-bis(2,6-diisopropylphenyl)] and X^- is a non-coordinating counteranion) is known to undergo an unimolecular decomposition *via* reductive elimination (Fig. 8). By confining the linear molecular geometry into a rigid framework, such as IRMOF-10 and bio-MOF-100, decomposition could be suppressed, and catalytic activity could be retained, whereas the homogeneous catalyst suffered from decomposition over time.

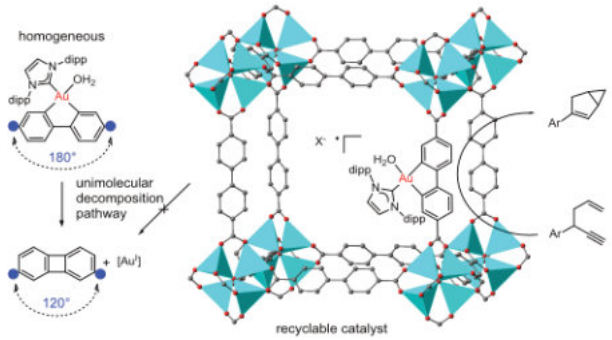


Fig. 8. **Architectural stabilisation of Au(III) catalyst in MOFs. The incorporation into the rigid framework hinders any geometrical transformations. This prevents unimolecular decomposition, observed for the homogeneous catalyst.**

In the same manner, monophosphine ligands were locked into a rigid framework, minimising disproportionation and ligand exchange reactions at the metal centres (Rh, Ir) which would lead to a decrease in catalytic performance.[44] The recyclable catalysts showed superior performance in the hydrosilylation of ketones and alkenes, the hydrogenation of alkenes and the C–H borylation of arenes compared to the homogeneous controls.

Outlook

The next step is to take advantage of the tunable pore environment of MOFs to rationally design the catalytic environment. A proof of concept for an organocatalyst incorporated into a MOF was reported recently by our group.[45] The MOF is built from three different linkers, each located at distinct positions in the framework (Fig. 9).

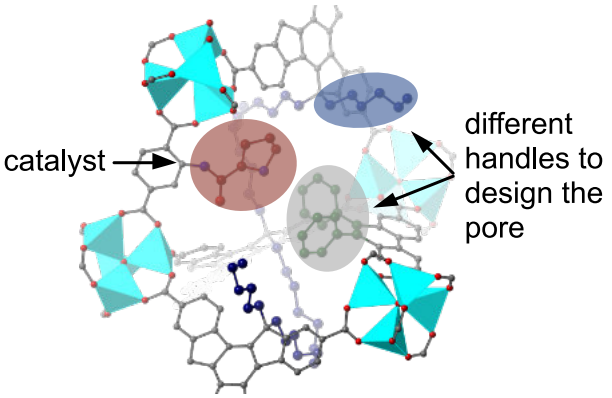


Fig. 9. **Possibilities to influence the pore environment in MUF-77**

This ligand arrangement offers three independent handles to design the pore environment around the catalyst. Thus, the activity and selectivity of the organocatalyst could be improved by carefully adjusting the other two linkers. Adapting this strategy for transition metal catalysts would allow control of the catalytic environment to a level beyond that which can be achieved by the ligand design of the homogeneous complexes. Improving selectivity for homogeneous transition metal catalysts is often limited to ligand design. However, the influence of the ligands is often limited to their coordination site. Shifting the reactions into a MOF pore would allow the catalytic environment to be shaped in all three dimensions, like a catalytic pocket in enzymes.

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A report on the 3rd International Conference on Metal Organic Frameworks and Porous Polymers (EuroMOF 2019)

Joel Cornelio

School of Fundamental Sciences, Massey University, Palmerston North

Email: j.cornelio@massey.ac.nz

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EuroMOF is series of biennial conferences focussed on MOF (metal-organic framework) chemistry held in Europe. The previous iterations of these conferences were held at Potsdam, Germany (2015) and Delft, The Netherlands (2017). EuroMOF 2019 was held 27-30 October at the Maison de la Chimie, Paris, France. The conference had around 450 attendees including scientists, students, postdoctoral researchers and industry representatives from around the world.

Two plenary lectures were held on each of the four days of the conference, which were given by some of the most prominent researchers in the field of MOF chemistry. There were also talks by industry representatives on the commercialisation of MOFs. A dinner party was organised on the third day of the conference, which was held in the Musée des Arts Forains, Paris. This party had carnival games and carousel rides followed by a delicious five-course French meal.

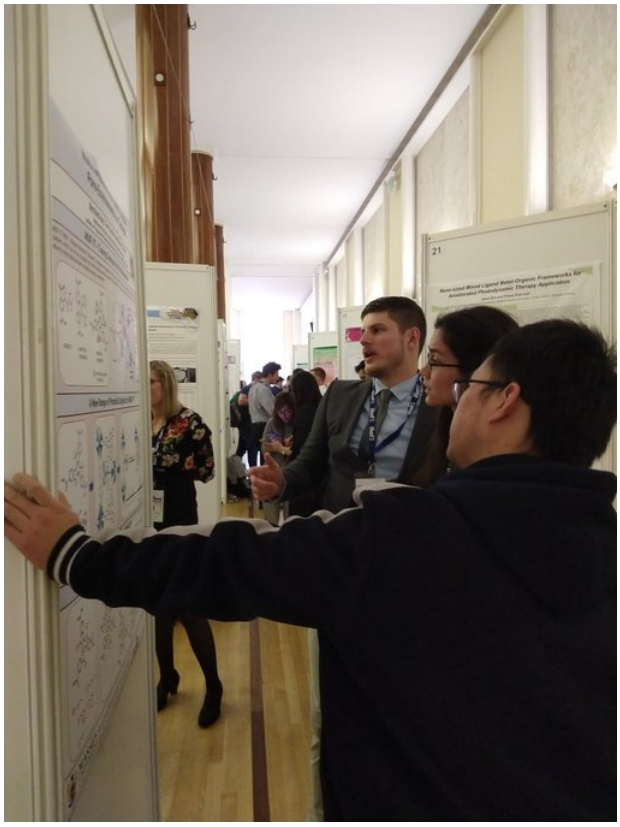
I had the opportunity to present my work as a 15-minute oral presentation on luminescent MOFs, which went well. I got a few questions which I could answer and many interesting discussions about our work here at Massey. Poster sessions were organised on the first two days, where a total of more than 250 posters were presented. One of them was from my colleague, Bernhard Auer, whose poster got a lot of attention as it dealt with using metalloligands for chiral catalysis.

My talk went well (Image credit: Bernhard Auer)

I visited some monuments in Paris. I have a bit of a fascination with death and hence the first site I visited was the Catacombs of Paris. These are underground ossuaries where the bones of more than 6 million people are kept. I visited many other places like the Eifel Tower (how typical!), Arc de Triomphe and Le Musée de l'Armée, but the Catacombs were by far my favourite.
After the conference, I visited Luxembourg, Belgium and Germany. I gave another talk in Leipzig University on multicomponent MOFs and discussed our collaborative work on some electron paramagnetic resonance (EPR) experiments. All in all, it was a wonderful trip.

The Catacombs of Paris - look at all of 'em bones

I wish to give my thanks to NZIC for funding my attendance at this conference. I would like to acknowledge additional funding from Massey University's Conference Presentation Grants and the School of Fundamental Sciences. I also want to thank my supervisor, Professor Shane Telfer, for this fruitful experience.



Bernhard Auer presenting his poster on tunable pore-environments for catalysis in multicomponent MOFs

Napoleon angry that his funding application was rejected, taken at Le Musée de l'Armée

A review of the impact of anthelmintic resistance on the New Zealand sheep industry: current scenario and potential solution

Arka Gupta,*[1] Preet Singh,[2] Catherine Whitby,[1] Bill Pomroy[2] and David RK Harding[1]

[1]School of Fundamental Sciences, Massey University, Palmerston North[2] School of Veterinary Sciences, Massey University, Palmerston North

Email: a.gupta@massey.ac.nz

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Introduction

Gastrointestinal nematode (GIN) infection (or stomach worm infection) represents a major threat to sheep production systems throughout the world.[1] GIN infection remains prevalent in the New Zealand sheep industry.[2] Infected lambs develop pathological changes in their gastrointestinal (GI) tract which result in a protein-losing gastroenteropathy. Most species live in the mucus layer of the GI where they ingest liquids.[3] Some nematodes such as *Haemonchus contortus* will also suck blood. Consequences range from poor feed conversion rates through to acute diarrhoea and death. In older sheep, infection also affects milk production.[4]

Internal parasites cost the sheep industry approximately NZ$300 million annually in lost production and drench use in New Zealand.[2] GIN infection usually involves multiple nematode species which largely affect the abomasum and upper small intestine in the host and is highly aggregated within the host population.[5] Each nematode will be producing a large number of eggs which pass into the faeces and, if environmental conditions are suitable, a proportion of these will successfully develop into infective larvae that are able to re-infect more sheep. Consequently, a susceptible host can propagate a cycle of the GIN infection affecting a huge number of sheep.[6] Common GIN species that infect sheep in New Zealand include *Haemonchus contortus*, *Teladorsagia circumcincta*, *Trichostrongylus colubriformis* and *Cooperia curticei* of the Trichostrongylidae family (Table 1).[7-9]

Table 1. Morphology, pre-patent periodand location of common GIN species of sheep in New Zealand. The pre-patent period is the time following infection through to the appearance of eggs in faeces.

	Morphology		Pre-patent period (days)	Location in the host
	Length (mm)	Characteristics		
H. contortus	♂ 10-20 ♀ 18-30	Appearance of a barber's pole.	18-21	Abomasum
T. circumcincta	♂ 7-8 ♀ 10-12	Small head and buccal cavity. Presence of a vulvar flap.	12-21	Abomasum
T. colubriformis	♂ 4-8 ♀ 5-9	Triangular tip.	15-23	Small intestine
C. curticei	♂ 4-5 ♀ 5-6	Transverse cuticle. Small cephalic vesicle and watch-spring-like posture.	14-15	Small intestine

Nematode life cycle in sheep

All GIN species have a six phase life cycle which can be divided into three stages: host, dung and pasture stages, all of which are linked (Fig. 1).[10] In the host stage, sexually dimorphic nematode adults are present in the digestive tract of the host where the female nematode produces eggs containing an embryo which are passed into the faeces.[6] The embryo develops and is followed by three larval stages, L1 to L3.[10] The first lar-

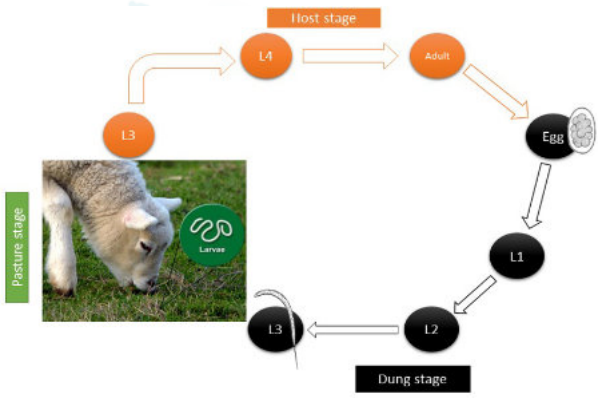
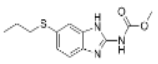
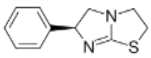
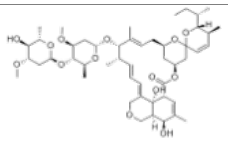
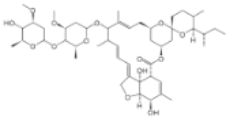
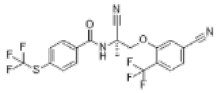
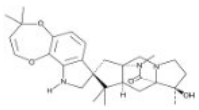


Fig. 1. Gastrointestinal nematode (GIN) life cycle

val stage, L1 develops in the egg and hatches, L1 feeds on bacteria in the faeces, and moults to the second larval stage, L2.[10] L2 then feeds and grows as before. Moulting follows but is incomplete so that the third larval stage, L3 retains the L2 cuticle as a sheath around it.[6] The time from egg to L3 is about 4-10 days.[10] It is usually slower in colder weather and faster in warmer conditions within the general range of 10-30°C, with the optimum temperature range being 20-25°C. The sheath provided by the old cuticle of the L2 surrounding the L3 provides some protection from harsh environmental conditions.[11] The ensheathed L3 is the infective stage and wriggles randomly on the pasture. L3 is ingested by the host whilst grazing and GIN infection of the host occurs. In the host stage, L3 exsheathes by discarding the L2 cuticle and moults to the L4 stage by entering the mucosal gland crypts. Exsheathment is triggered by chemical stimuli provided by the digestive tract environment. L4 feeds and moults to the immature adult by emerging on to the surface of the mucosa.[10] The immature adult feeds and grows to sexual maturity and the cycle is completed.

Table 2. Anthelmintic classes, drugs used, chemical structure and mode of operation

Anthelmintic class	Drug used	Structure of drug	Mode of operation
BZ Benzimidazole	Albendazole		Prevents microtubule formations by binding to β-tubulin to prevent polymerisation but does not affect normal breakdown of microtubules resulting in collapse of the microtubule cytoskeleton within cells. Starvation achieved through inhibition of glucose uptake and protein secretion.[15, 16]
LV Imidazothiazole	Levamisole		Cholinergic agonist which causes spastic paralysis of the parasite. Eradicated by gut peristalsis which leads to rapid removal of the worms present.[17]
ML Macrocyclic lactone	Abamectin		Causes flaccid paralysis by creating an opening of glutamate-gated chloride channels which leads to an increased Cl^- ion influx into nerve cells.[18]
	Ivermectin		
AAD Amino-acetonitrile derivative	Monepantel		Cholinergic agonist which causes spastic paralysis of the parasite. Eradicated by gut peristalsis which leads to rapid removal of the worms.[13]
SI Spiroindole + Abamectin	Derquantel		Cholinergic antagonist which causes hypercontraction of the body wall leading to paralysis.[13]

Anthelmintics

Anthelmintics are drugs that can kill parasitic worms (helminths), including GIN species. Some are able to kill a wide range of different helminths while some target a much narrower range. They act in various ways within the host by interfering in different biochemical pathways, killing the worms on contact, or by affecting the nervous system of the parasite, effectively stunning them and resulting in muscle paralysis, or by altering the permeability of their plasma membranes without doing any significant damage to the host. The paralysed or dead worms pass out of the host in the faeces.

Attempts at management and eradication of GIN species involve treatment with broad-spectrum anthelmintics belonging to three main chemical classes: (1) benzimidazole [BZ], (2) imidazothazoles/tetrahydropyrimidines [LV] and (3) macrocyclic lactones [ML].[12] Two more classes of anthelmintics have been released in the last decade but as yet are only represented by single products commercially. These are amino-acetonitrile derivative [AAD][13] and a combination of spiroindole and ML [SI].[14] A feature of all anthelmintics has been the very slow rate of development of new classes or new members of existing classes in recent years, largely due to the expense involved. Current anthelmintics are detailed in Table 2.

Anthelmintic resistance

Modern anthelmintics are expected to achieve in excess of 95% efficacy against GIN species with most achieving > 99% efficacy against most species of GIN. The reliance on anthelmintics for controlling nematodes, frequently with excessive use of these chemicals, has led to the widespread problem of anthelmintic resistance. This has become a global phenomenon, especially in ruminant livestock.[19]

Anthelmintic resistance is generally accepted to exist when efficacy has declined to < 95%. At this level, the drug does not kill enough GIN to avoid subclinical problems of parasitism. Anthelmintic resistance is now so widespread that resistance to all classes of broad-spectrum treatments has reached a serious level in New Zealand for the important GIN species found in sheep.[12] A parasite that is resistant to one drug from an anthelmintic class will be resistant to other products from the same class.[20] Additionally, multi-drug resistance to several anthelmintics from different classes has been well documented both in New Zealand and elsewhere.

Anthelmintic resistance costs an estimated additional NZ$20 million per year and is predicted to rise to NZ$60 million per year by 2022 for the New Zealand sheep industry.[2] Different mechanisms of resistance apply to different anthelmintic groups but in general all involve gene mutation causing a gain-of-function, which commonly leads to a more rapid removal of the drug or an inability to bind to its receptor and thus it can no longer produce an effective response.[21,22] However, the actual chemistry is still unclear for many, if not all, drugs.[6] The common GIN species in New Zealand sheep (Table 2) all have reported resistance to all broad-spectrum anthelmintic classes.[23]

A combination strategy and the current picture

One effective way to tackle resistance is to treat a ruminant simultaneously with a combination of two drugs from different anthelmintic classes. When administered together, even partial efficacy of individual anthelmintics from different classes can induce a more effective treatment.[24] This effect is most pronounced when the level of resistance to a particular anthelmintic class is low. For example, monepantel (AAD) was first introduced in 2009[25] and resistance to this drug was first reported in 2013.[26] Currently, a combination of monepantel (AAD) and abamectin (ML) is the most effective followed by a combination of derquantel (SI) and abamectin.[2]

It has been found that it takes about 15-20 years to develop widespread resistance to a class of drug, but once resistance alleles accrue in the GIN population, this combination strategy will not work.[20] In 2016, reduced efficacy was reported of the most recently released anthelmintic being the combination of derquantel and abamectin.[23] It is highly probable that the current combination of monepantel and abamectin will not be as efficient in coming years. Hence, there is an urgent need to introduce a new class of anthelmintic to the market.

Bioactive plant extracts as anthelmintics

The use of various bioactive plants has been found to have some anthelmintic effects against parasites at various stages of their life cycle.[27] The bioactive properties are perceived to be caused by plant secondary metabolites which are bioactive compounds with broad activity toward human cells, bacteria, viruses and parasites.[28] Recent results suggest that bioactive plants might be promising both as a direct and integrated option in GIN control. Bioactive substances from tannin-rich plants have attracted significant research attention for their effect on GIN management in ruminants. They have direct antiparasitic activity, as well as a direct or indirect effect on increasing the ability of a host to resist infection.[29] They may be effective on their own, but more likely will be useful to combine with existing anthelmintics to maintain the efficacy of those existing anthelmintics.

Tannins in the management of GIN infection

Tannins are secondary plant polyphenols with a high affinity for proteins and polysaccharides.[30] They can be classified as either hydrolysable or condensed tannins (CT) depending on their chemical structure.[31, 32] Hydrolysable tannins are gallic or ellagic esters of sugars and are degraded into gallic acid and readily absorbed in the digestive tract upon being consumed by ruminants.[33] Condensed tannins are polyphenols of higher molecular weight and upon consumption are metabolised to mainly cyanidin or delphinidin and hence have been classified as procyanidins (PC) or prodelphinidins (PD).[33] Condensed tannins are not as readily absorbed in the digestive tract. They form solu-

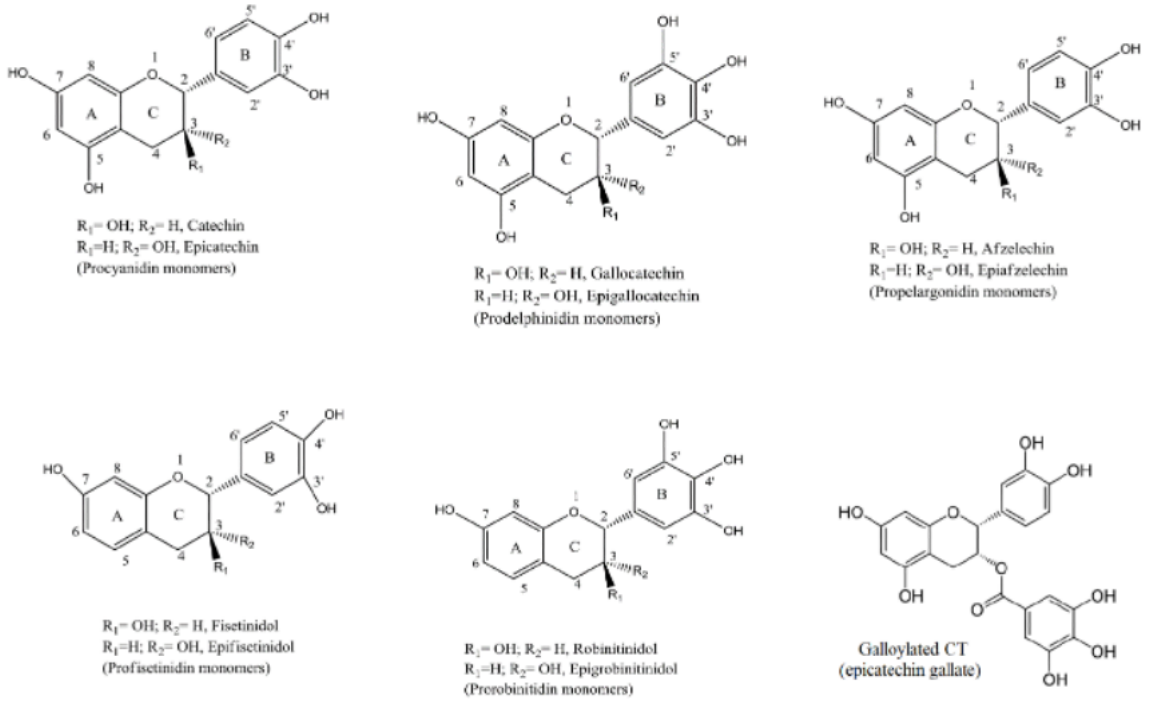


Fig. 2. The monomeric units of different types of CT

ble and insoluble complexes with macromolecules, such as proteins, fibre and starch, with a particular affinity for protein.[31] Currently, a great deal of research is going on concerning the beneficial effect of tannin-rich plants on livestock production and GIN management.[29]

Condensed tannins (CT)

It has been found that forages rich in CT grown under temperate conditions, e.g. sainfoin, chicory and big trefoil, can reduce worm burdens in small ruminants.[34] Direct interaction of CT with surfaces of nematode larvae is well established. CT can disrupt the life cycle and other physiological functions of GIN species *in vivo* by slowing the hatching process as well as preventing the hatched larvae from attaining full development to infective larvae.[35,36] This may reduce or prevent pasture contamination with infective larvae. *In vitro* studies have shown that CT can destroy the cuticle and kill L3 stage larvae which is the infective stage of the larvae.[37] The purified CT extracts also have anticoccidial activity as they have the ability to significantly decrease the sporulation of the parasite oocysts.[38]

CT are polymerised units of flavan-3-ol. CT-rich temperate forages have a relative molecular mass of 2,000-4,000 with ten to twelve units condensed together.[39] CT have complex chemical structures. The main difference is in the hydroxylation of the B-ring of the flavan-3-ol monomer unit. The stereochemistry of the heterocyclic C-rings can take the form 2,3-cis or 2,3-trans which determines how the monomeric units are linked with each other by either C4/C8 or C4/C6 interflavanoid linkages.[40] These structural differences result in a near infinite variety of chemical structures. CT-rich plants can have either a specific type of CT or be mixed.[29] CT differ greatly from one plant to another in their chemical structures and biological activity.[29] The different monomeric structures of CT are illustrated in Fig. 2. Types of CT and their sources are shown in Table 3.

Biological activity of CT

The biological activity of CT depends on the mean degree of polymerisation, polydispersity, cis/trans ratio and PC:PD ratio.[50] The characteristics of CT are defined by their strong affinity for proteins. It has been found that CT with higher proportions of PD reacts more strongly with proteins because of higher -OH contents in the heterocyclic B-ring.[51] CT affect GIN species by protecting dietary proteins from microbial degradation during their passage through the rumen.[52] Protein and CT interact during harvesting, grinding, extraction, mastication and digestion through H-bonding and hydrophobic interactions.[53] CT are known to dissociate from proteins in the abomasum (pH 3.5) and in the small intestine (pH 7.0).[54] This removes the cycle of rumen microbe fermentation and makes the ingested

Table 3. Types of CT and their plant source

Type of CT	Plant Source
Pure Procyanidin (PC)	Pine bark extract (*Pinus radiata*)[41]
	Willow leaves (*Salix spp.*)[41]
	Sorghum Seeds (*Sorghum bicolor*)[42]
	Apple (*Malus Pumilla*)
Pure Prodelphinidin (PD)	White Clover (*Trifolium ripen L.*)[43]
PC+PD; mixed CT	Birdsfoot trefoil (*Lotus coniculatus*)[43]
	Big trefoil (*Lotus pedunculatus*)[43]
	Sainfoin (*Onbrychis vicifoliae*)[44]
	Quebracho Colorado (*Schinosis sp.*)[44]
	Sulla (*Hedysarum coronarium*)[45]
A-Type CT	Dock (*Rumex obtussifolius*)[46]
	Cinnamon (*Cinnamomum verum*)[47]
	Peanut skins[46]
	Cranberry (*Vaccinium oxycoccos*)[48]
Gallolylated CT	Green tea[35]
	Grapes[49]
	Red wine[49]

protein/amino acids directly available to the ruminant which is far more efficient from a nutritional perspective. This in turn enhances the ruminant's resistance to GIN. The affinity of proteins to CT is influenced by high molecular weight and the open and flexible tertiary structures of the protein.[55] CT are not absorbed in the gastrointestinal tract of ruminants but instead remain intact and are eliminated with faecal matter.[56]

Anthelmintic efficiency of quebracho extract

Quebracho extract (originating from the bark of the tree *Schinopsis balansae*) is a commercially available rich source of polyphenols. This brown coloured fine powder contains 73% of CT, 19% of simple phenolics and 8% water.[57] Quebracho extract has been used in previous studies to observe the feeding effect on parasitised sheep.[57,58] These studies on the short and long-term feeding effects of quebracho extract on sheep infected with *T. colubriformis* have shown reduced worm burdens and fecundity. The direct anthelmintic effect of CT from quebracho extract has been observed through a reduction in the faecal egg count (FEC), which assesses the number of worm eggs passed per gram of faeces, over a 10-week experimental period.[57,58]

Limitations of CT

The beneficial effects of CT are due to their protein binding ability, as they prevent the degradation of dietary proteins in the rumen and increase the protein availability in the lower digestive tract. However, ruminants can only tolerate a low concentration of CT in their diet above which toxic effects occur. A number of detrimental effects associated with the consumption of a high concentration of CT have been reported.[29] These include growth inhibition in young lambs and reduction in food intake. They can also interfere with the morphology and proteolytic activity of ruminal microbes.[29] Hence, this protein-binding feature of CT has some adverse effects on livestock production.

Alkaloids in nematode management

Many naturally occurring alkaloids such as β-carboline alkaloids, matrine alkaloids, harmine alkaloids and pepper alkaloids are extracted from plant sources and possess remarkable biochemical effects and pharmacological properties such as antitumor, antithrombotic, antiviral and antiparasitic activity.[59] The existence of at least some nematocidal activity of naturally occurring alkaloids has been reported.[60] Several examples include steroidal alkaloids with *Panagrellus redivivus*[61], matrine and harmine alkaloid with *Bursaphelenchus* xylophilus[62], β-carboline alkaloids with *Spodoptera exigua* and *Meloidogyne* incognita[63], brucine and strychnine alkaloid with *Radopholus similis*[64] and pepper alkaloids with *Meloidogyne incognita.*[65] These alkaloids have been shown to inhibit the growth of nematode eggs and motility in the larval development assay. Thus, naturally occurring alkaloids have substantial potential for controlling nematodes by interrupting their life cycle and could also be effective against the infective stage.

Designing a new anthelmintic: potential route and formulations

As previously discussed, tannins, alkaloids, and other secondary plant metabolites have been found to possess significant anthelmintic properties. In our current research, fractionations and purification studies of bioactive plants and anthelmintic properties are being evaluated against L3 GIN larvae *in vitro* to evaluate their efficacy. The aim of this research is to find a novel anthelmintic formulation derived from bioactive plant extracts. Formulations will be made with different secondary metabolites from two or more bioactive plants

and the anthelmintic effect will be observed both *in vitro* and *in vivo*.

It is most likely that any plant-derived anthelmintic will not be fully effective in its own right but will have a useful function when combined with existing anthelmintics to enhance their efficacy, especially as anthelmintic resistance to these existing anthelmintics increases. If an effective combination can be obtained it may prove useful to delay the onset of anthelmintic resistance to the original drug in the first instance.

Another strategy that will be implemented is to investigate the effect of the formulations from plants on a GIN species with known anthelmintic resistance to assess synergistic effects, i.e. whether or not the natural material improves the efficacy of the less effective synthetic anthelmintic (e.g. ivermectin) to achieve an improved *in vivo* effect. *In vitro* anthelmintic studies of different plant extracts are currently in progress.

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Sentiment analysis: a lens for viewing chemistry narratives

Peter Hodder

School of Government, Victoria University of Wellington and HodderBalog Social and Scientific Research, Wellington

Email: peter.hodder@vuw.ac.nz; peterh@hodderbalog.co.nz

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Introduction

Decades ago, when I was a science student at Victoria University of Wellington, I – along with my brother, Michael, then a history student – were invited to dinner at the home of one of the History Department's relatively new members of staff:[1] Dorothy Crozier.[2] After dinner, Dorothy produced a book from her extensive home library, and gave it to me to read over the next week. The book was *The Double Helix*,[3] the then recently published reflections of one of the co-discoverers of the structure of DNA – James Watson (Fig. 1). I can't recall what was expected of me: whether I was supposed to critique it, review it, or learn something from it. But I certainly read it.

To get to Dorothy's home we walked up the western side of Kelburn Parade, at that time still occupied by a collection of maturing, large, mainly two-storeyed houses, several of which were occupied by a range of teaching departments and administrative offices of the University. I didn't realise it at the time, but one of the few single-storeyed buildings on the street also had a link with the double helix story: 30 Kelburn Parade was for a short time the boyhood home of Maurice Wilkins, one of the other co-discoverers of the structure of DNA (Fig. 2).

A plaque at the planter box outside the north end of the Murphy building records that Maurice Wilkins "lived here at 30 Kelburn Parade as a boy".[7] He and his family moved to the United Kingdom when he was six years old, but he recalled:

Fig. 1. Starting point of this paper. Left: Dorothy Crozier (with corsage, at far right of picture) at the History Department, University of Melbourne on VE Day, 1945 (Image: University of Melbourne Archives, reference number 1975.0033.00003, used with permission). Right: James Watson, author of The Double Helix, at the ceremony for Nobel laureates in 1962 (Image: a portion of Fig. 6).

"I have many vivid memories of our elegant one-storey house with its verandah and white palings on pretty, respectable Kelburn Parade... and 'Skerries' on our front gate [8]reminded my parents of where they first met in the Irish sun and air... Just across the way the large buildings of Victoria College [Fig. 2] reassured them [my parents] by expressing the value of education and learning."[9]

Fig. 2. Upper: Looking south up Kelburn Parade, early 1900s. The house occupied by the Wilkins family was the first to be built on the street, and predated Victoria College, which was built opposite it, beyond the left of photograph. The sign in the foreground advertises other sections for sale (Image: Wellington City Council Archives, 00138-11461). Lower: Looking west from Glasgow Street (foreground) towards Victoria University on the far side of Kelburn Parade (towards top of photograph), in 1958. The building at top left is the Robert Stout administration building (opened in1939),[4] while to its right – south – is the west wing of the Hunter Building (opened in 1910,[5] as an extension to the original 1906 structure, and for a time occupied by chemistry).[6] The Wilkins' home at 30 Kelburn Parade is the single-storey building almost opposite the tree-flanked entrance to the University (Image: Alexander Turnbull Library, Reference: ATL WA-47256-F).

Fig. 2 (continued). Looking east from Victoria University to former residences on the west side of Kelburn Parade in 1976, prior to their removal or demolition for the construction of the Murphy building. No. 30 is at the extreme right of the photograph. By the mid-1970s, the front of the building had been substantially modified and its front garden and picket fence replaced by a car-park (Image by Charles Fearnley, Wellington City Recollect, Reference 50003-2309).

The 'elegance' recalled by Maurice Wilkins is evident from the range and inferred quality of the chattels offered for sale as the family prepared to leave for England:

"A.E. Carver and Co. have been favoured with instructions from Dr. E.H. Wilkins, who is leaving for England to sell on the premises "high-class oak and rimu furniture, upright grand piano (Lipp and Son), a beautiful instrument, the entire contents of 8 well-furnished rooms. Also, English motor-car, 'Marlborough', 3-seater, with French engine, in perfect running order, well upholstered, does 30 miles to gallon."[10]

Built in the early years of the 20th century,[11] the "commodious 8-roomed residence and motor garage" was the first house built on Kelburn Parade, and was described when for sale in the late 1920s as:

"The solidly-built residence, containing 8 large rooms, sun porch, verandah, and usual offices, motor garage, etc., on land 41ft-6in x 104 ft... comprises large drawing room with alcove and double doors leading to a dining room 19ft x 17ft breakfast room, 4 bedrooms and maid's room, large kitchen, bathroom with porcelain bath and basin, scullery and washhouse. It is fully equipped with e.l., hot point, splendid hot water system, gas stove, and range. Most substantially constructed of hear timbers, and in excellent order throughout. Large concrete motor garage. Level section laid out in garden and lawns. ... It is a beautiful sunny spot, well sheltered from all prevailing winds."[12]

Once it was acquired by the University, the house at 30 Kelburn Parade was used for various administrative and academic purposes, including being the first language laboratory;[13] it was demolished in September 1979.[14]

The 'story' of the discovery of DNA

James Watson's book was controversial from the start. Objections from Maurice Wilkins, Francis Crick (a third co-discoverer) and other contemporaries led to pressure being applied to Harvard University to prevent its publication through Harvard University Press. However, the book was ultimately published – by Atheneum Press – in 1968, and has been controversial ever since. Much of the post-publication criticism centres on the book's portrayal of Rosalind Franklin (belatedly recognised as the fourth member of the group) as difficult to work with, and the inference that her work did not contribute significantly to the final discovery. In fact, her X-ray analysis was critical for the identification that DNA was of helical shape, as Watson himself concedes in the epilogue to his book.[15] Anne Sayre's 1974 analysis of events, written as part of her biography of Rosalind Franklin, admitted that Watson's "was a story worth telling and worth listening to", but observed that in the late 1960s very little had been written by scientists, "and even less by great scientists of great distinction, with the object of conveying to the laity either the nature of research or the attitudes toward the work of those who do it." Sayre asked rhetorically about Watson's "license" to write a "cheerfully uninhibited book", the object of which

"... was to deal not with the technical aspects of scientific research in particular or general, but with the way in which science was done which the author was careful to say was not necessarily representative. Written as a kind of memoir, frank and chatty and sometimes gossipy, it provided one man's view of the world of science and its inhabitants, and sometimes offered surprises."[16]

Maurice Wilkins was to later infer that Sayre's book was used by "activists to mount a campaign in Rosalind's name to improve the lot of women in science [which] was no doubt well-intentioned and indeed useful..."[17] Another biography of Rosalind Franklin published in 2002, observed that:

"Rosalind Franklin has become a feminist icon, the Sylvia Plath [18] of molecular biology, the woman whose gifts were sacrificed to the greater glory of the male. Yet this mythologizing, intended to be reparative, has done her no favours."[19]

While this later biography of Franklin concedes that *The Double Helix* is "a candid young-man's-eye view of one of sciences great discoveries [about which] Watson wrote what at twenty-three, he felt and saw happening",[20] it goes on to assert that Watson created 'Rosy' (the name commonly used by Watson in his book, instead of Rosalind, her real name) as a witch:

"A plausible hypothesis holds that the character was a rationalization of Watson's guilt – a creature so hostile and uncooperative that there was no alternative to taking what you need [in this case her X-ray photographs] by stealth."

In her efforts to 'construct' Rosalind, Maddox demonises Watson. In doing so, Maddox cannot resist taking a feminist point of view, writing:

"...the wicked Rosy is a variant of an older myth, 'She asked for it', that traces back to Eve: the woman is guiltier than the male. Unwittingly Nannie Griffith drew on this ancient lie when blaming young Rosalind for complaining that Colin [Rosalind's brother] had hit her with a cricket bat: 'Well dear, you shouldn't have been teasing him.'".[21]

Francis Crick's short pen-portrait of Rosalind has been interpreted as echoing the 'She asked for it' theme, by his suggestion that her "difficulties and failures were mainly of her own making":

"Underneath her brisk manner she was oversensitive and, ironically, too determined to be scientifically sound and to avoid shortcuts. She was rather too set on succeeding all by herself and rather too stubborn to accept advice easily from others when it ran counter to her own ideas."[22]

However, the details of the biographies of Rosalind Franklin are interpreted, it is clear that her time at

King's College (London) was not enjoyable either for her or Maurice Wilkins; or indeed for James Watson and Francis Crick, both of whom were at the Cavendish Laboratory at Cambridge. Despite this, Franklin's time at King's (1951-1953) was productive in terms of research outputs; these show an overall upward trend which started during her previous research appointment in Paris, and – apart from her having no publications in 1952 and 1954 – continued during her subsequent research appointment (1953-1958) at Birbeck College (London). There, her research productivity was probably reduced by her having a role as what would now be described as a team leader and certainly by the progression of her terminal illness.[23]

New interpretations of the DNA 'story'

A more ecological[24] than revolutionary[25] approach to interpreting scientific activities suggests that personalised accounts of scientific discoveries could be likened to a fictional quest.[26] As an example, the story of the development of the chemist's periodic table of the elements has been analysed from this perspective.[27] Fig. 3 shows that quests typically comprise five stages, for which a possible trend of sentiment as the story proceeds is also shown.

Other, more complicated, patterns of sentiment variation during the course of a novel[28] can be aggregated to make a simpler plot;[29] Fig. 4 is a schematic version of such a plot for the stages of 'Voyage and Return' and 'Comedy' stories.[30]

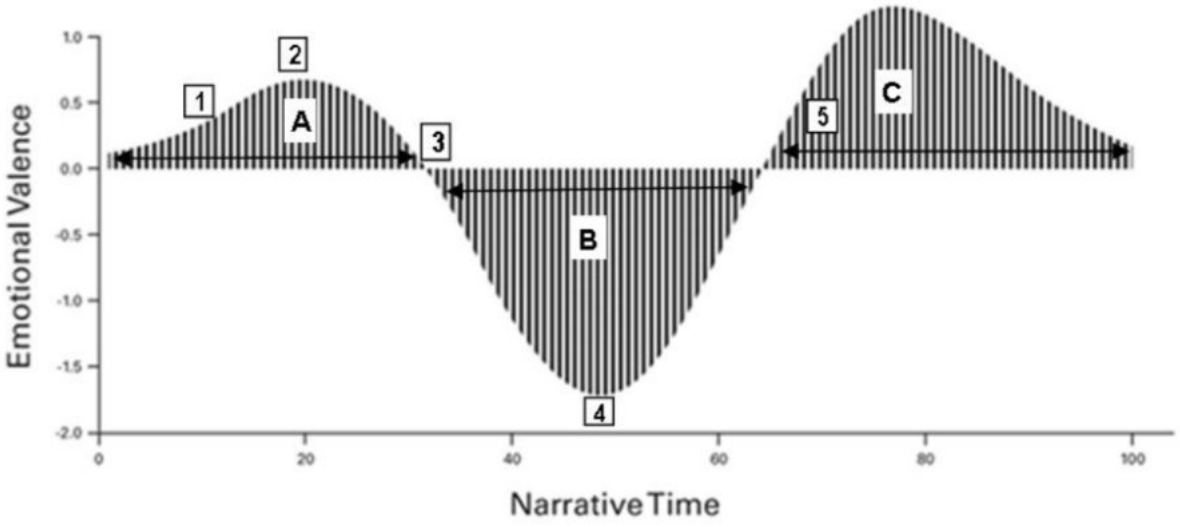
Mood or sentiment analysis – whether undertaken manually or by software – requires judgements on whether words evoke positive (e.g., "successful", "excited") or negative (e.g., "embarrassed", "angry") sentiments.[31] This simple approach of counting the frequency of such words is used here to determine the variation in mood during Watson's account of the double helix structure of DNA, and the portion of Wilkins' autobiography concerned with the same period of time. In each book, for each chapter or section the number of positive (N_p) and negative sentiments (N_n) can be combined into a sentiment score, $(N_p\text{-}N_n)/(N_p+N_n)$. This variation is shown in Fig. 5 as the story progresses. Although there is some similarity between the plots, the details differ for each author: the plot for Wilkins resembling a fictional 'comedy' (Fig. 4), while that for Watson has more of the complexity of a fictional 'quest' (Fig. 3).

That there are differences between the Watson and Wilkins plots in Fig. 5 is hardly surprising. The two men were at different stages of their lives and careers during the discovery period (Watson, born in 1928, was 25 years old by 1953; Wilkins, 1916-2004, was 37 years old by 1953; see Fig. 6), they also had different personalities, and their recollections may well have been affected by the elapsed time: Watson recalling the events of *ca.* 1953 some fifteen years later, and Wilkins some fifty years later.

Type of plot	Stages of the plot				
The Quest	1, The Call: recognition of need for journey	2, Journey across hostile terrain with companions and helpers, albeit with monsters and temptations to overcome	3, Success by 'arrival', but frustrations remain	4, The final ordeals – a last series of tests	5, After a 'last thrilling escape from death' the kingdom or life-transforming treasure is won
Sentiment	**Typical trend of sentiment through the story ➔**				
Positive					
Neutral					
Negative					

Fig. 3. Typical variation of mood with stages in a fictional quest

As the previous paragraphs describe, since the discovery of the structure of DNA, the criticism of Watson, Wilkins, and Crick has been relentless, asserting that their attitude to and treatment of Franklin was unprofessional. Somewhat lost in the 'chatter' has been the reluctant recognition of critics that Watson's account was, by his own admission, 'personal'; and that Wilkins' own reflections were



Voyage and Return	1 Anticipation and 'fall' into another world	2 Initial fascination, whose unfamiliarity may exhilarate	3 Frustration stage, with intruding shadow	4 Nightmare: a shadow dominates and threatens survival	5 Thrilling escape and return
Comedy	A, A 'little world' in which people are confused, frustrated and shut off from each other	B Worsening confusion and darkness; a 'nightmarish tangle'	C Previously unrecognized things come to light, changing perceptions and dispersing shadows: the 'little world' becomes happy		

Fig. 4. Stages in 'voyage and return' and 'comedy' fictional plots, overlain on a plot of aggregated compilation of 'emotional valence' (i.e., mood or sentiment) as a function of 'narrative time'

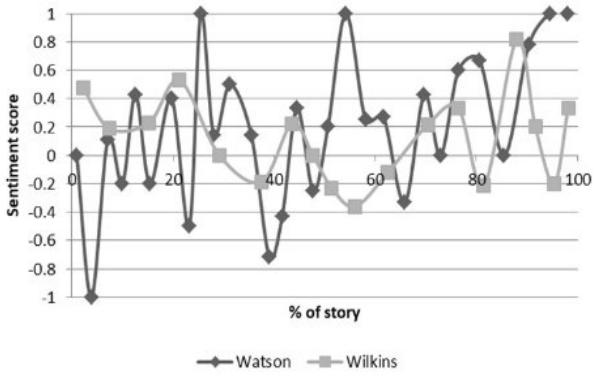


Fig. 5. Sentiment analysis as determined from specific text compiled from Watson's The Double Helix and a selection of chapters from Wilkins' autobiography. For each chapter of Watson's book and each section of Chapters 5 through 8 of Wilkins' autobiography the number of statements of positive and negative sentiment (N_p, N_n, respectively) are noted and a 'sentiment score' calculated, being $S = (N_p - N_n)/(N_p + N_n)$, where $-1 \leq S \leq 1$.

Maurice Wilkins	Max Perutz	**Francis Crick**	John Steinbeck	**James Watson**	John Kendrew

Fig. 6. The classic "winner takes it all" photograph: Nobel laureates in Stockholm in 1962; the names of those concerned with the discovery of the helical structure of DNA are in bold. That Rosalind Franklin was not included among the laureates has been of continuing contention (Image: Svenskt Pressfoto. Courtesy of the James D. Watson Collection, Cold Spring Harbor Laboratory Archives, used with permission).

published in an autobiography. The results of a form of sentiment analysis in this article confirms that the scientists involved differed in their recollections of the same events, in effect, each scientist was trying "to make sense of all information that they perceive, and that each individual therefore, "construct[ed]" their own meaning from that information",[32] in the same way that a poet might portray the process of scientific discovery (see *Box*). This, of course, runs counter to the common portrayal of mid-twentieth century scientists as impartial and non-emotive (Fig. 7).[33]

The results of computerised sentiment analysis[34] of excerpts from the reminiscences of events by the Noble laureates (i.e., Watson, Crick and Wilkins)[35] and in later commentaries by others (e.g., Sayre and

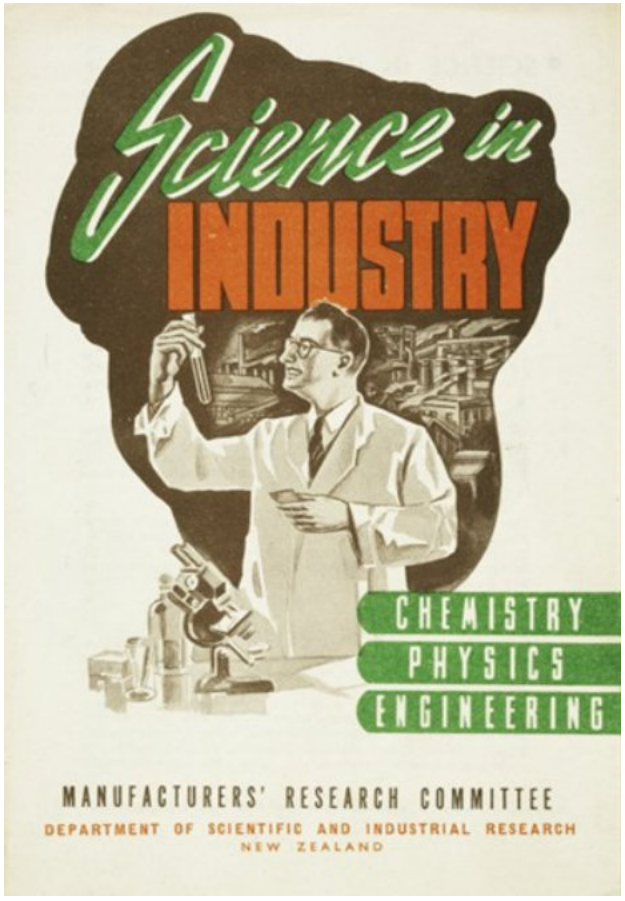


Fig. 7. An enduring 20th century image of science: the serious white-coated male scientist, as shown on the cover of a brochure 'Science in Industry – Chemistry, Physics, Engineering for the Manufacturers' Research Committee' (Image: Brochure cover. 1946-1950? Alexander Turnbull Library, Eph-A-SCIENCE-1948-01).

Maddox)[36] are very different (Fig. 8): Watson and Wilkins being positive, Crick, negative; Sayre, positive – despite her deprecating stance towards Watson; and Maddox, negative.

It has been suggested that *The Double Helix* "celebrates contingency and chance and the unscientific qualities of pride, secrecy, chauvinism and low cunning. It is raw, rash and unputdownable. In taking an impossibly complex subject and rendering an account for the ordinary reader, it has inspired a generation of accessible science writing ..."[37] Watson was unlikely to have seen this potential role for his book, and the low value of product sentiment score (Fig. 9) suggests it was not written with its being an acclaimed book in mind. By contrast, Wilkins' autobiography has a high product sentiment score, suggesting its writing was a deliberate intention to redress the opprobrium of the feminist critics that was directed at Watson's book specifically and the project participants more generally.

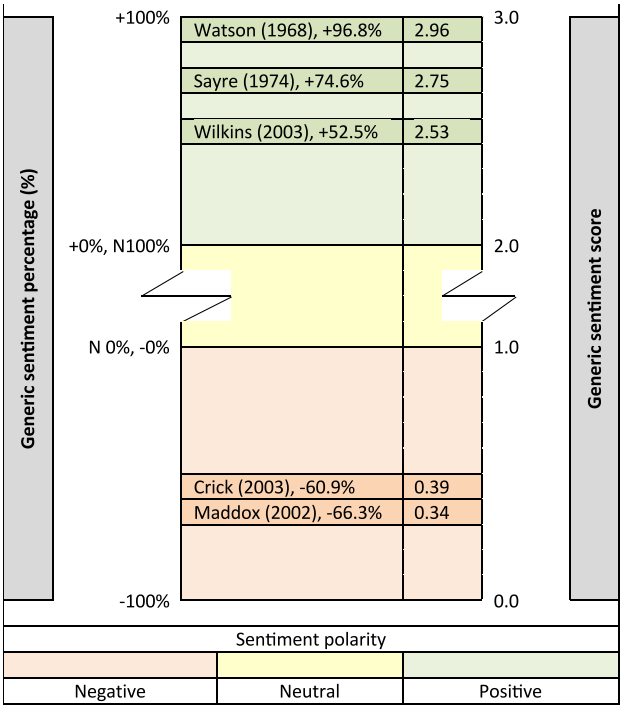


Fig. 8. Results of generic sentiment analysis for excerpts of reminiscences and commentaries referred to in the text. The polarity of generic sentiment can be positive, neutral or negative; the diagram also shows the relationship between sentiment percentages (-, N, +) and sentiment scores, ranging from 0-1.0, 1.01-2.0; 2.01—3.0, respectively.

Particularly in respect of the contribution of Rosalind Franklin to the DNA story, the discussion of the personalities, their genders and their roles in the elucidation of the structure of DNA was inevitably influenced by the feminist movement from the 1970s.[38] During those years, generic sentiments become more negative, possibly reflecting concerns

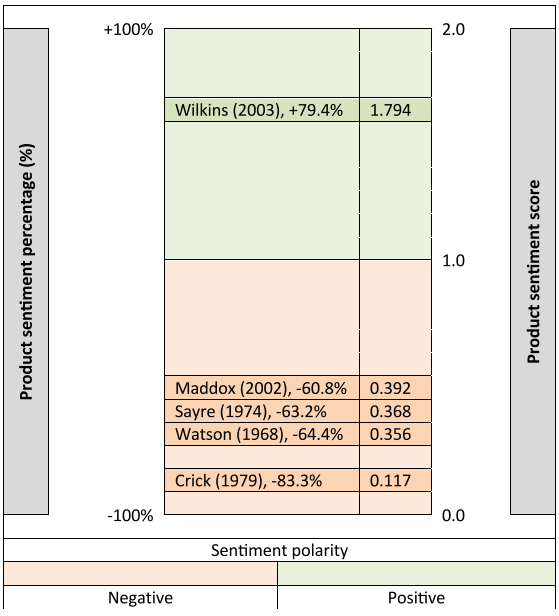


Fig. 9. Results of product sentiment analysis for excerpts of reminiscences and commentaries referred to in the text. The polarity of product sentiment can be either positive or negative; the diagram also shows the relationship between sentiment percentages (-. +) and sentiment scores, ranging from 0-1.0, and 1.01-2.0, respectively.

about ethical practices in scientific and medical research.[39] The subsequent more positive sentiments[40] (see Fig. 10) may be consistent with a changing scientific culture in which more women are encouraged to enter scientific occupations,[41] and are attaining higher educational qualifications and senior roles in scientific research and its management.[42]

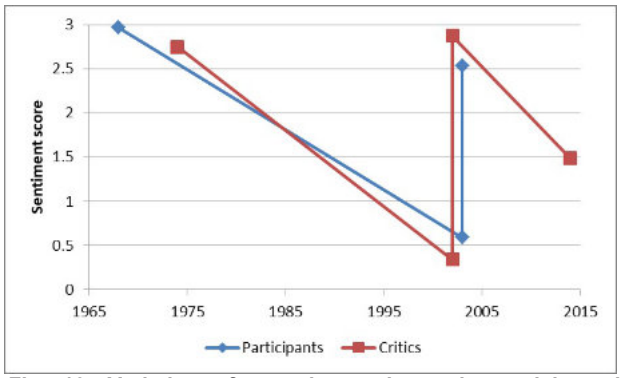


Fig. 10. Variation of generic sentiment in participants' reminiscences and critics' commentaries on the story of the structure of DNA, 1968-2014

The DNA 'story' in verse

Of a commissioned poem honouring Maurice Wilkins (see *Box*), its author, Chris Orsman commented:

"The poem was commissioned by the Royal Society of New Zealand to commemorate the achievement of Maurice Wilkins, New Zealand-born pioneer of DNA discovery and 1962 Nobel Laureate. It was read at King's College, London, in December 2002, at a ceremony to mark the unveiling of an official portrait of Wilkins. Emily Perkins, expatriate novelist and short-story writer, read the poem on behalf of the author.

"The poem itself is an amalgam of biographical and scientific detail, beginning with a contemplation of a vanished birthplace and moving out into specific detail of Maurice Wilkins' scientific field (x-ray crystallography) and the extraordinary blue-print of the DNA molecule that he discovered. The poem finishes with a play of imagery around the original x-ray plate itself." [43]

The results of sentiment analysis of each these three sections are shown in Table 1A. The opening section – Orsman's contemplation of Wilkins' 'vanished birthplace' – has a positive sentiment, the second section – Orsman's perceptions of Wilkins' 'scientific field' and his discovery of the 'extraordinary blueprint of the DNA molecule' – has a negative sentiment, while Orsman's final section which includes his 'play of imagery' related to the X-ray plate is of neutral sentiment. While the overall sentiment of the poem is positive, the 'shape' of the sentiment trend for Orsman's poem deduced from Table 1A is reminiscent of the 'comedy' plot of Fig. 4. In the absence of the poet's comments, the poem could have been analysed in terms of each verse's sentiment. This gives a very different distribution of sentiment as the poem progresses (Table 1B), attesting to the preference for adopting any subdivision of chapters, sections, etc., to be as provided by the author of the work, as was done in the construction of Fig. 6.

Positive generic sentiment percentage (sentiment score above 2.0; see Fig. 9) could be interpreted as potentially "winning of hearts and minds". However, this is not the only type of sentiment: there is also product sentiment, for which a positive product sentiment could be considered to have "commodification potential".[44] With that in mind, what does sentiment analysis of the scientific papers that revealed the discovery to other scientists tell us?

Table 1. Generic sentiment analysis of Chris Orsman's poem – Making waves for Maurice Wilkins*

A	**Orsman's progression of poem ➔**					
Sentiment polarity	***Wilkins' 'vanished birthplace' and 'light diffracted…'‡***		***Wilkins' 'scientific field' and 'blueprint of DNA molecule'***		***Orsman's own 'play of imagery'***	
	Generic sentiment %	*Sentiment score†*	*Generic sentiment %*	*Sentiment score*	*Generic sentiment %*	*Sentiment score*
Positive	+87.7%	2.877				
Neutral						
Negative			-68.3%	0.317	-81.9%	0.181

B	**Progression of poem by verse ➔**											
Sentiment polarity	***Verse 1¶***		***Verse 2***		***Verse 3***		***Verse 4***		***Verse 5***		***Verse 6***	
	%	*score*	*%*	*score*	*%*	*score*	*%*	*score*	*%*	*score*	*%*	*score*
Positive							63.3	2.63				
Neutral					N61.7	1.62						
Negative	-71.0	0.29	-44.0	0.56					-67.5	0.33	-60.0	0.40

* The generic sentiment score of the whole poem (2.873) is included in Fig. 10.
† The sentiment scores in this table are determined from positive and negative values as in Fig. 9.
‡ Orsman's sections (separated by **): Wilkins' "vanished birthplace", "Light diffracted…new information"; Wilkins' 'scientific field' and 'blueprint of DNA molecule', "And now…Well done!"; Orsman's own 'play of imagery', "To an amateur…into place";
¶ Verses: 1, "Light diffracted…window pane"; 2, "Next up…information"; 3, "And now…history"; 4, "Acclimatised…*Well done!*"; 5, "To an amateur…elevations"; 6, "Those…into place".

Box: **Making Waves for Maurice Wilkins –** ***a poem by Chris Orsman***

Light diffracted on a bedroom wall
at 30 Kelburn Parade, making waves
through a cloth blind, circa 1920;
outside, pongas and cabbage trees
lie just within memory's range,
a pattern and a shadow.
The silence here is qualified
but it draws you out, four years old,
or five. The world's a single room
where fronds and wind tap a code
against the window pane.

Next up you're wild sprinting down
a helix of concrete steps
from the hills to the harbour.
Or you're leaning into gale
commensurate to your incline
and weight; the elements support you,
and the blustery horizon
is fresh with new information.
**
And now the landscape changes
from island to continent to island
again,
and there's a sea-change as we fire off
certain rays to form a transverse
across your history.

Acclimatised,
you wintered over in laboratories
and made a virtue of basements
and arcane knowledge; you found
a scientific silence or a calm
in which things are worked out
at a snail's pace, a slime
stretched and scrutinized between
forefinger and thumb to yield
a feast of the truth, or a field
ploughed with frustration, if that
is where our guesses land us.

For Science is a railway carriage
rocking with big ideas, sometimes
stalled on the sidings or slowed
on branch lines near rural stations.
And still the whole is too huge for us
to comprehend, one metre long,
wrapped around each cell,
unread until it's unwound,
the scarf and valence of our complexity,
from which we derive our unique timbre
to say: *Well done! Well done!*
**
To an amateur an x-ray plate
looks like an old-fashioned
gramophone disc; yet it plays
scratchy music of the spheres,
jazz of an original order.
Or perhaps it's the ground-section
of a Byzantine cathedral, or a basilica
of double colonnades and semi-circular
apse –
and who builds upwards from that
to discover the grand design? Who
constructs with only a floor plan
to find the elevations?

Those
who are neither architects nor masons
but quiet archaeologists of the unseen
hand and mind of God, digging upwards
to the exquisite airy construction
of the double helix. Gifted clumsiness?
Genius? You are the start of it,
a chiropractor of the biophysical,
clicking the backbone of DNA into place.
**

Application of sentiment analysis to scientific papers

Three successive short papers in one issue of the journal *Nature* in 1953 collectively announced the discovery of the structure of DNA,[45] for which the numbers of citations and the results of sentiment analysis are shown in Table 2.

Table 2. Metrics and sentiment scores of papers announcing the discovery of the structure of DNA

Title of paper*	No. of citations†	Sentiment‡			
		Generic¶		*Product*§	
		%	Score	%	Score
❶ A Structure for Deoxyribose Nucleic Acid	13588	-74.7%	0.253	-52.2%	0.478
❷ Molecular Structure of Deoxypentose Nucleic Acids	1004	N 83.9%	1.839	-77.4%	0.226
❸ Molecular Configuration in Sodium Thymonucleate	1471	+96.8%	2.968	-67.1%	0.329

*Publication details: ❶ Watson, J.H., Crick, F.H.C., *Nature* **1953**, *171*, 737-738
❷ Wilkins, M.H.F., Stokes, R.A., Wilson, H.R., *Nature* **1953**, *171*, 738-740
❸ Franklin, R.E., Gosling, R.G., *Nature* **1953**, *171*, 740-741
† As at 29 January 2020
‡Sentiment analysis of text excluding acknowledgements and references, undertaken as in https://monkeylearn.com/sentiment-analysis/
¶ Cross-domain or generic sentiment analysis; scores calculated as indicated in Fig. 8
§ Product sentiment analysis, higher scores (calculated as indicated in Fig. 9) indicate greater potential for usefulness or commodification

Generic sentiment scores vary widely for these three papers, but overall lower scores are associated with higher number of citations.[46] Although the product sentiment scores are all negative, they are well correlated with the number of citations,[47] suggesting that scientist-readers could see application or value to their own research of the announcement in the papers, i.e., they saw the papers as 'products' in the commercial sense of the word, leading to their citing of these landmark papers.

In order to apply these ideas to a wider suite of research papers, generic and sentiment scores as well as citations of a noted New Zealand organic chemist's best papers in organic chemistry, which were identified in his autobiography, [48] are given in Table 3. Professor Brian Halton's own ranking of his papers shows an irregular variation with rank of their annual citations and generic sentiment, although there is a rising trend of product sentiment (Fig. 11 Upper). Although generic and product sentiment varies widely, the general trend of product sentiment with annual citations is positive, while the trend of generic sentiment with annual citations is negative (Fig. 11 Lower).

Analogously to the double helix themed papers discussed above, the generic sentiment of Halton's papers is generally negatively correlated with the annual number of citations,[49] whereas the product sentiment is generally positively correlated with annual number of citations,[50] as is also apparent from Fig. 11A. This suggests that organic chemists valued Halton's papers as 'products' in their work synthesising and characterising new compounds.

Table 3. Metrics and sentiment scores of Professor Brian Halton's ten best papers

Paper rank*	Year published	Years since publication	Total no. of citations†	No. of citations per year†	Sentiment‡			
					Generic¶		*Product*§	
					%	Score	%	Score
❶	1966	54	10	0.185	+57.6%	2.576	-60.2%	0.398
❷	1967	53	41	0.774	-42.2%	0.578	+54.4%	1.544
❸	1968	52	17	0.326	-55.2%	0.448	+50.9%	1.544
❹	1971	49	7	0.143	N 63.8%	1.638	-52.6%	0.474
❺	1985	35	22	0.629	-49.7%	0.503	+65.4%	1.654
❻	1983	37	18	0.486	+84.9%	2.849	+73.1%	1.731
❼	1984	36	46	1.278	-90.4%	0.096	+79.2%	1.792
❽	1994	26	9	0.346	+71.2%	2.712	+61.9%	1.619
❾	2005	15	7	0.467	-57.7%	0.423	+63.5%	1.635
❿	2007	13	8	0.615	-73.4%	0.266	+67.8%	1.678

*Publication details of papers in ranked order (❶inferred as the most highly ranked, and ❿ the lowest ranked):
❶ Arnand, N.K.; Cookson, R.C.; Halton, B.; Stevens, I.E.R. The α- and β-Cyclotriveratrylenols. Isolation of Two Conformational Isomers. *Journal of the American Chemical Society* **1966**, *88*, 370-371.
❷ Battiste, M.A.; Halton, B.; Grubbs, R.A. Thermal rearrangements in the tetra-arylcyclopropene series. *Journal of the Chemical Society, Chemical. Communications* **1967**, *1967*, 907-909.
❸ Battiste, M.A.; Halton, B.J. Mass spectrometry of carbonium ion salts: 3-halogeno-1,2,3-triphenylcyclopropanes . *Journal of the Chemical Society, Chemical Communications* **1968**, *1968*, 1368-1370.
❹ Halton, B.; Milsom, P.J. 7,7-Dichloro-2,5-diphenylbenzocyclopropene. *Journal of the Chemical Society, Chemical Communications* **1971**, *1971*, 814-815.
❺ Halton, B.; Dent, B.R.; Bohm, S.; Officer, D.L.; Schumuckler, H.; Schophoff, E. Studies in the cycloproparene series. The synthesis, trapping, and spectral characterization of 1H-cyclopropa[l]phenanthrene. *Journal of the American Chemical Society* **1985**, *107*, 7175-7176.
❻ Halton, B.; Randall, C.J. Cyclopropabenzynes: generation and trapping. *Journal of the American Chemical Society* **1983**, *105*, 6310-6311.
❼ Halton, B.; Randall, C.J.; Stang, P.J. Synthesis and Spectral Characterization of Methylenecycloproparene Derivatives. *Journal of the American Chemical Society* **1984**, *106*, 6108-6110.
❽ Halton, B.; Cooney, M.J.; Wong, H. Spectral Characterization and Rearrangement of an Oxaspiropentene. *Journal of the American Chemical Society* **1994**, *116*, 11574.
❾ Halton, B.; Dixon, G.M.; Jones, C.S.; Parkin, C.T.; Veedu, R.N.; Bornemann, H.; Wentrup, C. A. Cyclopropabenzenylidenethenone (propadienone) via a new route to alkylidenecycloproparenes. *Organic Letters* **2005**, *7*, 949-952.
❿ Halton, B.; Boese, R.; Dixon, G.M. The cyclopropa[b]naphthalene electron donor: nonplanar 8π 7C cycloheptatrienylidene derivatives. *Tetrahedron Letters* **2007**, *48*, 2167-2170.
†As at 4 February 2020; for the few papers for which citations are not available from Web of Science, those from Google or the journal in which the paper was published are used
‡Sentiment analysis of text excluding acknowledgements and references, undertaken as in https://monkeylearn.com/sentiment-analysis/
¶ Cross-domain generic sentiment analysis; scores calculated as indicated in Fig. 8
§ Product sentiment analysis, higher scores (calculated as indicated in Fig. 9) indicate greater potential for usefulness or commodification

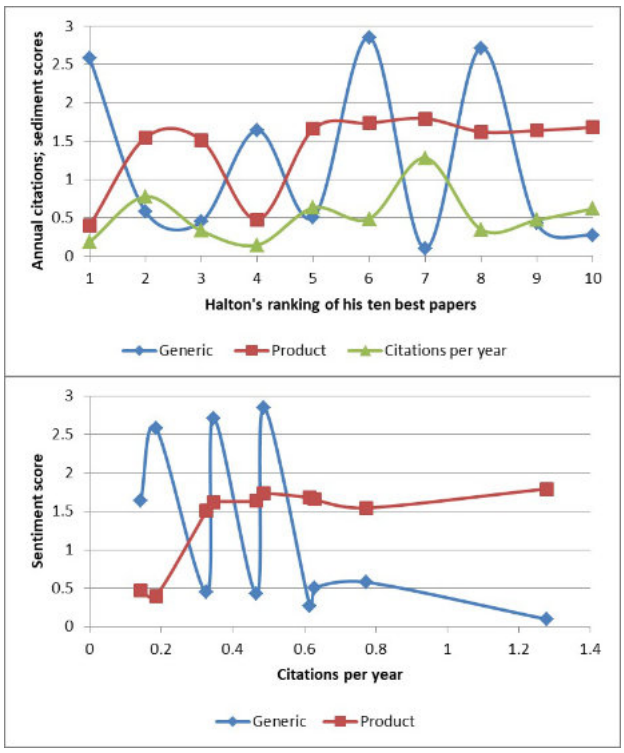


Fig. 11 Upper: Variation of sentiment scores and annual citations for Halton's best papers.

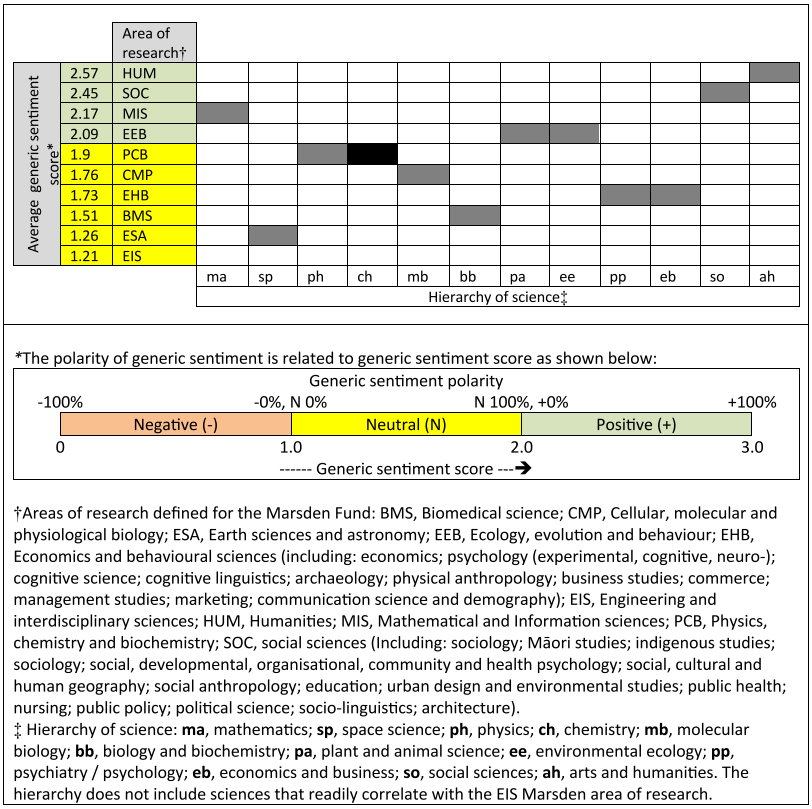
	Correlation coefficient for linear regression
Sentiment	*Annual citations*
Generic	0.332
Product	0.414

Fig. 11. Lower: Variation of sentiment scores with annual citations of Halton's best papers

Application of sentiment analysis to applications for research grants

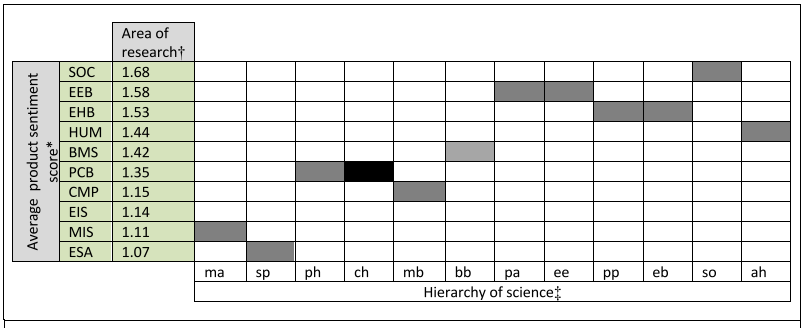
While chemists may not write their scientific papers with the explicit intention to change the hearts and minds of their colleagues or to be highly cited by them, their writing of grant applications is surely motivated by the desire to gain funds to support their research now and into the future. Thus, another potential area for sentiment analysis is applications for contestable research grants. As an example, the Marsden Fund distributes over one hundred awards annually across a range of research areas, ranging in value from $300,000 for early-career researchers (so-called 'fast-start' grants) to nearly a million dollars (so-called 'standard' grants), to academic staff in the universities as well as a few researchers in selected Crown Research Institutes and in independent organisations.

For the successful applications in 2018[51] there is a considerable variation of sentiment scores within and between subject areas, but the average scores for both generic and product sentiment determined from the abstracts submitted to referees are positive for all areas of research. Some of this variation may reflect differences directly related to the subject matter, but it may also reasonably be expected that those aspects deemed more likely to be viewed favourably by referees will be emphasised, either deliberately or serendipitously, by those writing the abstracts for the applications. Average sentiment scores for the social sciences are generally higher than for the pure sciences. The order of the average sentiment scores for the research areas, particularly for product sentiment, resembles that of a proposed hierarchy of science,[52] with chemistry projects in the middle of the range of sentiment (Fig. 12).

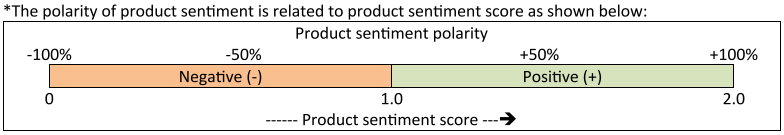


†Areas of research defined for the Marsden Fund: BMS, Biomedical science; CMP, Cellular, molecular and physiological biology; ESA, Earth sciences and astronomy; EEB, Ecology, evolution and behaviour; EHB, Economics and behavioural sciences (including: economics; psychology (experimental, cognitive, neuro-); cognitive science; cognitive linguistics; archaeology; physical anthropology; business studies; commerce; management studies; marketing; communication science and demography); EIS, Engineering and interdisciplinary sciences; HUM, Humanities; MIS, Mathematical and Information sciences; PCB, Physics, chemistry and biochemistry; SOC, social sciences (Including: sociology; Māori studies; indigenous studies; sociology; social, developmental, organisational, community and health psychology; social, cultural and human geography; social anthropology; education; urban design and environmental studies; public health; nursing; public policy; political science; socio-linguistics; architecture).
‡ Hierarchy of science: **ma**, mathematics; **sp**, space science; **ph**, physics; **ch**, chemistry; **mb**, molecular biology; **bb**, biology and biochemistry; **pa**, plant and animal science; **ee**, environmental ecology; **pp**, psychiatry / psychology; **eb**, economics and business; **so**, social sciences; **ah**, arts and humanities. The hierarchy does not include sciences that readily correlate with the EIS Marsden area of research.

Fig. 12A. There is a generally positive – albeit weak – association between the average generic sentiment score for projects in the areas of research assessed by the Marsden Fund in 2018 and the position of those areas in a 'hierarchy of science' advocated by Fanelli and Glänzel (2013); plotting these data gives a correlation coefficient for linear regression of 0.25. The average sentiment score for chemistry (ch), in the hierarchy, which are included in the Physics Chemistry and Biochemistry (PCB) area of research for the Marsden Fund, are in the middle of the range for all areas of research that were funded.



*The polarity of product sentiment is related to product sentiment score as shown below:



† Areas of research defined for the Marsden Fund: BMS, Biomedical science; CMP, Cellular, molecular and physiological biology; ESA, Earth sciences and astronomy; EEB, Ecology, evolution and behaviour; EHB, Economics and behavioural sciences (including: economics; psychology (experimental, cognitive, neuro-); cognitive science; cognitive linguistics; archaeology; physical anthropology; business studies; commerce; management studies; marketing; communication science and demography); EIS, Engineering and interdisciplinary sciences; HUM, Humanities; MIS, Mathematical and Information sciences; PCB, Physics, chemistry and biochemistry; SOC, social sciences (Including: sociology; Māori studies; indigenous studies; sociology; social, developmental, organisational, community and health psychology; social, cultural and human geography; social anthropology; education; urban design and environmental studies; public health; nursing; public policy; political science; socio-linguistics; architecture).
‡ Hierarchy of science: **ma**, mathematics; **sp**, space science; **ph**, physics; **ch**, chemistry; **mb**, molecular biology; **bb**, biology and biochemistry; **pa**, plant and animal science; **ee**, environmental ecology; **pp**, psychiatry / psychology; **eb**, economics and business; **so**, social sciences; **ah**, arts and humanities. The hierarchy does not include sciences that readily correlate with the EIS Marsden area of research.

Fig. 12B. A more convincing association is evident between the average product sentiment scores of a research area and their positions in the hierarchy of science; plotting these data gives a correlation coefficient for linear regression of 0.64. The average sentiment score for chemistry (ch), in the hierarchy, which is included in the Physics Chemistry and Biochemistry (PCB) area of research for the Marsden Fund, is in the middle of the range for all areas of research that were funded.

The trend of funding versus sentiment for the eight successful physics, chemistry and biochemistry (PCB) applications in the 2018 Marsden round is positive for generic sentiment,[53] and weakly negative for product sentiment, although the correlation coefficients are very low at 0.26 and 0.06 respectively.[54] Fig. 13 shows that over the five year-period 2015-2019, for modest Marsden grants awarded through the PCB panel, funding increases with generic sediment score. However, at grants near the maximum there is wild variation of generic sentiment scores. By comparison, product sentiment scores are generally high and show little variation with funding, but – once again – at grants near the maximum there is wild variation in these scores.

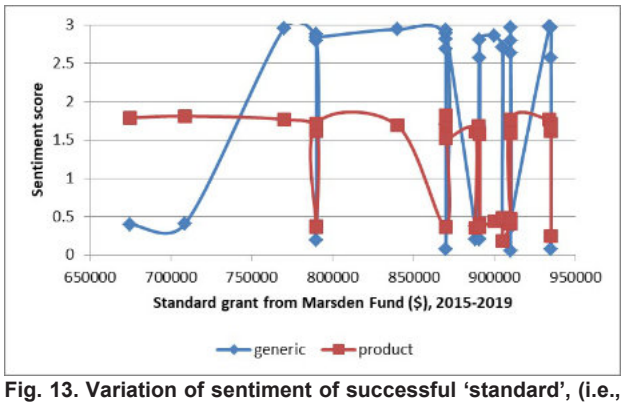


Fig. 13. Variation of sentiment of successful 'standard', (i.e., not 'fast-start') Marsden Fund applications in physics, chemistry and biochemistry assessed by the PCB panel, 2015-2019

This leads to a very tentative suggestion that – at least on occasion – a deliberate attempt by the Marsden applicant to win the hearts and minds of the referee might be rewarded. However, without knowledge of the unsuccessful grants, it is difficult to be certain of whether sentiment makes a difference in the success or otherwise of gaining research funds.

Over the last five years, the trends for both the average generic sentiment score and the average product sentiment score for the successful 'standard' PCB applications to the Marsden Fund have fluctuated, but overall both have decreased from 2016 (Fig. 14 Upper). For 'fast-start' grants, the trend of the average generic sentiment score over the last five years has similarly fluctuated, but is currently in decline; by contrast, the average product sentiment score has increased (Fig. 14 Lower).

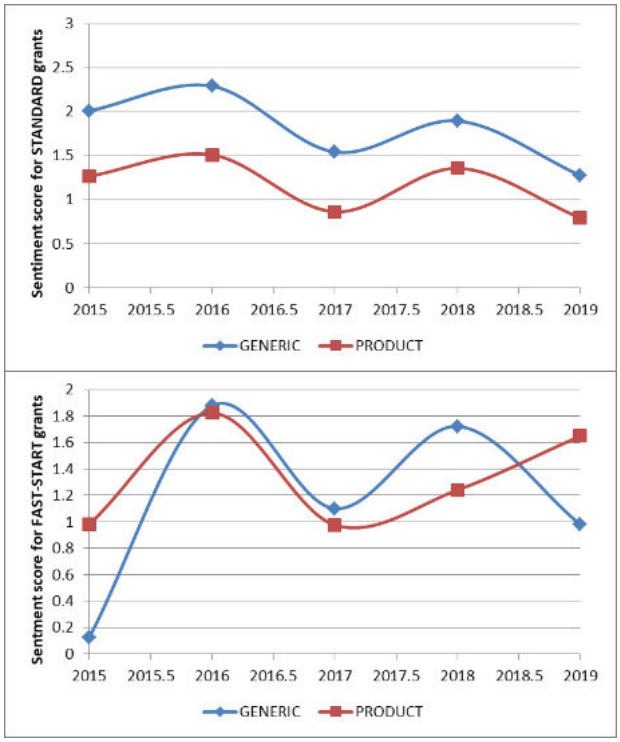


Fig. 14 Upper: Variation of generic and product sentiment scores for successful standard PCB applications to the Marsden Fund, 2015-2019. Lower: Variation of generic and product sentiment scores for successful fast-start PCB applications to the Marsden Fund, 2015-2019.

The fluctuations in sentiment within the five-year period on all plots shown in Fig. 14 may be natural variation; alternatively, they may reflect different behaviours of the review panels in each year (i.e., the panel members collectively react differently to sentiment).

Concluding comments

Sentiment analysis can provide different insights into chemists' writing about the work they do and the environment in which they operate. It can also provide unexpected insights into their scientific writing, applications for research grants, and probably applications for employment and promotion. An upsurge seems likely in the use of formal sentiment packages in the latter, and a greater use of both computerised and bespoke techniques in the analysis and understanding of the 'stories of science'.

Acknowledgements

Development of this paper was enhanced by the willingness of Wellington poet Chris Orsman for his poem to be used; and by a conversation with Peter Singleton, a co-attendee at a conference in Hamilton last year, who suggested scholarship and grant applications as a potential area of investigation. Staff at the University of Melbourne Archives must have been intrigued by my request for permission to use a war-time image of Dorothy Crozier (Fig. 1 Left), but granted permission willingly. Equally co-operative were the staff of Cold Spring Harbor Laboratory Archives, United States, in granting permission to use the photograph of the 1962 Nobel laureates (Fig. 1 Right & Fig. 6).

Notes and references

1. "Student and staff numbers at Victoria University of Wellington increased during the 1950s but the proportion of women staff members actually fell; by the end of the decade there had been virtually no improvement in the position of academic women... The 1960s were, however, to see the University open up opportunities for all women.... By 1965 the History Department had 5 women: Mary Boyd, Dorothy Crozier, and Lucie Halberstam as full lecturers, and Beryl Hughes and Jenny Murray (Ross) as junior lecturers... Women had gained most at the lowest levels – for example at junior lecturer rank they were 27 percent (7 out of 27) and at lecturer level they were 16 percent (13 out of 68)..." From: Hughes, B.; Ahern, S. *Redbrick and Bluestockings: Women at Victoria, 1899-1993*. Victoria University Press: Wellington, 1993, pp. 148-150.
2. Dorothy Crozier (1918-2001) "was among the ground-breaking generation of post-War Pacific scholars, though not a well-known one...Crozier had an outstanding reluctance to publish her work. Her legacy is her personal papers", as noted in 'From the Archives. Crozier papers', *The Journal of Pacific History* **2003**, *38* (3), 371-373. Perhaps her best remembered article is: Crozier, D. Kinship and occupational succession. *The Sociological Review* **1965**, *13* (1), 15-43. Collaborating with Her Majesty Queen Slote Tupou III of Tonga, she wrote the footnotes for Stratham, N. (translator). *Ko Ulukalala I Feletoa: Ko E Talanoa A Toki Ukamea : William Mariner's Story In Tongan*. Friendly Islands Bookshop Press, 2016. She left Victoria University of Wellington in 1971.
3. Watson, J.D. *The Double Helix. A Personal Account of the Discovery of the Structure of DNA*. Atheneum: New York, 1968, 226 pp.
4. Barrowman, R. *Victoria University of Wellington 1899-1999. A history*. Victoria University Press: Wellington, 1999, p. 29.
5. Barrowman (1999, *op. cit.*), p.27
6. Halton, B. *Chemistry at Victoria the Wellington University. A Personalized Account of the Hundred Years from 1899*. School of Chemical & Physical Sciences, Victoria University of Wellington: Wellington, 2012, p. 20 and p. 149.
7. https://www.wgtn.ac.nz/about/our-story/history/campus-plaques/campus-plaques.pdf (accessed 14/08/2018).
8. A photograph of the street frontage of 30 Kelburn Parade, that clearly shows the 'Skerries' name on the picket gate, is provided in Wilkins M. *The Third Man of the Double Helix. The Autobiography of Maurice Wilkins*. Oxford University Press: Oxford, 2003, plate 1, facing p. 114.
9. Wilkins (2003, *op. cit.*), p. 8.
10. "Tomorrow at 1 p.m. Important auction sale. On the premises: 30, Kelburn Parade (opposite Victoria College)." *Evening Post* **1923**, *105* (109, May 9): 8. The furnishings offered for sale included: "beautiful oak sideboard, oval oak extension dining table, oak H.B. chairs, superior Axminster carpet (blue and pink colouring), 12 x 13, 3-piece suite in shadow tissue (rose pink and blue colourings), rosewood corner seat, rosewood corner seat, with cushions in shadow tissue, Oriental carpet, 12 x 9 (blue and pink colouring), afternoon tea set, coffee cups, glassware, Indian rug, fadeless Madras sundu curtains, seagrass chairs, tea table, oxidized coal scuttle, e.l. radiator (latest design), Ax[minster] hall carper (12 x 8), large rimu wardrobe, double doors, with beveled mirrors, fashionable duchesse with side mirror, pair twin beds, together with horsehair mattresses, blankets and sheeting, Indian carpet (9 x 6), pedestal, 2 fadeless rugs (turquoise colouring), curtains, rimu extension table, k[itchen] chairs, oak writing desk, Victory sewing machine, kerb, fire-screen, tapistry square, 9 x 9, chineal curtains, hospital beds, horsehair mattresses, blankets, sheeting, etc., eiderdown, dropside cot, chest of drawers, several duchesse chests, with beveled mirrors, stretcher, pillows, toilet ware, 'Jaraso' personal weighing machine, k[itchen] table, cedar chest, fireless cooker,

Wedgwood crockery (willow pattern), set scales and weights, enamel dishes, etc., saucepans, copper kettle, bread crock, Peerless carpet sweeper, jugs, basins, cups and saucers, table mangle, wringer, door mats, brooms, etc., pair steps, 2 collapsible garden chairs, tools, vise, picture frame, clamp, glue pot, wheelbarrow, lawn roller, 30ft garden hose, garden tools. Pennant lawn mower (14-inch) blade, rose sprayer, child's tricycle and jigger, desert [sic] knives. Also, child's toys, toy house, child's table and chair, and many other useful things."

11. A consent for a drainage connection for the property was given in 1911 (Wellington City Archives, 00432-1528), although the building itself was constructed earlier, but certainly no later than the mid-1900s (see Fig. 2A), and possibly as early as 1898, being the first house built on Kelburn Parade.

12. "Commodious 8-roomed residence and motor garage. Opposite Victoria College. No. 30, Kelburn Parade." *Evening Post* **1929**, *107* (85, April 13): 16.

13. "Tidbits from the LLC's [Language Learning Centre's] 50-year history." https://www.wgtn.ac.nz/llc/about/news/tidbits-from-the-llcs-50-year-history (accessed 14/08/2018).

14. Wellington City Council Archives, 00058-C52492.

15. Watson, J.D. *The Double Helix. A Personal Account of the Discovery of the Structure of DNA.* Penguin: London, 1988, pp. 174-175. All page references to *The Double Helix* in the rest of this paper refer to this edition.

16. Sayre, A. *Rosalind Franklin and DNA*. W.W. Norton: New York, 1974, p. 17.

17. Wilkins (2003), *op. cit.*, p. ix.

18. Sylvia Plath was an American poet, novelist, and short-story writer. Her novel (Plath, S. *The Bell Jar*. Heinemann: United States, 1963) highlighted women in the workforce during the 1950s. She strongly believed in their abilities to be writers and editors, while society forced them to fulfill secretarial roles. See: Jernigan, Adam T. Paraliterary labors in Sylvia Plath's *The Bell Jar*: Typists, teachers, and the pink-collar subtext. *Modern Fiction Studies* **2014**, *60* (1), 1–27.

19. Maddox, B. *Rosalind Franklin: the Dark Lady of DNA*. HarperCollins: New York, 2002, p. xviii. For a summary, see also: Maddox, B. The double helix and the 'wronged heroine'. *Nature* **2003**, *421*, 407-408.

20. Maddox (2002), *op. cit.*, p. 314.

21. Maddox (2002), *op. cit.*, p. 318.

22. Crick, F. How to live with a golden helix. *The Sciences*. New York Academy of Sciences, 1979. pp 6-9, cited in Maddox (2002), *op. cit.*, p. 319. In an interview conducted by Sayre in 1970, Crick was rather more generous than his colleagues in his description of Rosalind Franklin's approach to her science; see: Sayre (1974), *op. cit.*, pp. 212-213.

23. For this purpose, Rosalind Franklin's publication record was reviewed from its compilation in Sayre (1974): p. 204 – footnote 23 to Chapter 2; pp. 204-205 – footnote 3 to Chapter 3; p. 215 – footnote 7 to Chapter 10; pp. 216-217 – footnote 21 to Chapter 10.

24. Scerri, E. (2016). *A Tale of Seven Scientists and a New Philosophy of Science*. Oxford University Press: Oxford, pp. 171-213.

25. The classic book on this topic is: Kuhn, T.S. *The Structure of Scientific Revolutions*. University of Chicago Press: Chicago, 1962.

26. Booker, C. *The Seven Basic Plots: Why We Tell Stories*. Continuum: London, 2004, pp. 69-86.

27. Hodder, P. The periodic table: revelation by quest rather than by revolution. *Foundations of Chemistry* **2018**, *20*, 99-110.

28. Jockers, M. A novel method for deducing plot, 2014. http://www.matthewjockers.net/2014/06/05/a-novel-method-for-detecting-plot/ (accessed 14/08/2018).

29. Jockers, M. Revealing sentiment and plot arcs with the Syuzhet package, 2015. http://www.matthewjockers.net/2015/02/02/syuzhet/ (accessed 14/08/2018).

30. Booker (2004), *op. cit.*, pp. 87-106 (for 'Voyage and return'); pp. 107-129 (for 'Comedy').

31. Whether 'neutral' sentiment should be included in such analysis has been debated; as an example, see: https://blog.datumbox.com/the-importance-of-neutral-class-in-sentiment-analysis/ 2013 (accessed 14/08/2018).

32. Bada, S.O.; Olusegu, S. Constructivism learning theory: A paradigm for teaching and learning. *IOSR Journal of Research and Method in Education (IOSR-JRME)* **2015**, *5* (6), 66-70. Constructivism in the learning and teaching of science has been the subject of research and debate for over two decades. Recent commentary includes: Dagar, V.; Yadav, A. Constructivism: A paradigm for teaching and learning. *Arts and Social Sciences Journal* **2016**, *7*, 200. doi: 10.4172/2151-6200.1000200; Dennick, R. Constructivism: reflections on twenty five years teaching the constructivist approach in medical education. *International Journal of Medical Education* **2016**, *7*, 200-205. An early dissident view of this stance in science education was: Matthews, M.R. Introductory comments on philosophy and constructivism in science education. In Matthew, M.R. (ed.), *Constructivism in Science Education: A Philosophical Examination*. Springer: Dordrecht, 1988.

33. Charlesworth, M.; Farrall, L.; Stokes, T.; Turnbull, D. 'The myth of objectivity and the impersonal scientist.' In *Life Among the Scientists. An Anthropological Study of an Australian Scientific Community.* Oxford University Press: Oxford, 1989, Chapter 5.

34. Sentiment of these excerpts is calculated as in https://monkeylearn.com/sentiment-analysis/ (accessed 14/08/2018).

35. Watson (1968), *op. cit.*, p. 13; Crick, F. (1979), *op. cit.*; Wilkins (2003), *op. cit.*, pp. ix-x, from the Preface.

36. Sayre (1974), *op. cit.*, p.24, from the Introduction; Maddox (2002), *op. cit.*, pp. xvii-xviii, from the

Prologue.

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41. For a New Zealand example, see: *Curious minds: Women and girls in science and technology.* https://www.curiousminds.nz/actions/community/women-and-girls/ (accessed 14/08/2018).

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46. For the three points, a plot of generic sentiment score (*GS*) versus log of citations (*C*) yields the equation: $GS = -1.89 \times \log_{10} C + 8.17$, for which the correlation coefficient (R^2) is 0.71.

47. For the three points, a plot of product sentiment score (*PS*) versus log of citations (*C*) yields the equation: $PS = 0.20 \times \log_{10} C - 0.34$, for which the correlation coefficient (R^2) is 0.92.

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49. For the ten points a plot of generic sentiment score (*GS*) versus log of citations (*C*) yields the equation: $GS = -2.25 \times \log_{10} C + 0.40$, for which the correlation coefficient (R^2) is a modest 0.33.

50. For the ten points, a plot of product sentiment score (*PS*) versus log of citations (*C*) yields the equation: $PS = 1.51 \times \log_{10} C + 1.95$, for which the correlation coefficient (R^2) is 0.69.

51. Compiled from https://www.royalsociety.org.nz/what-we-do/funds-and-opportunities/marsden/awarded-grants/marsden-fund-awards-2018/ (accessed 14/08/2018) and spreadsheets therein.

52. Fanelli, D.; Glänzel, W. Bibliometric evidence for a hierarchy of the sciences. *PLOS One* **2013**, *8* (6), e66938. https://doi.org/10.1371/journal.pone.0066938.

53. For the eight data-points, a plot of generic sentiment score (*GS*) versus the size of the Marsden grant (*F* in thousands of dollars) yields the equation: $GS = 0.009 \times F - 5.96$, for which the linear regression coefficient (R^2) is a rather modest 0.26.

54. For the eight points, a plot of product sentiment score (*PS*) versus the size of the Marsden grant (*F* in thousands of dollars) yields the equation $PS = -0.002 \times F + 3.13$, for which the linear regression (R^2) is a very low 0.06.

Oligonucleotide-based therapeutic agents: challenges and advances

Harikrishnan M. Kurup* and Vyacheslav V. Filichev

School of Fundamental Sciences, Massey University, Palmerston North and Maurice Wilkins Centre for Molecular Biodiscovery, Auckland

Email: h.kurup@massey.ac.nz

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Introduction

Oligonucleotide-based therapeutic agents (OTAs) include a wide range of target-oriented chemically synthesised entities with a modified or unmodified 2'-deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) backbone. The development of the human genome project and subsequent identification of genes associated with many diseases led to the evolution of therapeutic strategies acting on the specific genes responsible for a particular disease.[1] These advances led to a growing interest in finding therapeutic agents for complex diseases such as genetic disorders and different cancers. OTAs have an advantage over traditional small molecule therapy for their ability to modify genes directly or by targeting RNA and can be employed to act on cellular pathways that are otherwise not readily accessible. Despite their advantages, the number of OTAs approved by the Food and Drug Administration (FDA) is low compared to small molecule therapeutics. Challenges associated with the development of OTAs are associated with the physicochemical properties of nucleic acids in general. Advances in nucleic acid chemistry and understanding of the pharmacokinetic and dynamic properties of nucleic acids have led to the discovery of clinically approved OTAs. This review focuses on different ways by which physicochemical properties of oligonucleotides can be modified to achieve OTAs for clinical applications and is followed by a discussion of some clinically approved OTAs.

Nucleic acids chemistry and modifications

Nucleic acids are biopolymers made up of nucleotides, which are in turn monomers of nucleosides. Nucleotides have three main components: (a) a ribose or 2'-deoxyribose sugar, (b) a phosphate group and (c) a nitrogenous nucleobase. Sugars and phosphates are connected by a phosphodiester linkage (Fig. 1).

These natural oligonucleotides have a limited therapeutic application since they are highly hydrophilic compared to highly lipophilic small molecule counterparts. Hydrophilicity makes them inefficient to penetrate tissues and thus makes them less efficient as drugs. Another important drawback of natural nucleic acids is they can be readily degraded by nucleases when introduced into a biological system.[2] To design an efficient OTA, all these issues must be addressed and therein lies the opportunity for chemists. Different modification strategies employed in the past are discussed briefly below.

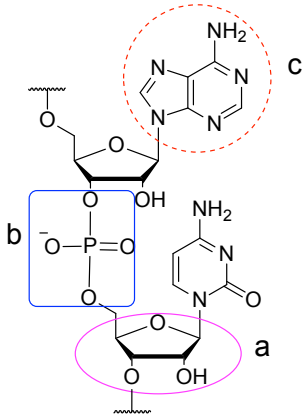


Fig. 1. An oligonucleotide unit and its main components

Sugar modifications

Being an important part of nucleic acids, both RNA and DNA have been extensively modified which led to a decreased nuclease activity especially in RNA, and increased thermal stability towards complementary DNA or RNA.[3] Some of the commonly employed sugar modifications are outlined below (Fig. 2). In RNA, the most widely employed modification is at 2'-OH. Modifying it to 2'-*O*-methyl, 2'-*O*-methoxyethyl and 2'-fluoro have been the methods of choice to date.[4-6] The electron-withdrawing group (F) at the 2'- position favours C3'-endo sugar puckering making it more RNA like. Furanose sugars with atoms puckered above the

plane are in an endo-form, where C3' refers to C3'-carbon is pointed up towards the nucleobase. C3'-endo sugar puckering is found in A-DNA, which has a shallow, wide minor groove and a deep, narrow major groove which can be accessible by polymerases. The specific sugar pucker conformation is critical for nucleic acid polymerisation and a high affinity for complementary mRNA. The additional anomeric effect can be imparted by the introduction of 4'-fluoro group which reinforces sugar pucker towards RNA. This can also be achieved by introducing a methylene bridge that links 2'-*O* with the C4 position as in locked nucleic acids (LNA) also known as 2',4'-bridged nucleic acids (BNA).[7-10] LNAs have numerous advantages as they form duplexes and triplexes with increased thermal stabilities.[11-12] 2'-*O*-methoxyethyl modification confers strong nuclease resistant properties in small interfering RNA (siRNA) and also improves the binding affinity towards RNA.[13-14] Unlocked nucleic acid (UNA) is an acyclic RNA mimic within nucleic acid analogs. The missing bond between the C2' and C3' makes a UNA monomer more flexible than an unmodified counterpart. This structural property makes it an RNA mimic and imparts destabilising effects in UNA-RNA duplexes.[15] Another example of conformationally restrained nucleic acid is tricyclo (tc)-DNA. This tricyclic system increases the RNA binding affinity and has also been found to have antisense therapeutic potential in various studies.[16-17]

Phosphate modifications

Nucleotides are linked together by a phosphodiester linkage in both DNA and RNA. This linkage is readily cleaved by endo- and exonucleases.[18] Due to this prime importance, extensive research has been done in the past to modify phosphate backbones. One of the most interesting and first reported modifications is PS, in which one of the oxygens attached to the phosphorous is replaced by sulfur. This modification is relatively easy to introduce into DNA/RNA during automated nucleic acids synthesis. PS-modified OTAs show fairly high resistance to nucleases.[19] However, fully modified PS-OTAs are shown to be cytotoxic and have a reduced binding affinity towards complementary RNA.[20] PS-OTAs contains a chiral center at each phosphorous atom and hence it gives a mixture of isomers. It has been established that the complementary binding affinity, RNAase H activity, etc., are dependent on the stereochemistry of the phosphorous atom.[21-22] Takeshi Wada and co-workers developed a stereo-controlled solid-phase synthesis of PO/PS chimeric oligodeoxyribonucleotides on an automated synthesiser using an oxazaphospholidine– phosphoramidite method.[23] Stereo-controlled oligonucleotide synthesis with an iterative capping and sulfurisation protocol developed by Wave Life Sciences addressed the disadvantage of Wada's method which suffers from the challenge associated with post-synthetic removal of the chiral auxiliary.[24] Natural oligonucleotides are negatively charged, resulting in extensive hydrogen bond formations and electrostatic interactions, making them hard to pass through membranes. Many modifications have been employed to address these issues. Peptide nucleic acids (PNA) and phosphorodiamidate morpholino oligomers (PMO) are amongst them having a neutral backbone (Fig. 3).[25] Apart from these modifications, as a strategy towards making either neutral or partially positive charged oligonucleotides, a variety of modifications including substituting one of the oxygens at the phosphate backbone by a positively charged residue or complete replacement of phosphate has been employed (e.g.: DNG, DNmt, guanidinopropyl phosphoramidate).[26]

There has been a substantial amount of research to develop a number of charged or neutral backbone modifications of varying length.[20] 5′-*O*-methylenephosphonate modification (5′-MEP) when introduced in oligonucleotides has shown a high binding affinity compared with unmodified oligonu-

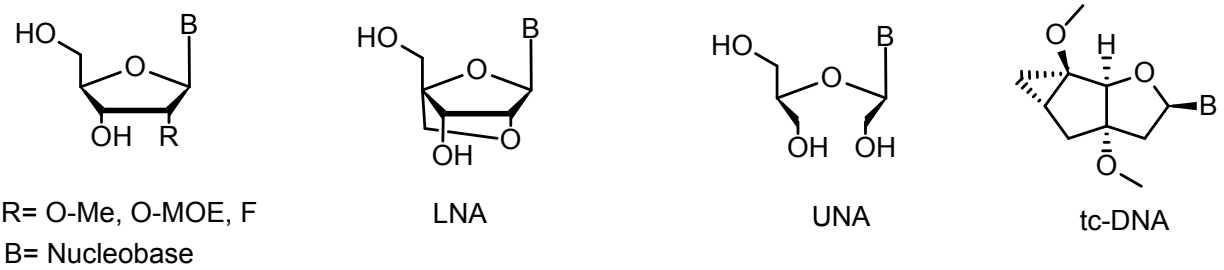


Fig. 2. Commonly employed sugar modifications

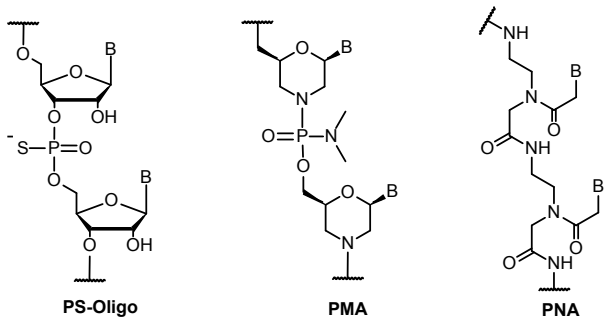


Fig. 3. Commonly employed phosphate backbone modifications

cleotide.[27] Deoxynucleic guanidine (DNG), deoxynucleic *S*-methylthiourea (DNmt) and guanidinopropyl phosphoramidate were developed as positively charged modifications and have also demonstrated high binding affinity (Fig. 4) to complementary DNA/RNA strands.[26] Cu(I) catalysed azide-alkyne cycloaddition (CuAAC) has provided a relatively easy means of introducing triazole modification as a neutral alternative that is biocompatible and copied by DNA polymerases during PCR amplification providing long DNA strands.[28-29] There are many modifications which are still being investigated for selective uptake by cells and to reduce toxicity and increase the binding affinity towards complementary DNA/RNAs.

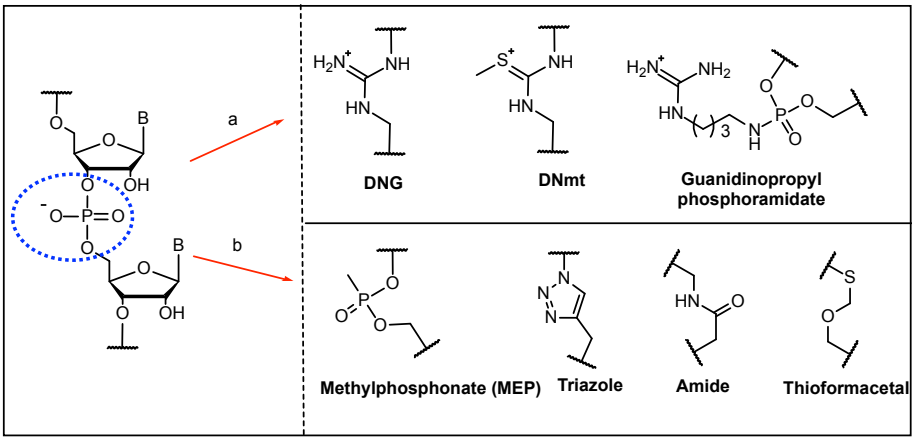


Fig. 4. Charged and neutral backbone modifications employed in the recent past

Nucleobase modifications

Nucleobase modifications have been explored as a means of enhancing the binding affinity with minimal or no effects on base pairing by maintaining or improving hydrogen bonding interactions (Fig. 5). The most widely employed modifications are at the 5-position of pyrimidine bases (C, U and T). For example, 5-methyl C increases the thermal stability of the duplex.[30] Substitution with a long alkyl chain decreases the binding affinity.[31] However, modification of pyrimidines with propyl chain increases duplex stability.[32] Modifications to the purine bases A and G were also proved to increase duplex stability. 2,6-diaminopurine, having an additional hydrogen bond to thymine and uracil, as well as N^2-imidazolylpropyl- and N^2-aminopropyl guanine contribute to the phosphate backbone electrostatic interactions.[33]

Oligonucleotide therapeutics success stories

Clinical development of therapeutically active oligonucleotides began about 40 years ago starting from antisense oligonucleotides (AOs).[34] The advance of this field led to the development of other OTAs like aptamers, gapmers and siRNAs. The continuous efforts for OTAs have led to 10 FDA approvals so far having a clear clinical benefit through stringent clinical trials. A brief outline of these agents is given below.

Fomivirsen

Fomivirsen, the first approved OTA was a 21 nucleotide long oligomer (21-mer) PS-DNA with the sequence 5'-GCG TTT GCT CTT CTT CTT GCG-3', intended for treating patients with cytomegalovirus (CMV) retinitis.[35] This antisense oligonucleotide was developed by a collaboration between ISIS (now Ionis Pharmaceuticals) and Novartis ophthalmic division. This agent targeted mRNA that encodes the CMV immediate-early protein (IE-2) vital for virus replication. The treatment was with 165 µg of the drug injected directly into the vitreous humor, followed by maintenance therapy till the symptoms abolish. The approval was in 1998 due to an unmet need of CMV therapeutics. Later, due to the development of antiretroviral small molecules and high-activity anti-retroviral therapy (hAART) CMV cases drastically reduced and Novartis stopped the marketing of Fomivirsen in 2006. The approval of Fomivirsen proved that OTA can meet regulatory requirements for approval and was a significant milestone in the history of OTAs.

Pegaptanib

Pegaptanib, also known as Mucagen is a nucleic acid aptamer targeting vascular endothelial growth factor (VEGF165).[36] Aptamers are engineered nucleic acids or peptides designed by repeated rounds of systematic evolution of ligands by exponential enrichment (SELEX).[37] It is a 27-mer oligonucleotide containing a PS-3'-

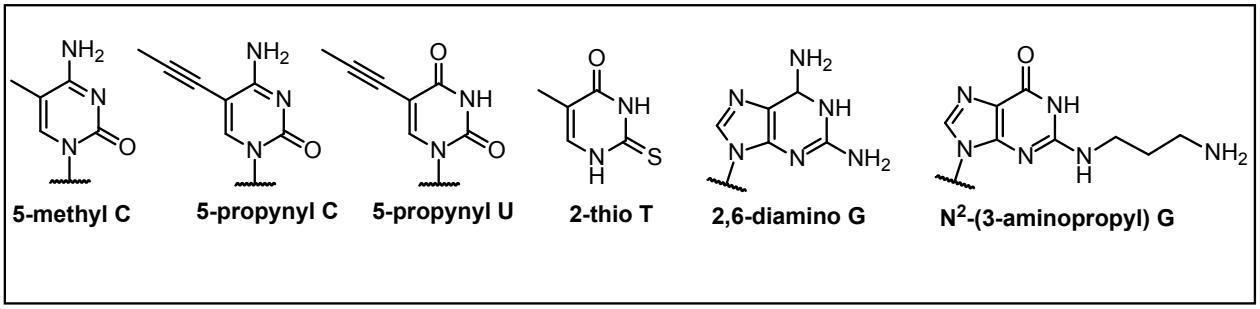


Fig. 5. Commonly employed purine and pyrimidine base modifications

deoxythymidine cap to enable nuclease stability. The purine ribose sugars are all 2'-O-methylated and pyrimidine sugars are all 2'-fluorinated. It contains a 40 kDa polyethylene glycol substituent at the 5' end (Fig. 6).

Pegaptanib was approved by FDA in 2004 to treat blindness caused by age-related macular degeneration (AMD) of the retina. It is an antagonist of VEGF 165, a protein that plays a critical role in the formation of new blood vessels and increased permeability, responsible for loss of eyesight in AMD. Pegaptanib works as

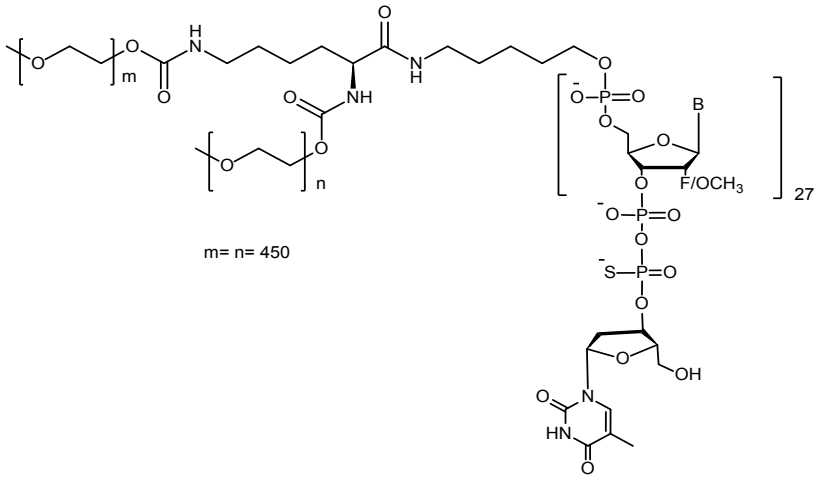


Fig. 6. Chemical structure of Pegaptanib (B: nucleobases in which purine ribose sugars are all 2'-OMe and pyrimidine sugars are all 2'-F)

an antagonist to VEGF, which when injected into the eye blocks the actions of VEGF. This then reduces the growth of the blood vessels located within the eye and works to control the leakage and swelling observed in AMD. It is given as 0.3 mg intravitreal injection every 6 weeks. No systemic toxicity was observed in patients treated with this drug.

Pegaptanib was developed by NeXstar and was acquired by Eyetech Pharmaceuticals. In 2005, Eyetech Pharmaceuticals was acquired by OSI Pharmaceuticals. In 2008, former Eyetech employees purchased the drug from OSI and established Eyetech, Inc. However, Eyetech, Inc. was acquired by Valeant Pharmaceuticals in 2010 and marketed by Valeant. Shortly after in 2011, sales began to decline due to competitor ranibizumab (a monoclonal antibody, Novartis) which proved more effective than pegaptanib.

Mipomersen

Mipomersen is a 20-mer PS gapmer antisense oligonucleotide therapeutic agent approved for the treatment of homozygous familial hypercholesterolemia.[38-39] Gapmers are chimeric antisense OTAs designed with a central block of natural or PS-modified nucleic acids and 2'-O modified ribonucleotides or other artificially modified ribonucleotide monomers in both 5' and 3' wings. This disease is characterised by a high level of low-density lipoprotein (LDL) in plasma and reduced clearance. All these can lead to benign tumours and cardiac diseases at a very young age. Mipomersen acts by binding to the coding region of the Apolipoprotein B (apoB) mRNA. ApoB is an important protein which binds to LDL receptors on liver and facilitates its clearance.[40] This protein is also critical in the production of very low-density lipoproteins (VLDL) by hepatocytes. The binding of mipomersen to mRNA leads to cleavage of mRNA by the enzyme RNAase H, consequently apoB is not translated. Mipomersen contains 2'-methoxyethoxy (MOE) groups at positions 1-5 and 15-20 in the structure to confer nuclease stability. This also increases the thermal stability of the mRNA-oligonucleotide complex, leading to enhanced RNAase H activity in the nucleus of the cell.[41] The drug is administered as a 200 mg subcutaneous injection once a week. The sequence of oligo is:

5'-G*-mC*-mC*-mU*-mC*-dA-dG-dT-dmC-dT-dT-dmC-G*-mC*-A*-mC*-mC*-3'

* = 2'-O-(2-methoxyethyl)

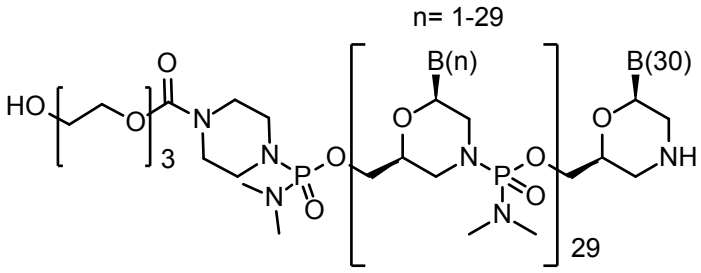
m = 5-methyl

d = 2'-deoxy

Mipomersen was developed by Ionis Pharmaceuticals and was approved by the FDA in 2013 but was rejected by European Medicines Agency (EMA) twice due to concerns over hepatotoxicity. The drug lost its commercial fight with an orally administered small molecule agent lomitapide, designed to lower cholesterol by blocking lipid transfer.[42] Both by effective marketing strategies and ease of administration of lomitapide compared to mipomersen, lead to the first systemic oligonucleotide therapeutic agent failed to find its market share.

Eteplirsen

Eteplirsen is a 30-mer uncharged phosphomorpholidate (Fig. 7), designed to treat Duchenne muscular dystrophy (DMD).[43] It is a devastating disease affecting young males characterised by mutations in the dystrophin gene. Children suffering from DMD lose the neuromuscular functions as they age leading to cardiac myopathy, respiratory failure and death in their twenties.[44] Premature RNA consists of parts of introns and exons. Exons are the coding regions for a protein which is separated from non-coding introns. The pre mRNA is modified by different mechanisms. Some remove the introns and others splice the exons to form mature mRNA, leading to the biological synthesis of a protein. Eteplirsen is one of the splice switching oligonucleotides (SSO) which usually binds to the key splicing regions. This masking of exons leads to the splicing mechanism acting on another site, skipping the exon



B(1-30): C-T-C-C-A-A-C-A-T-C-A-A-G-G-A-A-G-A-T-G-G-C-A-T-T-T-C-T-A-G

Fig. 7. Chemical structure of Eteplirsen

and producing mRNA which translates truncated but partially functional protein.[45] The drug specifically skips exon 51 of the dystrophin protein, which connects muscle fibres to extracellular matrices. This truncated protein can support the muscular activities of DMD patients to a certain extent and the life expectancy can be prolonged.[46] After several controversies regarding the efficacy of the drug and a few dissatisfying trials, eteplirsen, renamed as Exondys 51, received accelerated approved for DMD therapy in 2016.

Defibrotide

Defibrotide, also known as Defitelio is a natural product. It is a controlled depolimerisation product of porcine intestinal mucosal DNA. It has a complex non-specific mechanism of action based on the interaction of its poly phosphodiester backbone and proteins. The drug is developed as an agent to treat severe hepatic veno-occlusive disease (sVOD).[47] This disease occurs as a side effect of high dose chemotherapy or autologous bone marrow transplantation. The drug is a mixture of single-stranded and double-stranded oligonucleotides with an average molecular weight of 16.5±2.5 kDa. Pathophysiology of sVOD is often characterised by activation of endothelial cells by cytokines, leading to endothelial damage and activation of fibrinolytic pathway. All of these events lead to necrosis of hepatocytes and eventually multi-organ failure with an estimated mortality rate of 80%.[48]

The drug acts by mimicking heparin action in many ways because of the polyanionic nature of both agents. Any protein which binds to heparin can also bind to defibrotide. It is established that it binds to the heparin binding protein FGF2 leading to micro vessel formation and induces VEGF16.[49-50] Although the mechanism of action and specificity of the drug were questioned often by the authorities, the risk to benefit ratio of the agent in sVOD led the FDA to approve the drug in April 2016.

Nusinersen

Nusinersen is an antisense 18-mer PS- 2'-*O*-Me RNA therapeutic agent. The cytidines in the sequences are all methylated at the 5th position. This drug is used to treat spinal muscular atrophy (SMA), caused by mutation in the SNM1 gene, causing deficiency in survival motor neuron (SMN) protein.[51] SMA occurs in infants

and is estimated that about 400 infants are born in the United States every year with SMA. Infants affected develop general muscle weakness and progress to difficulty in breathing and swallowing. The drug induces splicing modulation and inclusion of exon 7 in the SMN1 and SMN2 mRNA by blocking intron 7.[52] This increases the translation of SMN protein. Nusinersen is labelled as one of the most expensive drugs in the world. In the USA, the price is US$125,000 per injection, leading to treatment cost at US$750,000 in the first year and US$375,000 annually in the subsequent years. The drug is given as 12 mg intrathecal injections once every 4 months. This potentially lifesaving drug developed by Biogen, who licensed it from Ionis Pharmaceuticals, was approved by the FDA in December 2016. It has an orphan drug status and is now available in over 40 countries for the treatment of SMA.

Inotersen

Inotersen is a 20-mer PS gapmer containing ten central 2'-deoxyribonucleotides, and five 2'-MOE-RNA at the 5'- and 3'-termini. This drug is designed as an agent to treat transthyretin amyloidosis, a hereditary disease. Transthyretin (TTR) protein is primarily produced in the liver, a tetramer form of the protein binds retinal binding protein 4 (RBP4)-retinal complex, which acts as thyroid hormone transport protein.[53] Autosomal mutations in the transthyretin gene produces less stable tetramer. Because of these mutations monomers aggregate and deposit in peripheral nerves, cardiac tissue, and kidneys, leading to peripheral neuropathy, gastrointestinal dysfunction, and cardiomyopathy.[54] Life expectancy of individuals with hereditary TTR (hTTR) is 3–15 years. Inotersen binds to the 3'-untranslated region (3'-UTR) of human TTR mRNA, promoting RNase H1- mediated cleavage of the mRNA, preventing the production of the TTR protein.

The small group of patients treated with this agent in phase III of the clinical trial developed severe platelet aggregation and glomerulonephritis. But the overall results proved to be beneficial comparing the risk to benefit ratio and the drug was approved by the FDA in October 2018 for hereditary transthyretin-mediated amyloidosis.

Patisiran

Patisiran was the first-in-class siRNA for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR) in adults and the first approved siRNA by FDA.[55] It is a double-stranded siRNA consisting of a partially complementary sense strand and an antisense strand each containing 21 nucleotides. Patisiran is capsulated in a lipid nanoparticle formulation, preventing mRNA from translating TTR proteins that build up in patients with polyneuropathy. Specifically binding to a genetically conserved sequence in the 3'-UTR of mutant and wild-type TTR mRNA, patisiran causes its degradation and reduces TTR protein levels and its deposition.[56] Developed by Alnylam Pharmaceuticals, the drug was a direct competitor to Inotersen for the treatment of the same disease. Patisiran was approved by FDA in August 2018 and granted orphan drug status.

Givosiran

Givosiran is a double stranded chemically modified siRNA containing a combination of 2'-F and 2'-*O*-Me RNA nucleotides, conjugated to a triantennary *N*-acetyl galactosamine (GalNAc) ligand for facile delivery into the liver. It is an aminolevulinate synthase 1 (ALAS1)-directed siRNA developed by Alnylam Pharmaceuticals as an agent to treat acute hepatic porphyria (AHP).[57] AHP is a rare and life-threatening genetic disease in which patients lack the enzymes needed to produce heme. ALAS1 is a liver enzyme which is involved in an early step in heme production. The drug lowers blood levels of aminolevulinic acid (ALA) and porphobilinogen (PBG), neurotoxic agents associated with AHP symptoms.[58] The siRNA binds with high affinity to asialoglycoprotein receptors on hepatocytes. Inside the hepatocytes, the antisense strand of Givosiran is incorporated into RNA induced silencing complex (RISC) and strands bind to ALAS1 mRNA, inhibiting the translation and expression of the ALAS1 protein, reducing systemic levels of neurotoxic ALA and PBG. The drug was approved in November 2019 by FDA for the treatment of AHP in the US only.

Golodirsen

Golodirsen is a morpholino antisense oligomer for the treatment of Duchenne Muscular Dystrophy (DMD). As described earlier, the hallmark of DMD is the lack of dystrophin protein leading to progressive muscle weakness. Developed by Sarepta Therapeutics, it is given as 50 mg/ml intravenous injection. It binds to exon 53 of dystrophin pre-mRNA on the DMD gene, skipping this exon during mRNA processing resulting in the out-of-frame mRNA to in-frame mRNA and trans-

lation of a truncated dystrophin. This truncated dystrophin resembles Becker Muscular Dystrophy (BMD), a condition in which there is production of a truncated dystrophin protein.[59] Patients with BMD generally can expect a longer lifespan and improved quality of life. Thus, the patients treated with golodirsen are expected to live longer than the untreated. In December 2019, golodirsen was approved by FDA for therapeutic use in the United States.

Conclusions and future perspective

Oligonucleotides as novel therapeutic agents have seen many disappointments when compared to their successes over the past 40 years. Understanding the mechanism of action of oligonucleotides, rapid technological developments in chemical modifications and targeted delivery of these agents to various tissues have contributed to the successes in this field. Antisense oligos and siRNAs have proven to be the most useful agents in the recent past and many therapeutic agents based on these technologies are still in clinical trials. Although the progress is significant, there are still questions around their adverse effects, efficacy, and future improvements as a new platform of therapy. Cost of therapy is currently still a big question. Apart from these hurdles, there is constant competition from small molecule therapeutic agents and antibodies for the same targets. A better understanding of the mechanistic pathways and off-target effects are crucial in the future of OTAs as a strong platform for treating unmet medical conditions. Recent advances in the field of nucleic acids chemical biology including specific chemical modifications has led to the emergence of agents designed for site specific action. Also, the emerging need for personalised medicines highlight the potential for oligonucleotides in future therapeutic needs. For example, in DMD, the selection of an OTA is based on the genetic analysis of the patient to determine the site of exon skipping (exon 51 or 53). Another example of personalised OTA is Milasen, which is a synthetic RNA consisting of 22 nucleotides that acts as a molecular band-aid, masking the exon. Milasen was designed to treat a single patient named Mila Makovec who had a unique mutation in the CLN7 gene leading to Batten disease.[60] The utility of OTAs in therapy will be revealed in the near future as around 50 agents are in clinical trials with 20 in advanced stages.

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Clayton (Ru) Bennett: world class industrial chemist

Laurence D. Melton

School of Chemical Sciences, University of Auckland, Auckland 1142

Email: l.melton@auckland.ac.nz

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Go Ru! Go RU! And he did, as he crashed through tackle after tackle to score under the posts. It was all so unexpected from such a modest, friendly schoolboy. Just a hint of the fierce determination he would show later as an industrial chemist dealing with seemingly insurmountable problems.

Clayton Ross Bennett was born on 4 October 1941 and grew up on a dairy farm at Ruawai, near Dargaville. He did well at school, so it was decided to send him to Mt Albert Grammar School (MAGS) in Auckland. This was facilitated by his being able to board with his grandmother in the adjacent suburb of Point Chevalier. He specialised in science along with mathematics and was promptly nicknamed Ru, after Ruawai. He was a conscientious student but unexpectedly failed School Certificate (the major exam taken in the 5th form, or Year 11) and had to repeat the year. This was a significant moment in his life; he drastically revised the way he studied and made sure he never failed again, no matter how great the challenge. As a teenager he grew to be a huge man, tall, barrel-chested, and with powerful legs and arms – an ideal rugby prop. He had reddish hair, and a shy modesty along with an infectious grin. He would have been an easy target for bullies, except for his strong physical build. A gentle giant, except when playing rugby; even then he had to be encouraged to be aggressive. In 1960 Ru was in the MAGS 1st fifteen rugby team and his great friend, Barry Stevens, was the captain. The two of them developed a game winning tactic. Late in the game Barry would grab the ball in a loose ruck and break through a couple of tackles and then he would pass the ball to Ru who was right on his shoulder. Ru would put his head down and batter his way through the rest of the opposing team to score. They were the Auckland Secondary School Rugby Champions that year, beating both Auckland Grammar and King's College, which was something MAGS seldom did. Ru went on to play rugby for the University of Auckland as an undergraduate.

Student days in the 60s

At the University of Auckland, Ru Bennett (Fig. 1) took a BSc in chemistry (Fig. 2) followed by a MSc in organic chemistry including research on reductions of totarol[1] (Fig. 3) under the direction of Professor Con Cambie. He was awarded as Duffus Lubecki Prize in 1965. He continued to work with Cambie on the chemistry of podocarpic acid (Fig. 4) and related compounds from New Zealand's Podocarpacea trees (e.g. totara, rimu, kahikatea) for his PhD,[2] which was completed in 1967. This collaboration was highly successful, resulting in six papers.[3] As well as rugby he enjoyed tramping and later exploring the wild caves around Waitomo. In

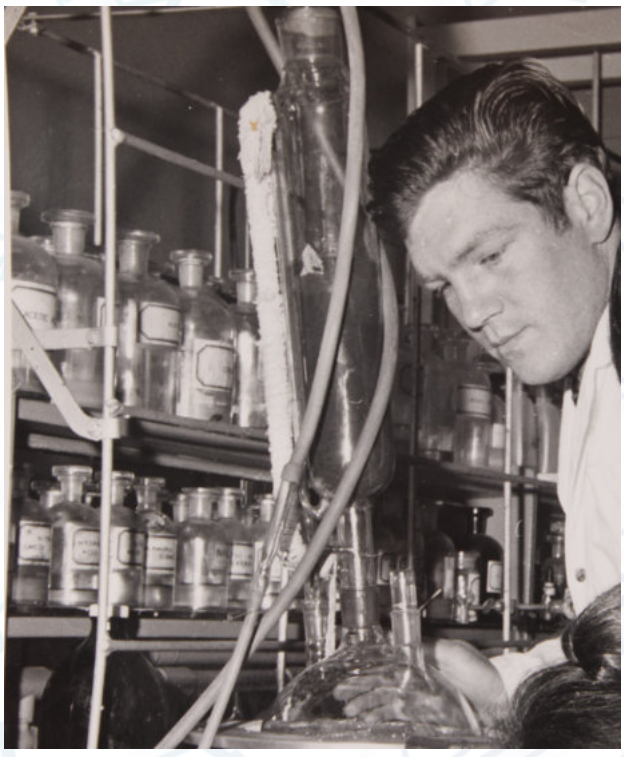

Fig. 1. Clayton Bennett as a young research chemist

Fig. 2. Graduation day for University of Auckland BSc chemistry students, May 1964. Back row (L to R) Eric Orgias, Clayton Bennett, Colin Le Quesne, Wayne Watkins, Ritchie Sims. Front row (L to R) John Buchanan, Paul Woodgate, Prakash Dhaneer, Rhys Montgomery, unknown.

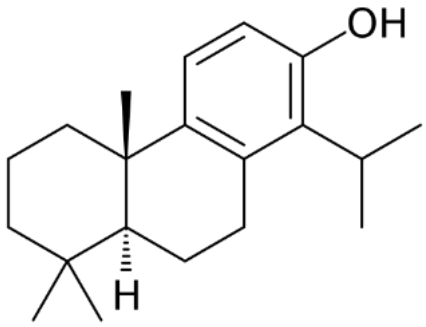

Fig. 3. Totarol

those days most students could only manage to get to university if they stayed home with their parents. Student flats were rare, always overcrowded, chaotic and typically near-derelict old villas in the slums of Ponsonby or Herne Bay. Consequently, Ru's place in Point Chevalier was a welcome haven where we could gather to discuss what was wrong with the world and play loud music; rock and roll was raving and couples danced in the aisles in cinemas. Ru's grandmother, Mabel Gardiner, was a very special person for her grandson. Unlike Ru she was tiny, barely 5ft tall and thin to the point of being scrawny. Conveniently, she was stone deaf once she took out her hearing aids. However, when a student party was at its height she would feel the floor boards moving and at about 1 a.m. she would emerge from her bedroom in her night dress and announce, "Clayton, turn the music down, the whole house is shaking. What will the neighbours say!" Clayton was very contrite, as we all were. Of course we didn't turn the sound down, but stopped dancing for a while until she got back to sleep. Parties at Ru's place were the best!

Postdoc followed by seasickness drug

A postdoctoral fellowship with Professor A. Ian Scott at Sussex University, Brighton, UK (1967 – 1968) followed. Professor Scott gained world renown later for elucidating the biosynthetic pathway of vitamin B_{12}. In 1969 Professor Scott moved to Yale University and Clayton went with him as an assistant lecturer in chemistry. From 1971 to 1972, Clayton worked as a research associate at the CNRS Laboratory at Gif-sur-Yvette, funded by a French Government Scholarship. NMR was the exciting new technique then and Clayton used it to study natural products[4] such as lanosterol and alpha-ecdysone. The tropane alkaloid, scopolamine (Fig. 5) was synthesised.[5] Scopolamine is an anti-nausea drug that can be used as a patch behind the ear to prevent seasickness. From this beginning he mastered French. Clayton Bennett married Helen Henderson in 1967, although the marriage did not last. They had two sons, Tony and Michael.

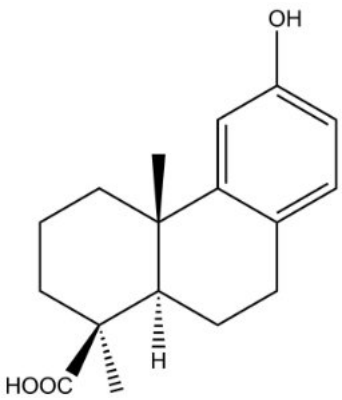

Fig. 4. Podocarpic acid

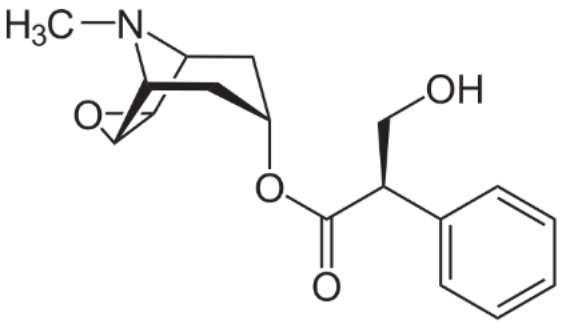

Fig. 5. The anti-nausea drug Scopolamine

Manufacture of cardiovascular drugs

From 1973 to 1980, Clayton worked for Bristol Myers SQUIBB, New Jersey, USA as section head and manager of technical operations. He was responsible for the development of the complete process from discovery through large scale pilot plant operations to bulk manufacture of the cardiovascular drugs, Corgard (Nadolol) (Fig. 6) and Capoten (Captopril) (Fig. 7). Corgard is used to treat high blood pressure, heart pain, and atrial fibrillation. It has also been used to prevent migraine headaches and complications of cirrhosis. Capoten is an angiotensin-converting enzyme (ACE) inhibitor, used for the treatment of hypertension and

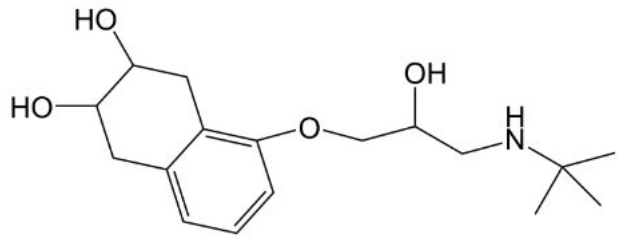

Fig. 6. Corgard (Nadolol) structure. It is a beta-blocker and used to treat hypertension

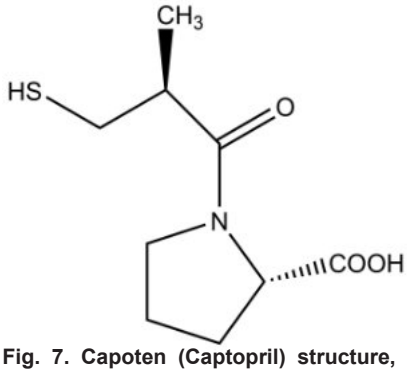

Fig. 7. Capoten (Captopril) structure, an ACE inhibitor

some types of congestive heart failure. Their combined sales in the following years were in excess of US$2 billion p.a. His job was also to maintain production standards and trouble-shoot all SQUIBB's USA manufactured drugs. He was the recipient of several substantial bonus awards from E.R. Squibb & Sons in recognition of excellence in research and development and manufacturing. He continued to publish scientific papers[6] and found time to complete an MBA.

Manufacture of the artificial sweetener, sucralose

From 1980 to 1987, Clayton was director of process development for Johnson and Johnson, New Jersey, USA and Dublin, Ireland. He was responsible for all process optimisation of new food products, including the successful manufacture of the artificial sweetener, sucralose. In 1976, Leslie Hough, Shashikani Phadnis and Riaz Khan[7] at Queen Elizabeth College, London, working in conjunction with the British Tate and Lyle sugar company, synthesised a trichloro-derivative of sucrose (Fig. 8), which was to become known as sucralose (Splenda). Phadnis was told to "test" the chlorinated sugar. Phadnis thought Hough asked him to "taste" it, so he did and discovered it was intensely sweet,[8] being 400 to 600 times sweeter than sucrose (table sugar)! It is probably the most successful of all artificial sweeteners because it has a clean sugar-like taste and is stable under most food processing conditions. Khan was unable to convert the synthesis to an industrial process and nor could anyone at Tate and Lyle so they sold the patent to the huge American drug company Johnson & Johnson, whose people also failed to commercialise the process. Clayton took up this challenge, which had defeated some of the most experienced industrial chemists in the world, and he succeeded. Johnson & Johnson management were delighted (sucralose sales were worth US$3.9 billion in 2018) and rewarded Bennett in 1986 with their first "Entrepreneurial Award" in recognition of "highest achievements and outstanding service". This award was open to all their 80,000 employees and included a generous monetary reward. By 1987 he was in such demand that he was crossing the Atlantic almost once a week and was a frequent flyer on the Concorde.

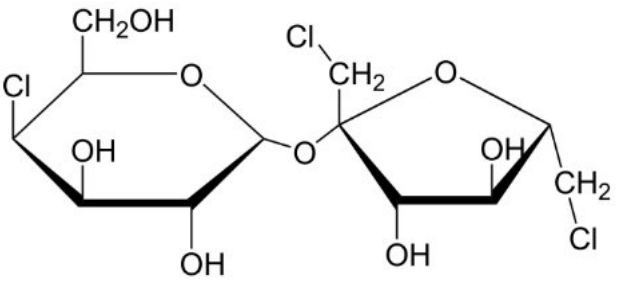

Fig. 8. Sucralose (1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside), a non-nutritive sweetener

Pharmaceuticals

Clayton was Corporate Vice President for Alliance Pharmaceutical Co., California from 1987 to 1990, overseeing the manufacture of sterile pharmaceutical products which included design and construction of facilities and pilot plant operations. Clayton met Mary O'Brien, a nurse, while working in Dublin and they married in 1987 and had three children, Brodie, Emilie and Harry.

From 1990 to 1991, Clayton worked at Kinerton Ltd, Dublin, a subsidiary of the French multinational, Ipsen International. As General Manager, he was responsible for the production and development of peptide active pharmaceutical ingredients (APIs) for two key products, Somatuline (Lanreotide), a cyclic octapeptide and Decapeptyl (Triptorelin), a decapeptide. Both drugs are used in cancer therapy including prostate cancer.

Irish entrepreneur

From 1991 to 1998, Clayton was Executive Chairman of Claymon Labs, Dublin, a clinical lab specialising in analysis of biological specimens. Forbairt (Enterprise Ireland) promoted and supported entrepreneurship, particularly indigenous enterprise. At that time in Ireland there were no clinical labs operating to good laboratory practice (GLP) or to any other internationally recognised quality standards. Companies were sending health screen samples to the UK for analysis to ensure

that the results were beyond reproach. Claymon Labs became the first medical laboratory to receive accreditation by the Irish National Accreditation Board. In 1998 he was nominated for "Entrepreneur of the Year for Ireland" by Forbairt. During this time he gave lectures and published articles on drug abuse.[9]

As well as spending most of his career in the USA and Ireland he was a consultant in Bahrain on food products for the Ministry of Science and Technology and in Jordan on pharmaceuticals and health care products for ACTIMA (Pan-Arab Pharmaceuticals).

Fig. 9. Clayton Bennett aged 70

Bennetts of Mangawhai chocolates

In 1998 Mary and Clayton and their three children came back to NZ and settled in Mangawhai, a small community next to the surging Pacific Ocean. They started making fine chocolates calling their business *Bennetts of Mangawhai*. With Clayton and Mary's experience of setting up and running businesses and Clayton's experience as an industrial chemist, they were bound to succeed. They used only authentic fillings, such as boysenberry and feijoa, with the best Belgian coverture. The company continues to this day to make some of New Zealand's finest chocolates.

Clayton Bennett (Fig. 9) was diagnosed with pancreatic cancer and was treated at The Cancer Research Centre of Marseille by some of France's finest oncologists. He died in France on Bastille Day, 2012, as the rockets burst overhead. One of the best industrial chemists in the world. New Zealand's finest chocolatier. His steadfast determination to overcome any challenge, his modesty and good humour continue to inspire all who knew him.

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A meeting report on the first nucleic acid chemical biology workshop in New Zealand

Vyacheslav V. Filichev,* Tracy K. Hale, Elena Harjes and Geoffrey B. Jameson

School of Fundamental Sciences, Massey University, Palmerston North and Maurice Wilkins Centre for Molecular Biodiscovery, Auckland

Email: v.filichev@massey.ac.nz

Keywords: *DNA, RNA, enzyme, chemical biology*

The first nucleic acid chemical biology workshop in New Zealand took place on 10 March 2020 in the iconic Sir Geoffrey Peren Building on the Manawatū campus of Massey University in Palmerston North. More than 80 participants from various New Zealand universities working on different aspects of nucleic acids attended the workshop. The diversity in disciplines was reflected in the talks presented which spanned from biophysics, physical chemistry and organic chemistry to protein biochemistry, cell biology and genetics. It was pleasing to see that 2/3 of the audience were post-graduate students who were exposed to various aspects of nucleic acid chemical biology on that day.

After morning tea, Paul Plieger, Head of the School of Fundamental Sciences at Massey University, welcomed participants to the workshop and wished everyone a productive day. The morning session was devoted to *Biophysical analysis of nucleic acids*. Naoki Sugimoto (Konan University, Kobe, Japan) introduced the audience to the world of DNA beyond the classical Watson-Crick model. He illustrated how molecular crowding conditions destabilised classical duplexes but stabilised non-canonical structures, such as G-quadruplexes (G4s), triplexes and i-motifs.[1] Naoki showed that G4-formation affected the rate of transcription[2] as well as protein folding (pausing on G4-RNA allowed proper protein folding). His work suggested that G4-DNA formation was influenced by the level of K^+ in cancer cells.[3] He also showed that a short G-tract having a pyrene residue tethered to DNA was able to restore formation and function of G4-DNA bearing one oxidised 2′-deoxyguanosine.[4] By using microinjection of a fluorescently labelled G4-forming oligonucleotide into the cell, he illustrated that various organelles had different microenvironments and that the nucleolus is very different from the rest of the nucleus.[5] Naoki showed that similar DNA sequences with similar GC content but different nearest neighbour distributions have different thermodynamic parameters.[6] Finally, Naoki concluded that the "Watson-Crick world is not enough".[7]

Geoffrey B. Jameson (Massey University, Palmerston North) presented several scenarios of the origin of life followed by a discussion of chemical stability of cytosine and cytidine at high-temperature and high-pressure, conditions found next to black-smokers deep in the ocean.[8] Geoffrey also showed that a cytosine (C)-rich tract of DNA that folds into a so-called i-motif is less thermally stable as pressure is increased, provided that pH of the solution is corrected for the effects of pressure.[9]

Wanting Jiao (Victoria University, Wellington) described computational characterisation of 5′-methyladenosine nucleosidase (MTAN), which catalyses the hydrolysis of the *N*-ribosidic bond of a variety of adenosine-containing metabolites. Wanting used computational tools to study the elementary steps of this reaction in MTAN from *Helicobacter pylori* and *Escherichi coli*. Quantum mechanics (QM) was used to determine the position of atoms involved in the chemical reaction at the active site of the enzyme, while molecular mechanics (MM) was applied to the rest of the complex resulting in the calculation of the energy landscape for the entire reaction. The dissociating glycosidic bond was slightly longer in the transition state calculated for *Helicobacter pylori* than for *E.coli* (2.4 vs 2.0 Å) and other distances between atoms were similar. Interestingly, when crystal structures of transition state analogues of these enzymes were overlaid with the calcu-

lated structures, the position of atoms in the structures matched those calculated. She also found that Asp involved in protonation of the purinic nucleobase changes its configuration upon substrate binding and accepts H^+ from external water, suggesting H^+ shuttling in the environment next to the active site.

Elena Harjes (Massey University, Palmerston North) presented the *method of small changes* that compares pairwise the 2D ^{15}N-^{1}H nuclear magnetic resonance spectra of APOBEC3A protein in the presence of slightly different DNA substrates.[10] She used this methodology to reveal that single-stranded DNA adopts an unusual U-shape upon binding to DNA-mutating APOBEC3A enzyme. Later on, Vyacheslav V. Filichev (Massey University, Palmerston North) demonstrated how Cu(I)-catalysed azide-alkyne cycloaddition was applied to lock flexible single-stranded DNA into the unusual U-shape that led to creation of the first nanomolar inhibitor of APOBEC3 enzymes.

Ruby J. Roach (Massey University, Palmerston North) presented her work on interactions of heterochromatin protein 1α (HP1α) with RNA and DNA G4s. She showed that HP1α binds with a faster association rate to RNA and DNA G4s of parallel topology.[11] In contrast, antiparallel G4s bind slowly to HP1α or not at all. Ruby presented a model of how TELomeric Repeat-containing RNA (TERRA) transcribed from the telomere can lead to enrichment of HP1α at telomeres to maintain heterochromatin, the transcriptionally silent part of the eukaryotic genome.

After lunch, Rakesh N. Veedu (Murdoch University, Perth, Australia) opened the second session devoted to *Nucleic acids and their components as drugs*. In the first part of his talk, Rakesh described antisense oligonucleotides approved by the Food and Drug Administration (FDA, USA) in the last 20 years. In particular, he explained the mode of action of exon-skipping antisense oligonucleotides targeting Duchene muscular dystrophy, a genetic disease that affects boys with approximately 300,000 cases reported only in India. In the second part of his talk he showed recent results obtained in collaboration with Marvin Caruthers (University of Colorado, Boulder, USA) using thiomorpholine oligonucleotides in exon skipping. In the last part, Rakesh described how conjugation of vitamin E to the 5'-end of the oligonucleotide was used to enhance delivery of oligonucleotides into the cells. The efficiency of such conjugates for exon skipping that occurs in the nucleus of the cell was improved by using a dithiol linker between vitamin E and the oligonucleotide. The dithiol linker is reduced after delivery of the conjugate into the cytosol, releasing vitamin E, which allowed further transport of the antisense oligonucleotide into the nucleus. Finally, Rakesh explained evolution of aptamers towards a particular target and presented interesting results on muscle-targeting aptamers.

International speakers: Rakesh N. Veedu (left), Tracy M. Bryan (centre), Naoki Sugimoto (right)

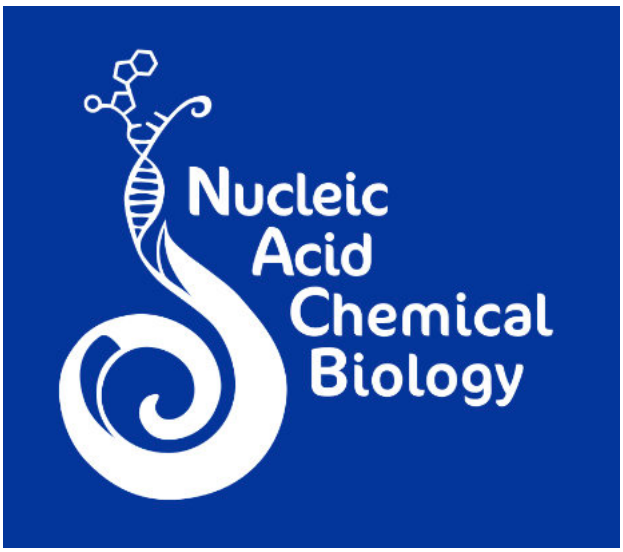
Gavin Painter (Victoria University of Wellington) described how immune response to cancer can be restored. He particularly focussed on treatment vaccines and immune system modulators. Gavin showed how DNA containing the CpG motif is recognised by toll-like receptor 9 (TLR9), which induces production of cytokines necessary for the innate immunity and subsequent adaptive immunity. He also showed that a glycolipid-peptide conjugate vaccine improved T cell responses.[12] T cells can kill tu-

mour cells. He then showed on-going work devoted to development of improved vaccines that comprise a combination of CpG oligonucleotides with glycolipid-peptide conjugates. Preliminary results indicate synergism of NKT cell adjuvanted peptide vaccines.

Nucleos(t)ides are used by cancer cells, viruses and parasites as DNA/RNA building blocks. In this regard, chemically modified nucleosides and nucleotides can be extremely valuable in the design of novel anticancer, antiviral and antibacterial drugs. More than 60% of all antiviral drugs on the market are based on modified nucleos(t)ides.

Peter Tyler (Victoria University of Wellington) presented results from a recently resurrected project by the National Institutes of Health (USA) devoted to the design of transition-state analogue inhibitors of protozoan parasite enzymes in collaboration with Vern Schramm (Albert Einstein College of Medicine, New York, USA) and Thomas Meek (Texas A&M Uni, Texas, USA). Malaria kills a child every 40 s and is caused by a protozoan parasite (*Plasmodium falciparum*), which is spread by mosquitos. *T. cruzi* is the cause of Chagas Disease in Central and South America and is transmitted by Triatomine bug. *T. brucei gambiense* and *T. brucei rhodosiense* is the cause of African Sleeping Sickness and is transmitted by the Tsetse fly. Protozoan parasites do not make their own purines, so by blocking one enzyme one can block all salvage of purines in protozoans. In the past, this group at the Ferrier Research Institute developed four generations of human purine nucleoside phosphorylase inhibitors based on enzymatic transition-state theory. This has already led to one drug, Mundesine, approved in Japan for peripheral T-cell lymphoma. Another compound under the name Ulodesine went successfully through phase IIb clinical trials for gout. Peter described the rationale behind the design of inhibitors against protozoan parasite enzymes, presented trends for inhibitor affinities and challenges in the design of pro-drugs, which are required for the delivery of active compounds inside the cell.

The theme of chemically modified nucleosides was continued in the talk by Lawrence Harris (Victoria University of Wellington) who explained an action of antiviral nucleosides as terminators of a growing viral DNA chain. Lawrence also explained a pro-tide technology pioneered by L. McGuigan[13] and how nucleotide pro-drugs are enzymatically converted to free 5′-monophosphates inside of the cell. He presented on-going work on the design and synthesis of a pro-drug for the naturally occurring 3′-deoxy-3′,4′-didehydro-cytidine triphosphate that acts as a chain terminator for the RNA-dependent RNA polymerases from multiple viruses.[14]



Logo of the nucleic acid chemical biology workshop designed by Raoul Solomon

Anthony Poole and his PhD student, Alannah Rickerby (both University of Auckland), are interested in evolutionary aspects of the transition from the RNA to the DNA genome.[15] It was suggested that DNA building blocks may have first been synthesised via a chemically simple route – the reversal of the deoxyriboaldolase (DERA) step in the current deoxyribonucleotide salvage pathway.[16] However, levels of acetaldehyde required for such synthesis are lethal to live cells. Anthony demonstrated the possibility of replacing the current ribonucleotide reduction (RNR) pathway with DERA in cells, but it was recognised that it is impossible to synthesise 2′-deoxycytidine without RNR. Alannah wonders if a U-DNA world existed in which 2′-deoxyuridine was used in DNA prior to evolution of thymidine.[17] She focused on the creation of U-DNA cells and demonstrated that strains have been evolved that do not require supplementation with thymidine.

Jennifer Soundy from AuramerBio (Wellington, New Zealand) described evolution of DNA and RNA aptamers using systematic evolution of ligands by exponential enrichment (SELEX) and compared their properties to antibodies. In particular, it was possible to raise aptamers against toxic molecules, where antibodies cannot be developed. She explained develop-

Some organisers (on the left) and overseas speakers (on the right) in front of the Wharerata function centre. From left to right: Ruby Roach, Vyacheslav V. Filichev with Elias and Mila, Tracy K. Hale, Elena Harjes, Naoki Sugimoto, Tracy M. Bryan and Rakesh N. Veedu.

ment of an electrochemical sensor based on chemically modified aptamers for portable detection of illicit drugs. Finally, Jennifer mentioned that AuramerBio performs custom service projects for development of "best in class aptamers" in a very short timeframe and welcomed scientists to approach them.

The last session was devoted to *Molecular and cell biology of nucleic acids*. The session started with the talk by Tracy M. Bryan (Children's Medical Research Institute, Sydney, Australia) explaining structures at the 3'-ends of telomeres, possible formation and topologies of telomeric G4s and extension of telomeres by telomerase. She mentioned that telomerase can extend parallel G4s[18] and demonstrated using single-molecule FRET that telomerase binds to and fully unfolds inter- as well as intramolecular parallel G4s. This is the result of invasion of the telomerase RNA template into G4s, followed by templated extension of telomeric DNA and telomerase translocation. Moreover, telomerase has the ability to dislodge small-molecule ligands that usually stabilise G4s. Tracy concluded that the data suggest that parallel G4s can form at telomeres *in vivo* and are not a barrier to telomerase extension even in the presence of G4 stabilising ligands.

Paul Teesdale-Spittle (Victoria University of Wellington) presented Pateamine A, a natural product isolated from the sponge *Mycale hentscheli* exhibiting anticancer and antiviral properties. It is a potent inhibitor of eukaryotic translation stimulated by eukaryotic Initiation Factor 4A (eIF4A). eIF4A resolves secondary structure in the 5'-UTR of mRNA, allowing assembly of the pre-initiation complex.[19] However, sub-inhibitory concentrations of Pateamine A can be beneficial, for example in control of cachexia,[20] a muscle-wasting syndrome, one of the major causes of death in cancer, AIDS and sepsis patients. Using proteome analysis Paul demonstrated that up-regulation of proteins occurs as a direct response of cells to the suppression of translation by Pateamine A. On the other hand, down-regulated proteins reflect weak association with protein production, mRNA catabolism and presence of polypurine motifs in mRNA.

Tayaza Fadason (University of Auckland) presented results of his recently defended PhD on *Predicting gene targets of disease-associated variants in the 3D genome*. His work is driven by the realisation that almost 90% of single-nucleotide polymorphisms (SNPs), which are a major source of shared heritability of polygenic disorders, are not present within coding regions of the genome.[21] He explained the methodology of his investigation in which the interactions between different regions of chromatin are captured by DNA cross-linking with formaldehyde, followed by DNA digestion, biotinylation of sticky ends, ligation of biotinylated ends, DNA purification and sequencing. Tayaza demonstrated that disease SNPs regulate gene expression, but most of such SNP-gene regulatory relationships is missed due to assumed proximity of SNP and genes. This approach allows understanding of the common genetic aetiology of multimorbid traits,[22] and asthma.

Adele Williamson (Waikato University, Hamilton) explained the mode of action of unique DNA ligases that are targeted to the bacterial periplasm and are postulated to play a role in DNA uptake. Adele presented this minimised type of DNA ligases, Lig E, that lacks

any domains or loops appending the catalytic core and therefore, might use a different mechanism to bind its DNA substrate. Indeed, in the structure of a Lig E type DNA ligase with a nicked DNA-adenylate reaction intermediate, the DNA is only partially encircled, the nicked duplex is bent and the terminal nucleotides adopt A- and not classical B-form.[23] Conserved as well as unique DNA binding interactions with Lig E were discussed in relation to the evolution of DNA ligases, and a scenario for the involvement of these enzymes in antimicrobial resistance of bacterial pathogens was outlined.

Scientific discussions continued during dinner served at the Wharerata function centre located at Massey University.

Acknowledgements

The workshop organisers would like to thank the Manawatu branch of NZIC, the New Zealand section of the Royal Society of Chemistry, the Maurice Wilkins Centre for Molecular Biodiscovery and the School of Fundamental Sciences (SFS) at Massey University for their support. We would also like to thank our administrative support at SFS provided by Justine Hearfield, Ann Truter, Cynthia Cresswell and Fiona Richmond. We are grateful to Raoul Solomon for the design of the logo for our workshop.

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Memento vivere!
Remember you have to live!

Michael Moore, a giant, much loved figure in the Australasian chemistry community, passed away on May 22 this year. Michael was born on 30 December 1971 and spent his formative years in Christchurch, where he attended Christ's College.

He completed a BSc(Hons) in chemistry at the University of Canterbury (1990-1993) and then undertook research on serine protease inhibitors for his PhD degree under the supervision of Professor Andrew Abell (1994-1998). He defended a thesis titled, "The design and synthesis of mechanism-based inhibitors of serine proteases" with the epigraph (in Latin, of course) Res ipsa loquitur, "the thing speaks for itself."

He followed his PhD with postdoctoral stays at Trinity University in San Antonio and Cancer Research UK at University College, London. Here he published a very well cited article in the *Journal of Medicinal Chemistry* on "Trisubstituted acridines as G-quadruplex telomere targeting agents." He subsequently returned Down Under in 2005 to continue research at Fluorotechnics and Microbiogen in Sydney, which showcased the diversity of his talents. A scholarly article on "Techno-economic implications of improved high gravity corn mash fermentation" was one of his many outputs. He then moved into the legal profession as a patent attorney and most recently practised at FB Rice.

Affectionately known as Burger, Michael had lasting impact on all those fortunate enough to enter his orbit. As a PhD student he was perennially indebted to the Cookie Time supply, which spoke to both the typical diet of a PhD student and an irreverent view of formalities. Michael saw the UC departmental touch rugby team christened 'Dean Stark Naked.' On the field, his talents as a sportsman were evident and he showed good pace for a big man. This included cleaning up the competition over 22 metres on Lancaster Park when he rounded up a bunch of chemistry students to help his dad, Brian, lay the first drop-in cricket pitch.
The NZIC conference in Dunedin in 1996 provided many highlights. The long drive south has hypnotised many a Cantabrian, including Burger, who was so influenced that a late night incident involving lost keys and a series of unfortunate miscommunications culminated in him spending the night as a spontaneous visitor in a nearby scarfie flat. This was just one entry in a long rap sheet of delightful peccadillos. Another occurred on his first night in San Antonio, when he presumed a female police officer would search him for a "concealed weapon".

Forever quirky, engaging and humorous, Michael was always full of warmth and good stories. He was great at keeping in touch. The conversations would pick up seamlessly from where they last left off, whether they be about the kids' latest fad or shifts in the research landscape. Burger was a master of the unfinished phrase. No need for more words when the meaning was already clear. It's heartbreaking that the next time that the phone rings it won't be Burger on the line to reignite the chat.

In 2005, Michael married Louise, whom he had met in London. Their first date had been to a quantum physics seminar. God clearly does not play dice. Although their relationship encountered difficulties of late, he was always deeply cared about by Louise and her extended family. They have two beautiful kids, Giselle and Alexander, who will surely connect with Michael's Kiwi heritage via his much-loved parents, his sister and brother and their partners, and his nephews, nieces and community of friends.

Michael was a good mate and his own, unconventional man. He was fiercely intelligent with inimitable wit, and he had steadfast loyalties. He will be missed tremendously.

In the immortal words of Paul Kelly and as sung at Michael's funeral in Sydney:

Fear not death's dark shadow
I will meet you in the middle of the air.

Footnote: Because no-one in New Zealand could attend Michael's funeral in Sydney in person, a tribute in Christchurch is being planned. If ever a man deserved send-off with lots of laughs and lots of bonhomie, it is Burger.

Contributed by Shane Telfer

Michael JB Moore PhD (Cant.), 1971 - 2020

Something old, something new: foldamers as catalysts

Suraj Patel* and Gareth J. Rowlands

Department of Chemistry, School of Fundamental Sciences, Massey University, Palmerston North

Email: S.Patel2@massey.ac.nz

Keywords: *foldamers, biopolymers, secondary structure, hydrogen bonding*

Introduction

Nature is able to form the foundations of life by linking together small, yet versatile, building blocks to produce functional biopolymers. With the aid of non-covalent interactions these biopolymers form architectures that allow them to function as information carriers,[1] catalysts[2] or structural materials[3] amongst many other roles. Biopolymers can be split into three key categories based on their monomeric units: polynucleotides, polypeptides and polysaccharides. The building blocks used in the primary sequence play a crucial role in determining the structure formed, which will influence the function of the molecule. Due to limitations in biologically available building blocks, these classes are generally confined to either an α-helix or β-sheet structure. But are chemists with a limitless choice of building blocks able to improve on nature and create new structures with alternative functions? Researchers in the field of foldamers are trying to answer this question.

Foldamers

A foldamer is a synthetic oligomer, i.e. a molecule comprising a number of repeating units, that self-organises into a reoccurring secondary structure in solution.[4] As such, foldamers mimic biopolymers such as proteins and polysaccharides. They can vary in size and shape, which results in them having different properties. Foldamers have been used in cell penetration,[5] interactions with the phospholipid bilayer and nucleic acids,[6,7] catalysis,[8] and for medical purposes.[9] The shape of the foldamer is driven by various non-covalent interactions between the residues in the chain, and this can give rise to a variety of architectures (Fig. 1).[4]

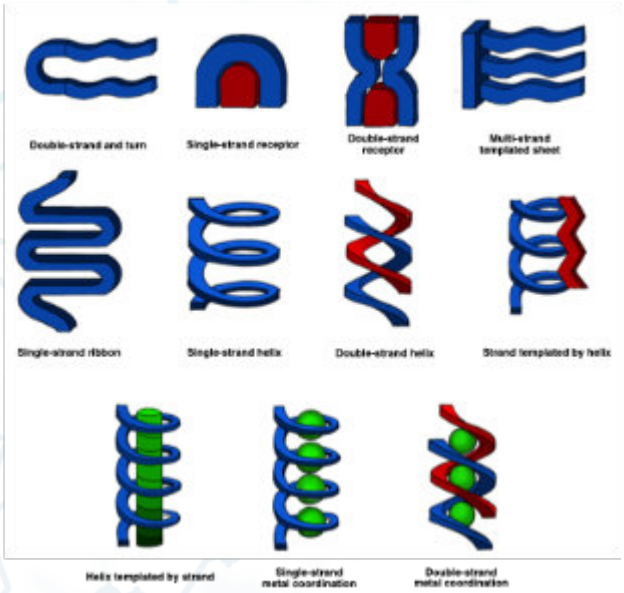

Fig. 1. Various foldamer structures that have been reported in the literature[4] (adapted with permission)

The goal of foldamer research is not to recreate natural biopolymers, since nature has already perfected these structures, but to be inspired by the same principles to form new structures with new properties not found in nature. The remarkable diversity of both large and compact structures reported in the literature demonstrates that foldamers have the ability to form architectures outside of the typical α-helices and β-sheets found in nature.

Initial research into what are now known as foldamers commenced over 60 years ago. This article focusses on key interactions driving the formation of foldamers, notable examples of foldamers, the pioneering work already completed, and future goals for the field. The interested reader is directed to more comprehensive reviews for more detail.[4,10–13] Foldamers can be divided into aliphatic and aromatic foldamers, determined by the presence or absence of aromaticity within the backbone of the foldamer. Aliphatic foldamers have

been a key focus for the majority of studies, while aromatic foldamers have not been explored as thoroughly

Intermolecular interactions driving foldamer formation

Hydrogen bonding

As with the secondary structure of proteins, hydrogen bonding between repeating units is a key interaction. In supramolecular chemistry, hydrogen bonding is one of the most commonly exploited driving forces in the formation of ordered structures.[14] A variety of foldamers have been reported in the literature, highlighting the flexibility of hydrogen bonding in the primary structure of a foldamer.[14,15] This interaction will be highlighted throughout this article, demonstrating the importance it has in the formation of new architectures.

Solvophobic effects

Another important non-covalent force involving the formation of supramolecular structure is the solvophobic effect.[16] This effect is responsible for the association of poorly solvated molecular surfaces but unlike hydrogen bonding and other specific interactions, solvophobic effects rely on the collective interactions among solvents and solutes and not specific functional groups.[17] Solvent effects break into two core effects: direct and indirect. In the direct effect, solvents compete for the supramolecular reactive sites and impede folding, which is often why hydrogen-bonded supramolecular structures break down in water or dimethyl sulfoxide.[18] The indirect effect is illustrated by the hydrophobic effect where the driving force for association of non-polar groups in aqueous solution is from the unique properties of water (size and hydrogen bonding) and not the dispersive interactions among association solute molecules.[17,18] This has led to many known interactions and processes including protein folding,[19] protein-protein interactions,[19] membrane formation,[15] ligand-receptor binding,[20] and countless other processes.

π-π interactions

In aromatic foldamers, π-π interactions play a large role in creating the secondary structure. Such interactions are formed by the electrostatic attraction between two aromatic rings.[12] Fig. 2 shows the π cloud is a region of high electron density that sits above and below the plane of the benzene ring, while the C—H bonds are polarised towards the carbon atoms.[21] The balance of repulsive and attractive forces determines the structural conformation the two benzene rings will adopt.[21] Two main possible motifs are used in forming aromatic foldamers, i.e. face-to-face and offset face-to-face (Fig. 2).[12,21] The surface area overlap is maximised when a face-to-face conformation is adopted.[21] However, this is a high energy arrangement due to the repulsive electrostatic forces caused by the π electron clouds being in close proximity to one another resulting in the offset face-to-face.[21]

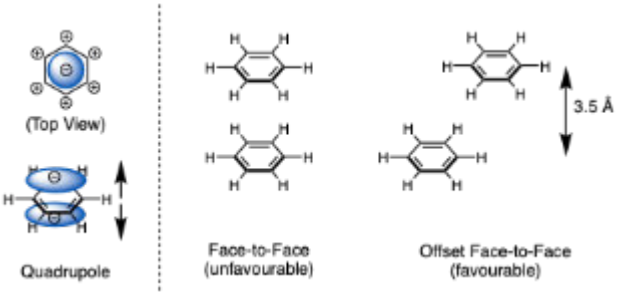

Fig. 2. Electronic properties of an aromatic ring and an illustration of π-π structural conformations

Examples of foldamers and their applications

Macrocyclisation induced by catalytic foldamer

One goal of foldamer chemistry is to synthesise structures that have a function not seen in natural systems. A means of achieving this is by combining two or more types of unnatural amino acids; one set gives the molecule structure while the other set adds functionality.[22] This extends the scope of available transformations in comparison to those seen in nature. Gellman *et al*. have produced a heptapeptide foldamer which catalyses the macrocyclisation of various compounds, including two natural products, robustol and nostocyclyne A.[23] The formation of macrocycles is an entropically unfavourable process and is considered a challenge for chemists.[23] This process is usually very specific and limits the broad applicability of macrocycle formation. A sequence of α and β amino acids was used to create a specific secondary structure, a helix.[22] This created a stable three-dimensional framework, from which reactive functionality could be positioned to allow a selective intramolecular aldol condensation reaction to occur.[23] Gellman *et al*. analysed multiple derivatives, altering the position of the two reactive functional groups and this influenced the efficiency of cyclisation.[23] The optimal sequence is shown in Fig. 3. This sequence was then compared to small-molecular catalysts which served as analogues to the active site of the foldamer and showed under the same

condition utilising the small-molecular catalysis results in no formation of the desired macrocycle.[23] This demonstrates the three-dimensional structure formed by the foldamer plays a crucial role in macrocyclisation. The foldamer was capable of synthesising macrocycles as large as 22 atoms, demonstrating foldamers can control the selectivity and reactivity through targeted design of substrates, which were previously limited to only enzymes.[23] This recent example demonstrates how the development of a new foldamer catalyst opens up the possibility of alternative transformations beyond the aldol reaction, enriching the general synthetic repertoire currently available to chemists.

Foldamers for biological cures

Huc *et al*. have developed aromatic foldamers containing phosphonate and carbonyl groups that mimic B-DNA both in the charged surface and solid-state structure, as determined by X-ray crystallography.[24] This type of foldamer has been reported to be a competitive inhibitor of DNA topoisomerase 1 (Top1) and human immunodeficiency virus integrase (HIV-1 IN).[25] The group synthesised a foldamer using Q^{Pho}, $^{m}Q^{Pho}$, and Q^{5Pho} building blocks. Altering the sequence of $^{m}Q^{Pho}$ and Q^{Pho} or Q^{5Pho} was shown to develop a helical structure with a ~35° minor groove twist.[24] The helical structure is a result of electrostatic repulsion and offset face-to-face orientation of the aromatic building blocks stabilised by hydrogen bonding, similar to the helical structure adopted by DNA (Fig. 4). Although initially designed to resemble DNA, the most remarkable properties are due to their differences. Overall, these alterations result in the formation of a more versatile sequence, while maintaining stability. A homogenic sequence of $(Q^{Pho})_8$ showed remarkable stability of the secondary structure in protic solvents. The helical structure was maintained even at 120°C in dimethyl sulfoxide, whereas DNA begins to denature at 60 °C.[24] The foldamers were found to be able to bind and inhibit several DNA-binding enzymes at a higher affinity than DNA itself. Mutation of a single amino acid had previously prevented DNA binding enzymes to inhibit HIV-IN.[25] However, $(^{m}Q^{Pho}Q^{Pho})_8$ was shown to inhibit HIV-IN, while $(^{m}Q^{Pho}Q^{5Pho})_8$ had lower binding affinity.[25] Camptothecin and raltegravir are considered the best inhibitors for

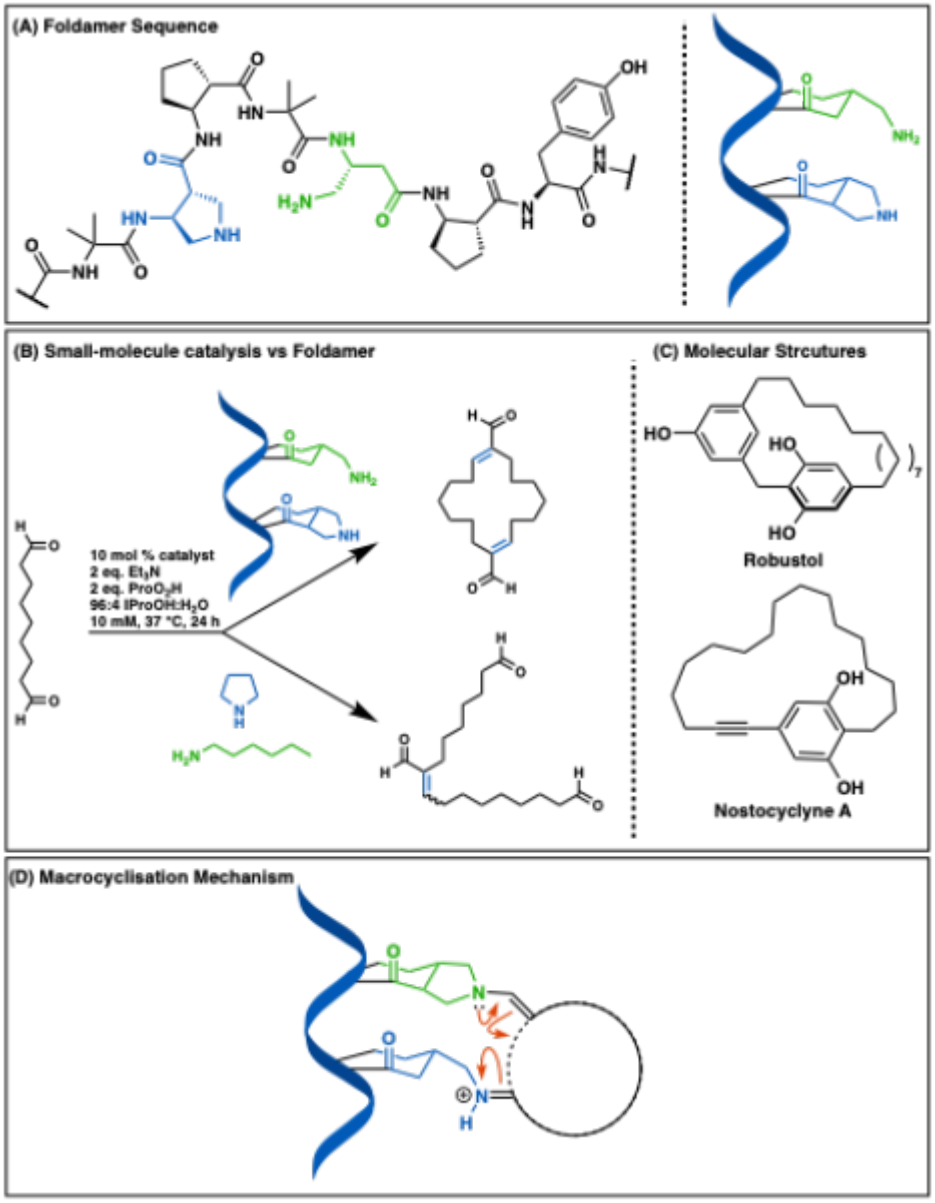

Fig. 3. (A) Molecular structure of the most effective foldamer sequence synthesised for macrocyclisation. (B) Reaction conditions for macrocyclisation comparing small-molecular catalysis vs synthesised foldamer. Utilisation of small-molecular does not result in macrocyclisation. (C) Molecular structure of the two natural products synthesised using foldamer sequence. (D) Macrocyclisation mechanism utilising the foldamer developed by Gellman et al.[23]

conformations

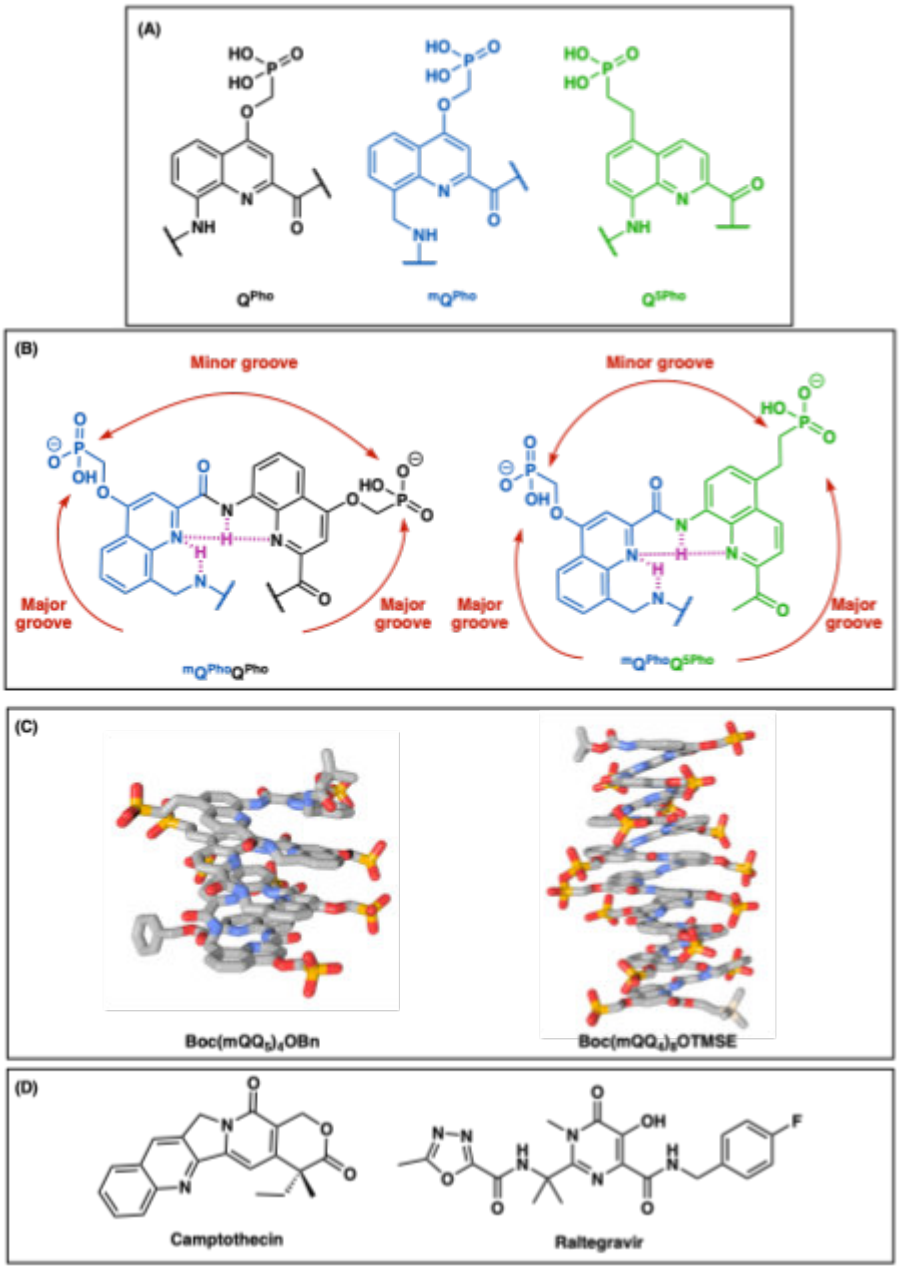

Fig. 4. (A) Building blocks used to mimic DNA synthesised by Huc et al.[24] (B) Foldamer heterogenic sequence synthesised for HIV-IN and Top-1 inhibition highlighting the major and minor groves. (C) X-ray structures of the two foldamer sequences synthesised and reported in the literature.[25] (D) Molecular structure of Camptothecin and Raltegravir, the two leading drugs currently used for HIV-IN and Top-1 binding.

Top1 and HIV-1 IN, respectively, and were shown to have a lower affinity than the designed foldamer, demonstrating the versatility of these compounds and their potential to improve on nature and current enzymatic options.[25]

Aliphatic foldamers

Peptidomimetic foldamers

The vast majority of foldamers are designed to mimic the structure of peptides and are known as peptidomimetic foldamers. There is considerable interest in the development of viable peptidomimetic foldamers to replace natural peptide substrates of enzymes or protein receptors.[26] There are three popular strategies for making such mimics. The first modifies the amino acid side chain. The second separates amine and acid functionality to give β and γ amino acids instead of the normal α. The third method changes the amide bond to form hydrazide and urea-based peptides, as shown in Fig. 5.[4] A range of these peptidomimetic foldamer structural lineages can been seen in Fig. 6.[4]

α-peptides

A variety of α-peptide backbone sequences, i.e. peptides made from α-amino acids, have been utilised in the synthesis of foldamers.[10,27] The most notable were produced by Zuckermann *et al*. who demonstrated peptoids are able to form stable helices despite lacking a hydrogen bonding network.[28] Peptoids (Fig. 5) are amino acids where the side chain is bonded to the nitrogen atom. Due to the absence of chirality at the α-carbon position, the helicity must be controlled utilising chiral branched side chains on the nitrogen substituent. Cis-trans isomerisation of tertiary amides governs the folding of these unique structures, forming helical structures from a range of building blocks.[28] An example of these foldamers was synthesised by the Zuckermann group and a water-soluble 36-mer oligopeptide was formed.[28] A sequence of (*S*)-*N*-(1-carboxyethyl)glycine (Nsce) and (*S*)-*N*-(1-phenylethyl)glycine (Nspe) were utilised in a $[NsceNsceNspe]_{12}$ sequence, adopting a stable right-handed 14-helix, which was further stabilised by cis-amide bonds and steric effects in the backbone structure.[10,28]

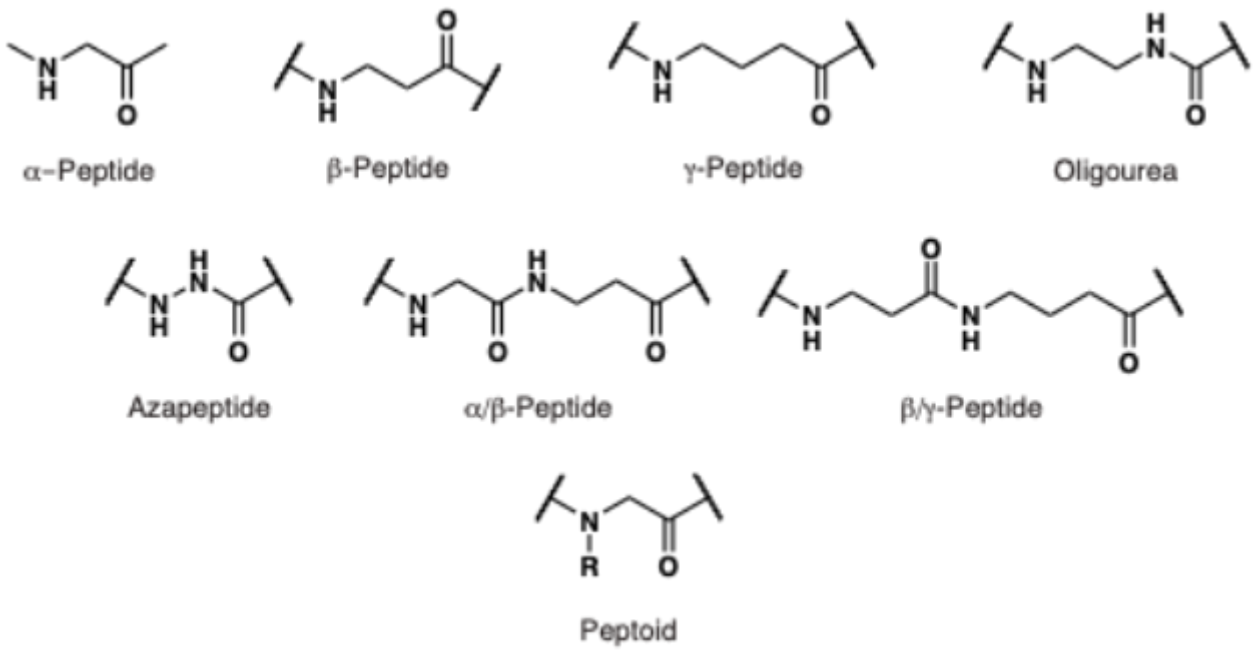

Fig. 5. Various peptidomimetic backbone sequences utilised in the literature

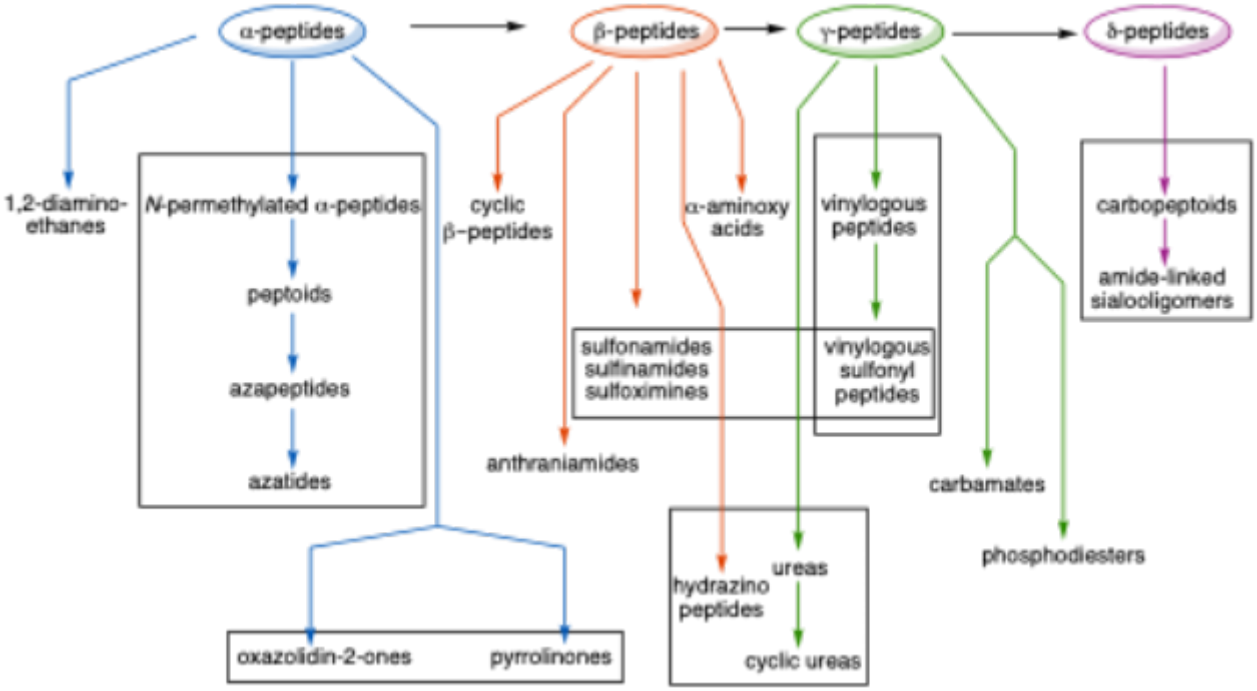

Fig. 6. The structural lineage of peptidomimetic foldamers[4] (adapted with permission)

Since then a variety of new structures have been formed producing different helical structures. A general peptoid backbone using a variety of different side groups can be seen in Fig. 7, highlighting the helical conformation the sequence adopts and the modularity of the Zuckermann sequence.[4] Similar foldamers were made by *N*,*N*′-linked oligoureas, oligopyrrolinones, oxazolidin-2-ones, azatides and azapeptides and all showed the formation of a 14-helix structure.[11] However, these foldamers were formed early in the development of this field and have been suspended due to the difficulties in functionalising them. This led to relatively low interest in their development due to the limited secondary structures possible to form as a result of the limited hydrogen bonding pattern of α-peptides. This highlights the importance of the hydrogen bonding in the backbone sequence for future aliphatic foldamers. Other intermolecular interactions are simply not strong enough alone to form secondary structures for aliphatic foldamers.

β-peptides

The use of β-peptide foldamers has led to a wide range of new architectures. Initially, research focused on de-

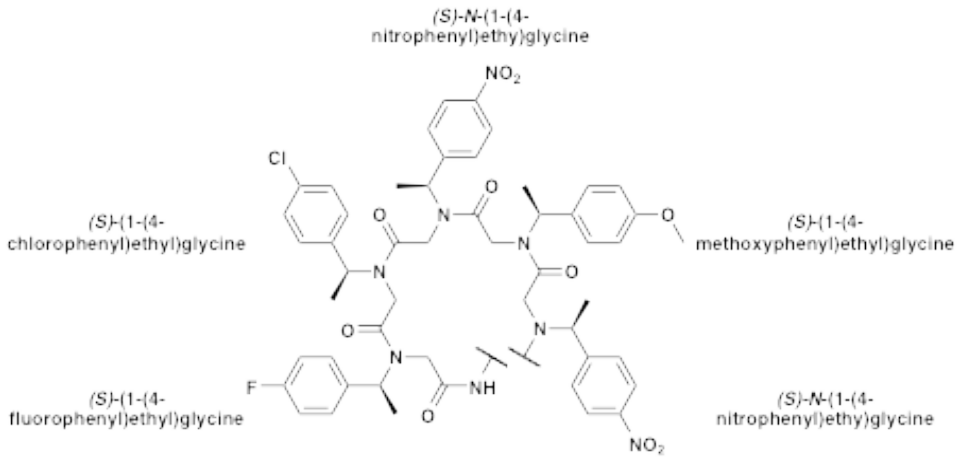

Fig. 7. Zuckerman et al. sequence[4] utilising a range of peptoids highlighting the versatility of the backbone sequence

termining how shifting the amino acid group one atom further away from the acid would alter the secondary structure.[29] One may expect the β-peptide to be entropically unfavoured to form a periodic secondary structure due to the additional conformational flexibility. However, by careful design of the monomer, it is possible to predispose the molecules to fold into a regular secondary structure. Studies on β-amino acid homopolymers have been ongoing for more than 50 years, with the first example of a helical structure reported by Kovacs *et al*. in 1965 based on a poly(β-L-aspartic acid) sequence.[30] This was followed by the synthesis of poly(β-L-glycine) which was shown to develop a helical structure through a gauche conformation, as shown in Fig. 8.[4] This gained much interest as the hydrogen bonding pattern stabilised the conformation making it more stable than the anti-conformation. This led to numerous studies on the helical arrangement of β-peptides through NMR and X-ray crystallography.[10] Fig. 9A illustrates the various hydrogen bonding arrangements for the formation of different helices. These hydrogen bonding patterns have been extensively studied in the literature and implemented into alternative β-peptides (Fig. 9B), continuing to be used in the design of new foldamers.

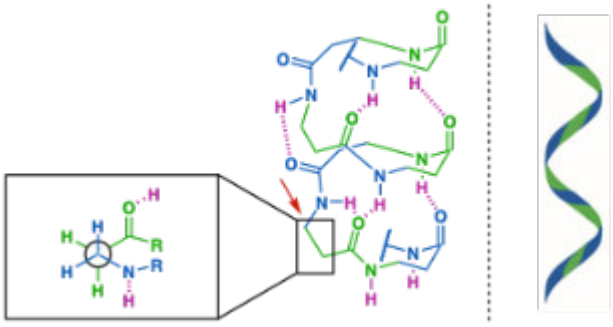

Fig. 8. Poly(β-L-glycine) sequence highlighting hydrogen bonding pattern as a result of the gauche-conformation adopted by the helical structure

Carbohydrate-based aliphatic foldamers

Synthesis of multiple sugar-based amino acids linked together was initially pursued and exploited due to the rational design of a β-turn mimic, as these compounds had the potential to replace dipeptides.[4,31,32] A variety of techniques have been reported to stabilise the formation of secondary structures to lower the entropic cost of the unfolded state using sugar-based foldamers.[32] Much like in nature, chemistry has developed some clever techniques to both drive and stabilise the formation of a secondary structure. Synthesis of efficient biomimetic drugs has been successfully achieved by subjecting compounds to macrocyclisation through disulfides, metal-mediated bridges, hydrogen bond surrogates, lactam rings or hydrocarbon stapling. These techniques have been adapted into the backbone sequence of oligosaccharide foldamers to force a particular helical structure.[32] The decreased flexibility of stapled glycols results in a lower entropic cost when binding, which in turn produces a higher affinity constant, as shown in Fig. 10.[32] Although there are countless examples of naturally occurring stapled biopolymers, there has been only moderate success for synthetic examples. The structural complexity of glycans leads to a bottleneck in the design of stapled glycomimetics, as conformational control is difficult to achieve. Also, the stapled structure adopts a conformation that is difficult to predict during design.

Aromatic foldamers

An alternative strategy to synthesise new architectures is to form structures built around aromatic building blocks. Amide linkages are still used to promote hydrogen bonding but other non-covalent interactions play an important role.[33] Since the 1990s, a range of aromatic foldamers with unique architectures have been constructed.[12,24,33,34] One may intuitively presume the backbone sequence of a foldamer is unable to use constrained compounds like aromatic rings but the rigid backbone allows for a predictable scaffold to form. Also, isomeric structures can be readily created by

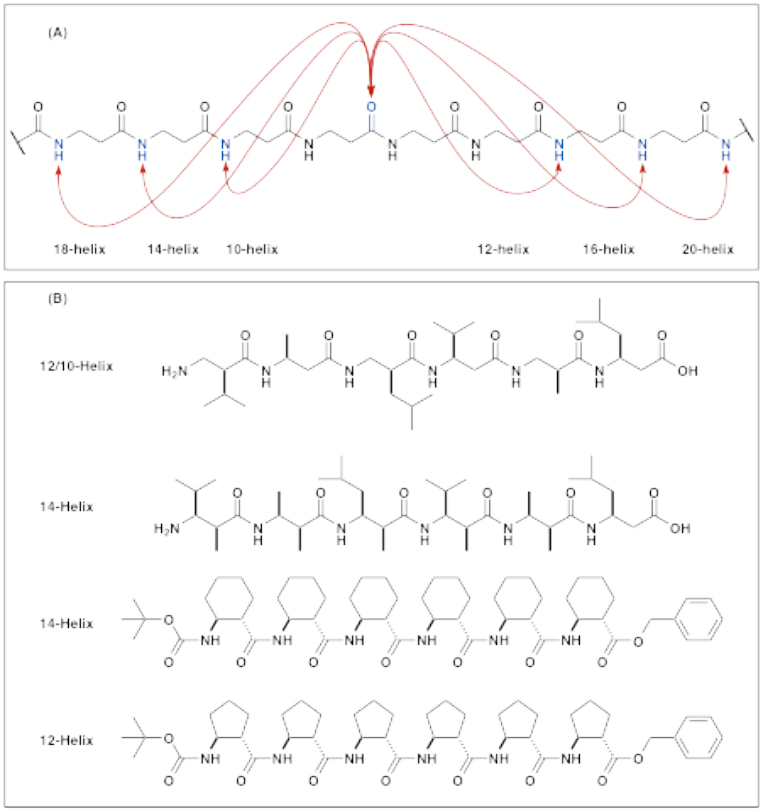

Fig. 9. (A) Hydrogen bonding pattern for a β-peptide sequence resulting in alternative helixes, with (B) β-peptide examples and the helix length associated with each peptide

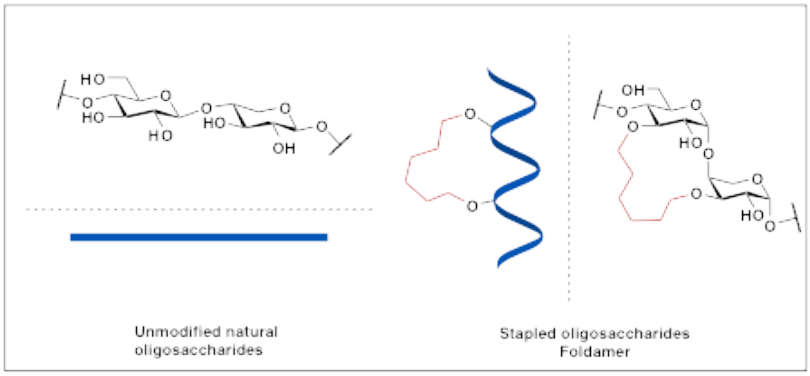

Fig. 10. Molecular structure of an unmodified natural oligosaccharide highlighting its natural linear structure compared to a synthetic stapled derivative forcing the desired helical conformation

changing the substitution pattern of the aromatic ring, each giving a different secondary structure. Alternatively, different aromatic rings (benzene, naphthalene, anthracene, pyridine etc.) change the backbone meaning a variety of structures can be accessed.

Water soluble aromatically stacked foldamer

While aromatic foldamers permit greater control and predictability of secondary structure this comes at a cost. The lipophilic nature of aromatic rings reduces water solubility and makes it more challenging to prepare biologically active constructs. Chemists have risen to the challenge with a number of innovative solutions. Iverson *et al.* synthesised a water soluble aromatic foldamer called an "aedamer".[35] This involved alternating 1,5-dialkoxynaphthalene (DAN) and 1,4,5,8-naphthalenetetracarboxylic acid diimide (NDI) linked by amino acids (Fig. 11). The success of this system comes from the strong interactions between the electron rich DAN core or donor and the electron deficient NDI core or acceptor. The complementary groups allow for charge-transfer absorbance from the HOMO of the donor excited to the LUMO of the acceptor, stabilising a face-centered geometry of the aromatic rings.[35] This system is now an archetypal foldamer, due to its π-π interactions and electrostatic complementarity, and this motif is now a common design feature in new foldamers as it promotes secondary structure formation. Two oligo sequences were designed with aromatic units that are linked by aspartic acid residues resulting in water solubility.[35] The use of aspartic acid residues is chosen to mimic DNA, where the negative charges result in non-specific oligomer aggregation, driving the DAN-NDI interaction and showing a 1:1 binding stoichiometry with the ability to discriminate between the two strands.[35]

Moore *et al.* showed *m*-phenylene ethynylene will fold into a dynamic helical conformation when dissolved in polar solvents like CH_3CN.[36] Solvophobic interactions cause the organisation of the structure in less polar solvents, such as $CHCl_3$, and the helices unravel into a random coil.[36] The foldamer is photoresponsive and irradiation causes the helix to switch directions, a characteristic which has been rarely cited.[36] Modelling shows the diameter of a foldamer of 12 units has an interval cavity of 8.7 Å. This cavity has been shown to host small solvent molecules that are readily displaced in a mixture of 40% water and CH_3CN.[36] Hydrophobic molecules with binding energies in the range of 4-5 kcal/mol are able to bind within the cavity. Due to the larger size of oligomers built from 22 monomers, it is able to constrain rod-like guest such as cis-(2*S*,5*S*)-2,5-dimethyl-*N*,*N*'-diphenylpiperazine, as shown in Fig. 12.[36] The host-guest interaction is driven by burial of

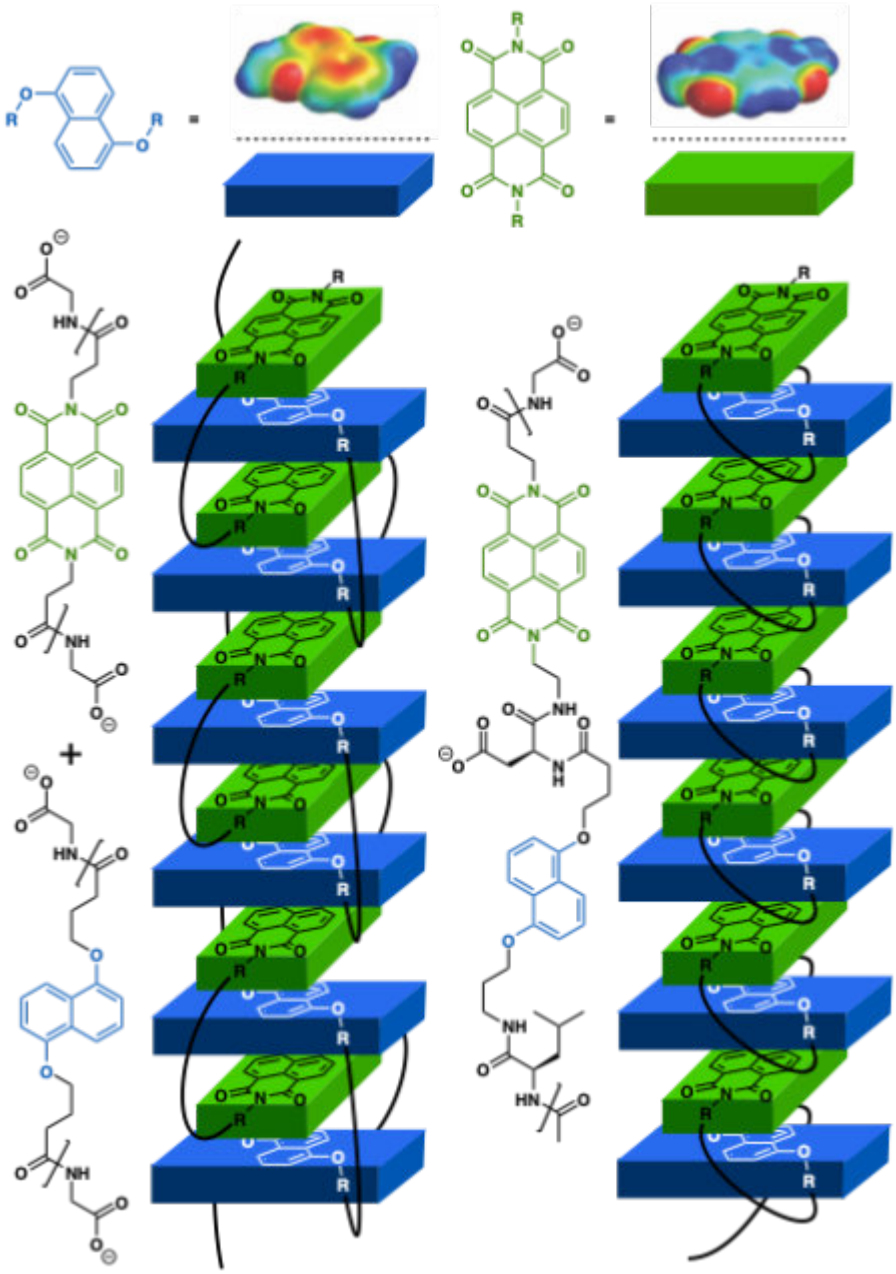

Fig. 11. Molecular structure and folded conformation of two DAN-NDI foldamers

poorly solvated surfaces resulting in solvophobically-driven molecular association. Minimum exposure of the solvophobic surface occurs when the host and guest molecules are complementary in terms of shape and size, leading to the tightest binding.[36] The binding affinities were determined between the rod-like guest and varying lengths of the foldamer by circular dichroism measurements which showed a saturation behaviour with an isodichroic point as expected for a single stoichiometry relationship and binding affinities of cis-(2*S*,5*S*)-2,5-dimethyl-*N*,*N*'-diphenylpiperazine peaks when n= 20 and 22.[36] Despite these aromatic oligomers relying on non-covalent interactions, the restricted rotation and strong geometric constraints provide an essential feature allowing the secondary structures of these foldamers to be predictable and stable.

Metal-based foldamers

Helicates are oligomers that bind to ionic species, and in particular to metal ions, and exist in a grey area between aliphatic and aromatic foldamers. A significant amount of research has been carried out in the formation of helicates. Although most contain a rigid aromatic backbone, they do not rely or utilise aromatic intermolecular interactions. Instead, they consist of a rigid backbone with a flexible arm for the molecules to wrap around a metal core, as shown in Fig. 13. Due to their twisting and folding nature when co-ordinated to a metal, they are often referenced in foldamer reviews and textbooks. These helicates have been found to have applications in a variety of fields due to their twisting nature, from the formation of molecular knots,[37] host-guest recognition,[38] magnetic materials,[39] and selective binding of DNA,[40] to metal detection.[41]

The addition of metals can result in structures other than the commonly reported helicates. Zhao *et al*. developed a "helical hair clip" architecture for the fluorescent detection of Zn^{2+} by using a sequence of cholate, glutamic acids and pyrenyl groups, shown in Fig. 14.[42,43] Synthesis of Zn^{2+} sensors continue to attract the attention of chemists due to their physiological importance. With the oligomer containing six cholates the structure produces two full helical turns with space-filling cholate models showing the folded state stretches out to a length of 1-1.5 nm.[42] The hair clip structure plays a crucial role in the detection of the Zn^{2+} ion as it results in the pyrenyl rings stacking upon one another leading to an increase in fluorescence.[42] This increase does not

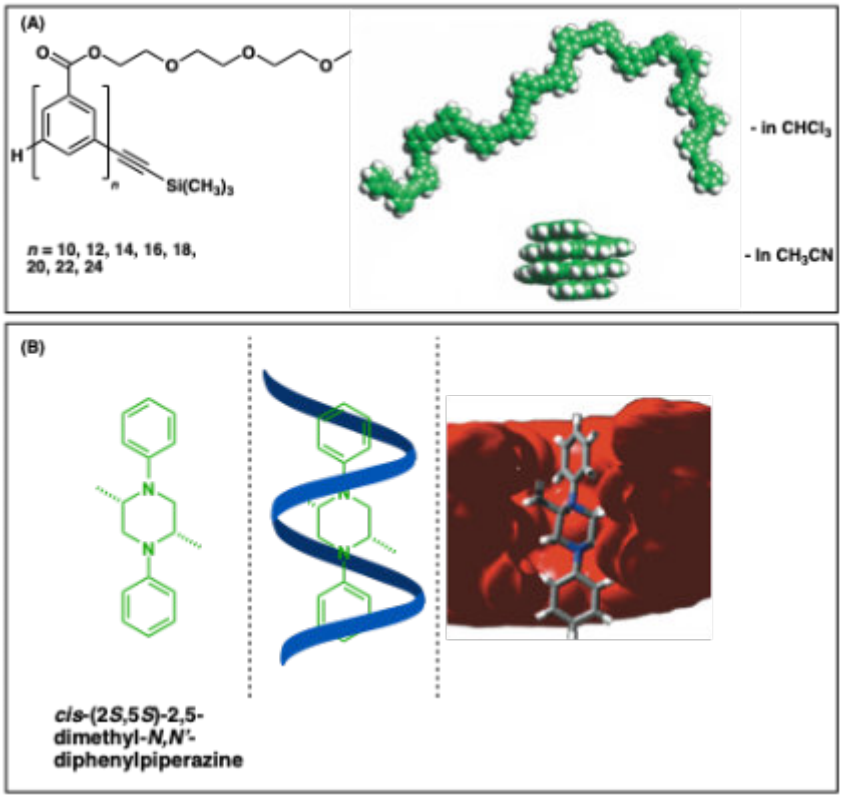

Fig. 12. (A) Chemical structure of an oligo (m-phenylene ethynylene) based foldamer with X-ray crystal structure (with PEG R group omitted for clarity). (B) Chemical structure of rod-like guest, cis-(2S,5S)-2,5-dimethyl-N,N'-diphenylpiperazine with modelling showing host-guest interaction reported in the literature[4] (adapted with permission).

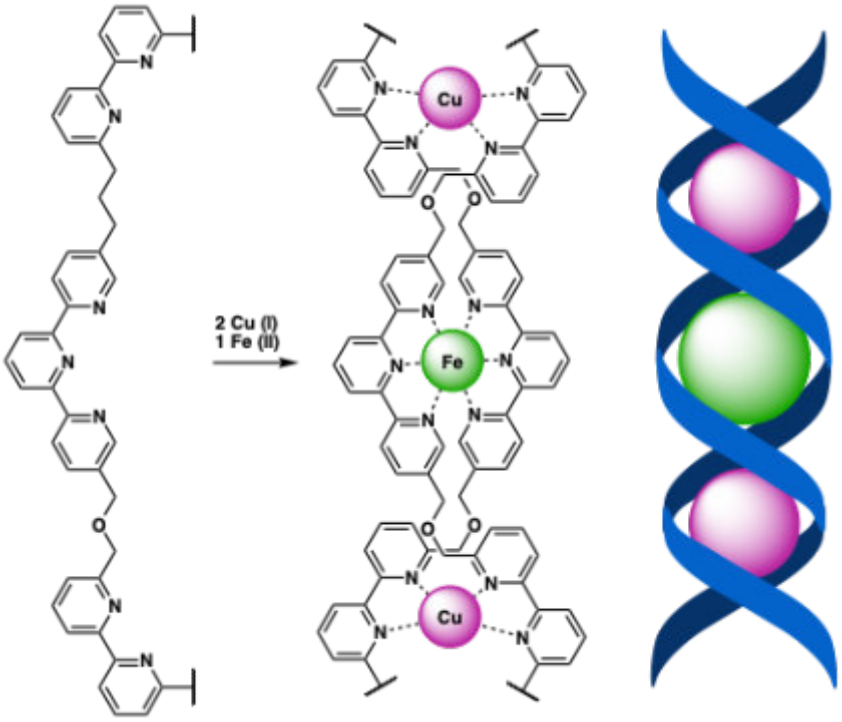

Fig. 13. Double stranded heteronuclear helicate synthesised from terpyridine and 2,2'-bipyridine ligands

occur if the metal ion is not coordinated to the glutamic acid residues and prevents the detection of the metal ion. Various other metals were examined but these showed lower binding affinities compared to Zn^{2+}. Detection of Zn^{2+} ions was shown to be dependent on the relative concentration of folded and unfolded conformations.[42] Peak detection is achieved when 10% of the foldamer is in a folded conformation and when in a 15% MeOH 85% EtOAc mixture.[42] The group also showed this concentration of MeOH resulted in folding occurring without complexation, whereas higher concentration resulted in the destabilisation of the foldamer causing lower affinity for the Zn^{2+} ion.

Conclusions

This review highlights some key aspects of the field of foldamer chemistry. Following the development from early examples that focused on structure to the modern variants that add an application to the shape, we can see that the design and synthesis of new monomers is critical, along with a better understanding of how to control shape. Significant advances in the formation of novel architectures have been made in the past three decades, from the common α-helices, first produced using β-amino acids in the 1990s, to the formation of rod-helix templates and double-stranded helicates. A wide range of foldamer examples have been illustrated (peptide, DNA, cyclophane, and metallic based structures), highlighting the key folding interactions with many backbone sequences found in the literature influencing and overlapping in all areas of chemistry.

The successful synthesis of new foldamers will need to take into consideration two key design principles. Firstly, the balance of attractive and repulsive non-covalent interactions to stabilise the desired structure. Secondly, the flexibility and rigidity of the backbone as these structures need to be able to readily form. There is still a significant

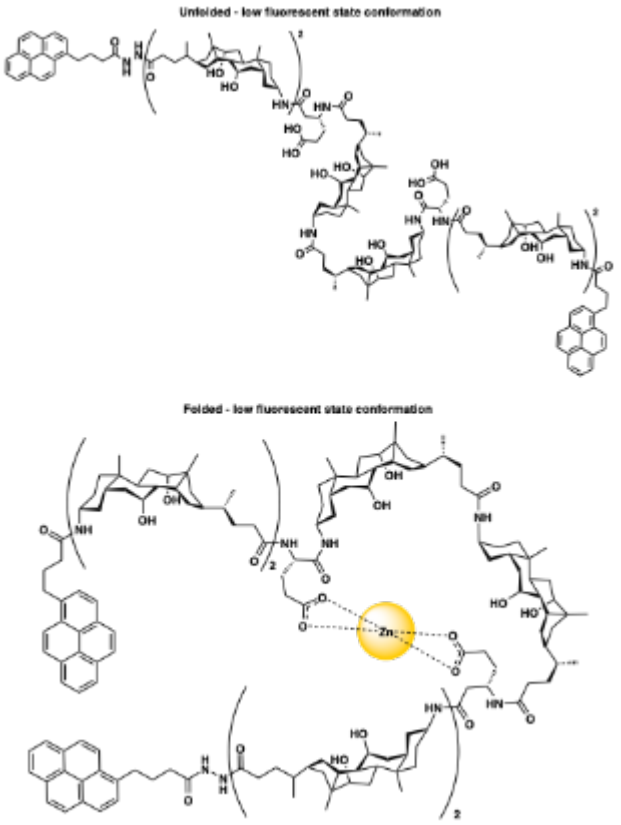

Fig. 14. Molecular structure of cholate-glutamic acid foldamer used for fluorescent detection of Zn^{2+} ions

amount of work to be completed within this field, with many more avenues to be explored. It is clear that nature is not alone anymore, and synthetic chemists are indeed able to improve on the foundation nature has provided.

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Rebecca Severinsen

School of Fundamental Sciences, Massey University, Palmerston North

Email: r.j.severinsen@massey.ac.nz

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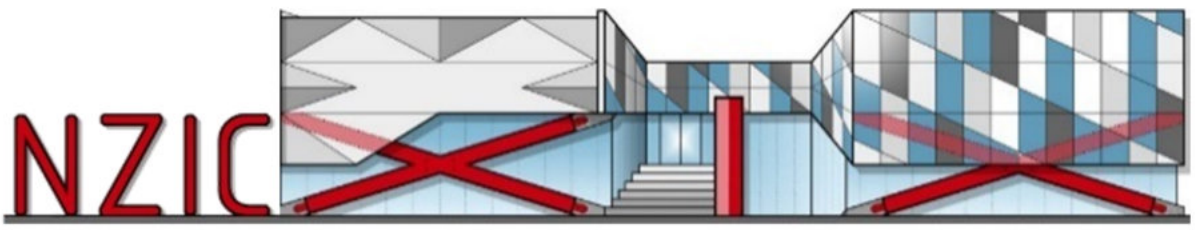
November 2019 saw the highly successful return of our national chemistry conference, NZIC2019. This was well attended by researchers at all career stages from across New Zealand, Australia and beyond. A lecture block at the University of Canterbury served as the conference venue, providing an opportunity for attendees who had not already done so to explore the beautiful city of Christchurch. A highlight for the Manawatu group was the introduction to public e-scooter hire (and the sight of their professors zipping around on them...).

The conference started with the opening ceremony in the afternoon of Sunday 24 November before the first round of presentations began. Covering topics in organic, biological and physical chemistry, the excellent speakers were well received by the diverse audience. First up was plenary speaker Professor Katrina Jolliffe from the University of Sydney, who kicked off the talks with an interesting discussion on peptides and peptidomatics for anion recognition. Keynote presentations followed from Professor Anthony Fairbanks (UC) and Professor Timothy Schmidt (UNSW) discussing ENGases and molecular exitons respectively.

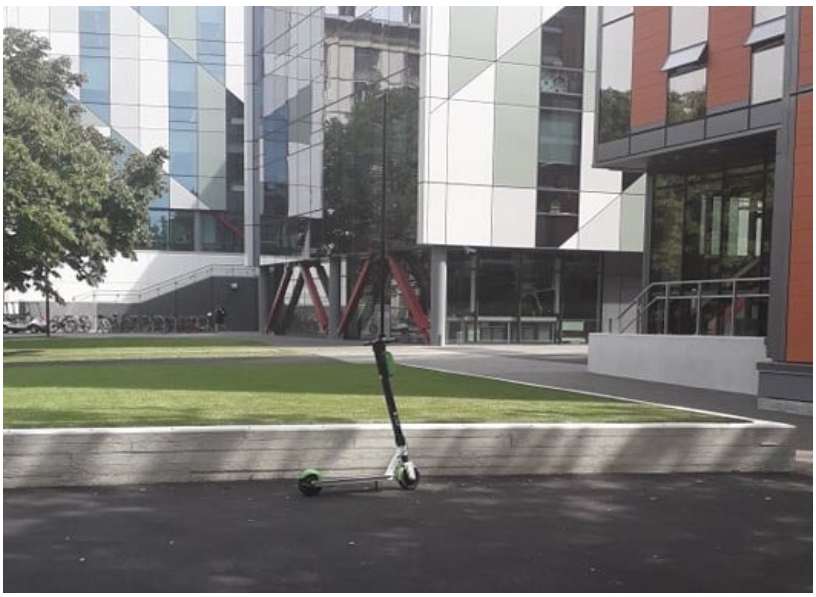
A move to the foyer of the Ernest Rutherford building followed, where postgraduate students and researchers of all disciplines had the opportunity to mingle over drinks and canapés.

The first full day started at 8.30am on Monday with plenary and keynote lectures. After morning tea the talks were split into three parallel sessions featuring physical chemistry/theoretical and computational chemistry, medicinal chemistry/chemical biology and inorganic/organometallic chemistry. For a local flair, the typical end-of-speech time warning buzzers were replaced by toy kea, kakapo and kiwi birds, with bird-call signals. Lunch preceded the afternoon sessions, where attendees reconvened for another plenary and keynote lecture, before the student oral competition began. This featured quality talks from student representatives from each NZIC branch and was won by Emma Wrigglesworth from Wellington.

Up for grabs at the poster session that evening were a number of prizes sponsored by the *Journal of Physical Chemistry* and the Royal Society of Chemistry (New Zealand Branch). Accompanied by generous refreshments, visual research displays of close to 50 researchers were presented and discussed with the circulating crowd. Prizewinning topics covered a wide scope of chemical specialties, including supramolecular cages, peptides and ionic liquids.



The next (third) day again started with excellent keynote and plenary speakers followed by parallel sessions of supramolecular chemistry, organic chemistry and chemical education in the morning. The afternoon's sessions featured inorganic/organometallic chemistry, environmental/analytical chemistry and again organic chemistry, before coming to a close for afternoon tea.



Other keynote and plenary speakers followed, before people went their own ways to enjoy Christchurch, including some to the conference-organised beer tasting excursion.

Wednesday (day 4) followed a similar pattern, with parallel sessions on chemical biology/ medicinal chemistry, materials chemistry/ nanoscience and physical chemistry/theoretical and computational chemistry. The first-rate conference dinner took place that evening at the Christchurch Town Hall, which featured prize presentations and included excellent food, drink and dancing.

The final conference day (Thursday) featured more parallel sessions, including the emerging research talent section, before the final keynote and plenary lectures. The closing ceremony marked the end of this highly successful conference, setting a good tone to follow for the organisers of the next NZIC conference.

Atoms and elements

Richard Sorrenson

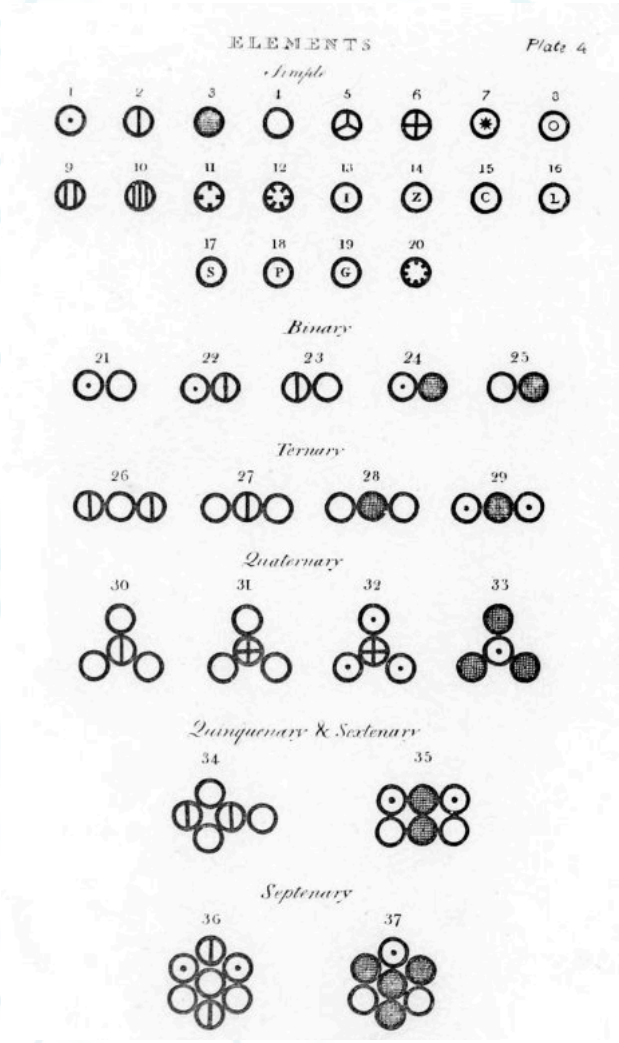
Email: r.sorrenson@auckland.ac.nz

This article is one of a series on the history of chemistry authored by Richard Sorrenson. Richard is General Manager of the University of Auckland Foundation. He gained an MSc in chemistry from the University of Auckland and a PhD in the history of science from Princeton University.

John Dalton's "Plate IV" from his *A New System of Chemical Philosophy* (London, 1808) is one of the most famous images in the history of science and deservedly so.[1] It is deceptively simple but contains underlying theoretical assertions and was by no means universally accepted in his lifetime or for the remainder of the century. It argues that chemical elements are formed from many identical microscopic physical atoms in combination with varying amounts of caloric (a principle of heat that explained the differences between solids, liquids and gases) and likewise chemical compounds are made up of great numbers of identically combined atoms.[2]

Both Lavoisier and Davy were sceptical about the existence of physical atoms to explain the behaviour of chemical elements. In part this scepticism came from the rather fruitless application of atomism to chemistry in the seventeenth century; assuming an underlying physical atom led to very little that was useful to a chemist in the days of Robert Boyle or Isaac Newton or on into the eighteenth century. For Lavoisier, as we have already seen, the methods of chemistry gave no insight into the fundamental nature of matter; rather an element was that substance which could only be made heavier by the prevailing chemical procedures.[3] For Davy, an element was a substance that could not be broken down into simpler parts by the tools of chemistry including, at times, the action of a battery.[4] While such scepticism was reasonable, it was also somewhat unsatisfactory as the list of elements would be forever changing as chemical methods and technologies developed. Would a new instrument or process demonstrate what was thought to be elemental could indeed be broken down and thus was no longer an element? Conversely, at what point of only ever making a substance heavier by chemical action could it be deemed to be an element?

John Dalton, like Priestley an auto-didact and religious dissenter from the north of England, broke with Lavoisier and Davy and asserted the reality of physical atoms and hence the stable existence of the corresponding elements. What is quite remarkable about



John Dalton's "Plate IV" from A New System of Chemical Philosophy[1]

Dalton is that despite working within a British philosophical tradition that hewed to experimental facts and avoided speculation, he adopted a central hypothesis -- the existence of atoms -- which could not be experimentally proven by any contemporary techniques and he introduced axioms from which to deduce his whole system of chemistry.[5]

The first axiom was simplicity, hence water (the only known combination of hydrogen and oxygen in 1808) was a combination of one atom of hydrogen and one of oxygen (symbol 21 of Plate IV). The second, which broke with certain aspects of the Newtonian tradition of atomism, was that just as every element differed from another, so too did the underlying atoms; an atom of hydrogen irrevocably differed from that of oxygen and neither could undergo any changes. The third, and most powerful, was that the relative weights of chemical elements and physical atoms were in identical proportions. For example, from the measurements of relative weights of hydrogen and oxygen that made up water, he could calculate that elemental oxygen was approximately 7 times heavier than elemental hydrogen.[6] In combination with his simplicity axiom (i.e. water is one atom of hydrogen combined with one atom of oxygen) he inferred that an atom of oxygen (symbol 4) was 7 times heavier than one of hydrogen (symbol 1).[7]

The facts of chemistry in 1808 only demanded that (simple) compounds had a fixed composition and that they combined in simple ratios or multiple proportions. However, the simplicity and power of Dalton's ideas gave an orderliness to chemistry that was very helpful and many chemists chose also to adopt the associated atomic theory.

Davy remained unconvinced and even when, as President of the Royal Society of London, he delivered Dalton's Royal Medal address in 1826, he focussed on Dalton's work on multiple proportions and not his atomic theory.[8] Dalton, in demonstrating empirical regularities, was the Kepler of chemistry Davy argued; by implication the Newton of chemistry had not yet appeared. Putting aside Davy's damnation by faint praise, the analogy is more apt than he realised. Dalton, like Kepler, looked deeper into nature for simple harmonies and his axiomatic system proved to be both useful and enduring even if the existence of atoms was not fully demonstrated (at least to the satisfaction of physicists) until a century after "Plate IV" was published.

References and notes

1. Dalton, J. *A New System of Chemical Philosophy*, London, 1808. See: https://en.wikipedia.org/wiki/John_Dalton#/media/File:A_New_System_of_Chemical_Philosophy_fp.jpg
2. This assumption breaks down with complex compounds like glasses and alloys.
3. Sorrenson, R. *Chem. NZ.* **2019,** *83(3)*, 121-122.
4. Sorrenson, R. *Chem. NZ.* **2019,** *83(4)*, 162-163.
5. Brock, W. *The Fontana History of Chemistry*, Fontana Press: London, 1992, pp 128-147.
6. The modern value is 8.
7. The modern value is 16 (excluding isotopes).
8. Levere, T. *Transforming Matter: A History of Chemistry from Alchemy to the Buckyball*, Johns Hopkins University Press: Baltimore & London, 2001, p 87.

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