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Issue: #103

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WELCOME...

In this edition we celebrate the increasingly diverse and interdisciplinary nature of the life sciences. The life sciences now encompass a wide array of disciplines and scientists are coming to understand the value of interdisciplinary cross-collaboration, leading to maximised outputs, paradigm shifts and the pooling of expertise. In this edition, we showcase a variety of life science research from a diverse array of fields and demonstrate that scientists increasingly blur the lines between disciplines, with encouraging results.

The first section introduces the interwoven fields of psychology and neuroscience, where we highlight how the physical damage caused by traumatic brain injury expresses itself through the impairment of social and emotional function. The areas of psychology and genetics merge in our second section, where Dr. Hilary Coon's research investigates the genes responsible for suicidal tendencies. In this section we will also demonstrate how exploring the genes of zebrafish offers insight into the evolution of life on earth. From here we are plunged into the world of biotechnology, a booming multidisciplinary industry which relies on the expertise of biochemists, geneticists, microbiologists, molecular biologists, agricultural scientists and pharmacologists, to name just a few. The blood takes the spotlight in our penultimate section, where we look at its role in both cancer and nutrition, which integrates fields as diverse as molecular biology and smartphone app development. To wrap up, we explore the dependence of public health on the health of the environment. In this final section we highlight the work of Professor Pamela Lein, who in addition to investigating environmental contaminants as risk factors for neurodevelopmental disorders, is also helping to train up the next generation of environmental health experts, ensuring the longevity of this multifaceted, and vital field of research.

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CONTENTS

ISSUE : #103

Do you want to become a regular **READER OF SCIENTIA?**

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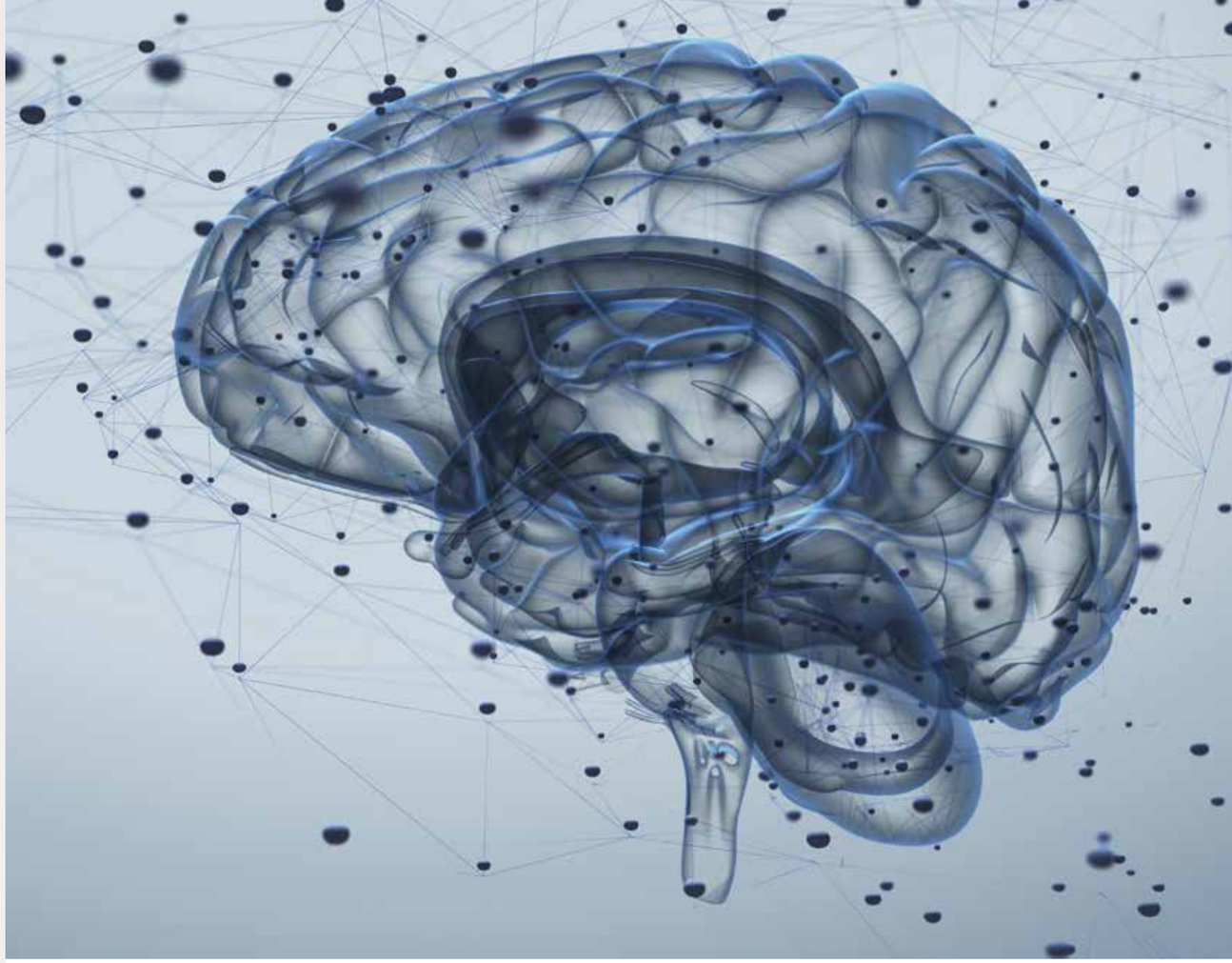


THE BRAIN AND BEHAVIOUR

The brain is the most complicated structure that we know of, containing an estimated 86 billion neurons communicating through electrical and chemical processes that allow us to breathe, walk, hear, think, speak, create and experience. How this complex machine evolved from the first unicellular life forms that existed an estimated 3.5 billion years ago still largely remains a mystery. While our understanding of how the brain works has increased significantly in recent decades due to breakthroughs in neurological and psychological research, along with advancements in imaging technologies, we're really just beginning to scratch the surface.

In this section, we introduce three researchers, each investigating a different aspect of the human brain, and its connection to our behaviour and experience. In the first article, we present the work of Professor Alison Fleming and her team, who are uncovering the effects that hormones have on maternal feelings and behaviour at various stages during pregnancy and the postpartum period. Her work also includes investigating the detrimental effects that postpartum depression in mothers can have on the cognitive, emotional, motor and neural development of their infants. Identifying the physiological and psychological factors involved in maternal behaviour will aid the development of interventions that help to enhance parenting. From the brain's mothering centre – the hypothalamus, we move to the parietal lobe, an area of the brain believed to play a significant role in how we perceive the space around us. Here we discuss the research of Dr. Hans-Joachim Maempel, who has designed virtual environments to probe the interactions that exist between auditory and visual perception. This fascinating work has provided insight into how we perceive room size based on visual and acoustic information, and how the two modalities interact. Finally, we introduce Professor Skye McDonald who examines social and emotional impairments in patients suffering from traumatic brain injury. Uncovering the nature and mechanisms that underlie these disorders aids the development of diagnostic and treatment techniques, that improve the quality of life for patients and their families.

Dissecting the Maternal Mind

With a row of highly inspirational people shaping her early thinking, Professor Alison Fleming started studying maternal behaviour as an undergraduate student. She has now spent her entire research career trying to understand how 'nature and nurture' interact to enhance mothering.

Describe the early influences inspiring you to pursue a lifelong career investigating the biological basis of mothering.

I believe the first influence was my mother, in part because she was a professional economist at the United Nations at a time that women didn't hold professional jobs like that. She also travelled a great deal, working in New York and only coming home to us in Washington DC for weekends. I knew she had an important job and greatly admired that. But I also resented the fact that she was not around very much. I suspect my interest in the study of mothering derived in part from not understanding why she was absent. However, my desire to go my own way was likely derived from the fact that she pursued her goals the way she did.

I became interested in psychology as an undergraduate at Columbia. I particularly admired two Professors in psychology; Ted Schaeffer who studied the effects of early 'handling' of rat pups on development of brain and behaviour, and Burt Slotnick, who studied the role of the brain's septal region for maternal behaviour in mice. Once in graduate school at Rutgers University, I came to work with Dr. Jay S. Rosenblatt, who has been the biggest influence on my research career directed at the study of mothering. He studied maternal behaviour and development in the rat, just as I did. I consider Jay the Father of Mothering.

You have been involved in studies showing strong intergenerational effects of adverse early life experiences on mothering. Is your research being used to design interventions for mothers with a known history of adverse early life events?

While we don't do intervention studies ourselves, we are of course interested in interventions to enhance mothering, in particular in studies building on our knowledge that many behavioural systems become activated when women give birth and become maternal. Hence, factors that we know can affect mothering can be brought into the development of parenting interventions to help mothers (and fathers) respond more appropriately to their infants.

For instance, we know that mothers with post-partum depression are less responsive and display problems with attention and ability to shift attention. Interventions that ameliorate depression or anxiety in depressed mothers would also enhance maternal behaviour. Mothers can also be trained to focus attention on salient cues and to be more attentive to cues emanating from their babies. Focusing attention allows them be more sensitive, and respond more contingently to their babies. This process also often enhances the reward value of the infants. Another approach is to film mothers with their infants. By watching the videos, mothers receive feedback on aspects of their behaviour that are maladaptive or not sufficiently attuned.

Your data supports the notion that brain changes also occur in non-biological mothers. Is there any research on potential fathering brain changes?

From animal studies we know that the same brain systems are involved in regulation of parental behaviour in females who care for babies but who are not mothers, as well as in fathers. In fathers, we also know hormones can play a role. In humans, a decrease in testosterone levels along with increased prolactin levels, are associated with more nurturance among fathers. Experience interacting with young and being parented well are however the largest predictors of quality of parenting, whether we are talking about mothers, fathers, or 'alloparents' (relatives, other children, community members, SH). Fathering research and research on 'alloparents' exist and we have done some, but there is a lot more that can and should be done.

Your neuroimaging data shows that many brain regions, connected through complex pathways, are involved in mothering – how can this knowledge impact the science of social and psychological aspects of mothering?

Knowledge of brain function and pathways is not a goal in itself. However, pathways related to perception, memory, reward, executive function, cognition, attention and affect reflect behavioural functions important for appropriate mothering, and understanding how these functions and their pathways intersect with a maternal circuit helps us understand how mothering is regulated and why it is sometimes dysregulated.

Speaking of pathways, it is also crucial to include knowledge of neurochemistry. There are now a number of ways in which our knowledge of neurochemistry can be used to impact behaviour. Examples involve the use of selective serotonin reuptake inhibitors (SSRI's) for depression, the effects of oxytocin on memory, the importance of dopamine for reward and the regulation of stress by cortisol. These neurotransmitters and hormones are important for brain function and are involved in the regulation of behaviour.

In general however I believe interventions should be based primarily on psychological phenomena, based on knowledge of how they are regulated by the brain, and not based on physiology and neuroscience alone.

Defining Psychobiological Correlates of Maternal Behaviour

Optimal maternal behaviour is a cornerstone of the survival of the human race. But what is characterizing the transition into motherhood on a psychological and physiological level, and what can cause the process to go awry?

AN INTEGRATED VIEW

Human babies are born into a helpless state, entirely depending on others for survival and optimal development, and for this to take place, it takes more than just providing food and shelter. Being a highly sociable species, human infants also require intimate social bonds to thrive and usually, but not always, the mother is the first affectional bond. The strength of the attachment between an infant and its mother is, in fact a solid predictor of further cognitive and psychosocial development of the child. In some cultures the infant is cared for by multiple affectionate caregivers (fathers, grandparents, aunts) and these relationships can serve the same function.

For such a connection to develop, an infant needs to make the mother aware of its needs, and the mother, in turn, must find it rewarding to act upon these demands. Consequently, optimal mothering behaviour depends on a number of highly integrated psychological processes.

One fundamental aspect of mothering behaviour is sensitivity in picking up, interpreting and acting upon cues related to the infant needs. Such cues need to be salient and able to activate the intrinsic reward system in the mother's brain. Additionally, mothering is often taking place against a backdrop of multiple, rapidly changing and competing stimuli. Therefore, the ability to both focus and to briskly change the focus of attention when necessary is also essential for successful maternal behaviour. Finally, it is fundamental to harness impulsivity to maintain a consistent and restrained behaviour.

These features are all built up by well known cognitive building blocks; executive function, cognitive flexibility, working memory and attentional control – processes that are effectively studied in experimental animals. Studying maternal behaviour in rats was therefore where Professor Fleming started out, only later transitioning into the field of human mothering studies. Although they present the advantage of allowing experimental manipulation, rat studies cannot mirror the complexity of human mothering. "In humans, we are left to correlational studies, for example measuring the hormones in blood or saliva as a mother engages with her offspring", says Professor Fleming, adding that although the study techniques are different, the questions they ask of animal and human mothers are similar.

It is obvious that the process of mothering may depend on brain circuitry in animals and humans alike – but what constitutes the changes in the body and brain when a woman transitions into motherhood?

HORMONAL SHAPING

The cascade of hormones a woman is subjected to during pregnancy and birth is a well studied phenomenon, likely to increase the mother's attraction to infant cues and impact her affective state. A typical pregnancy presents with high and shifting levels of progeserone, estrogens and lactogens/prolactin, and a parturitonal rise in oxytocin.

In nursing mothers, the postpartum period, in turn, is characterized by elevations in levels of prolactin and oxytocin and a reduction in the stress response (see work by Barbara Woodside and Dominique Walker). Both prolactin and oxytocin are strongly linked to formation of attachment in a mother infant pair, and a mother typically displays high levels of oxytocin both during affectionate interactions and while engaging in attachment related thoughts. These effects of prolactin and oxytocin are believed to be a result of earlier priming of the brain by oestrogen.

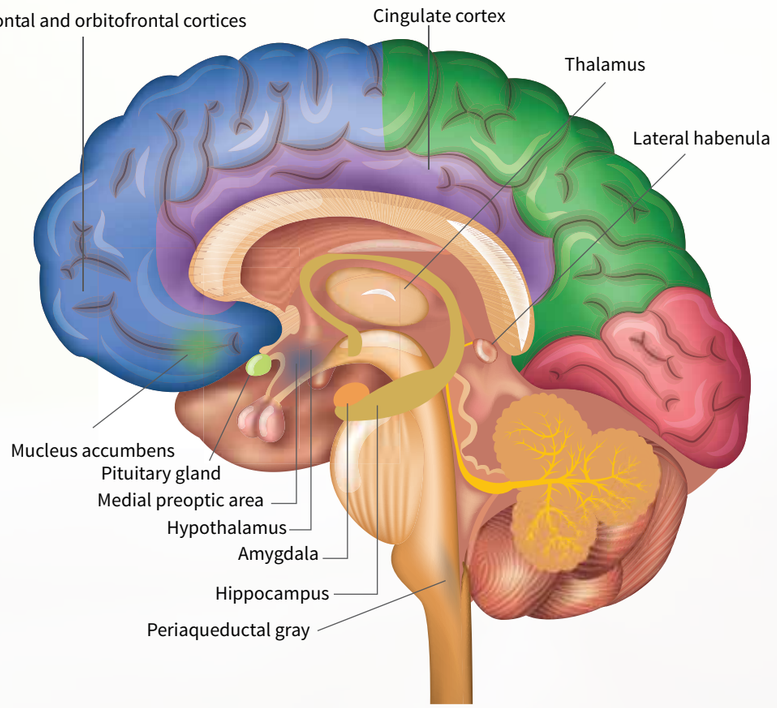
Consistent with rat studies by Bob Bridges, Harold Siegel, and Cort Pedersen, research by Professor Fleming also shows that in human mothers a robust increase in the ratio between estradiol and progesterone, during the period from early to late pregnancy, is associated with strong attachment, thus displaying the profound effects of hormones on the maternal brain. Mothers, in which this shift in ratio during pregnancy was larger, also experienced higher levels of feelings of nurturance and well-being postpartum – another predictor of stronger attachment.

Yet another hormone – cortisol – which we usually associate with a negative stress reaction, are also associated with maternal feelings and behaviour. Cortisol levels at day 3-4 postpartum are strongly associated with approach behaviour, positive maternal attitude and more vocally active infants. They are also associated with more positive reactions to infant odors and an enhanced ability to recognize own baby 's odors in a choice test. Later in the postpartum period, nevertheless, cortisol might have the opposite effect, contributing to a negative mothering development. The relation of these cortisol effects with effects of oxytocin is now being explored in new mothers.

NEUROANATOMICAL KEYSTONES

But how is it then possible that shifting levels of hormones affect the way we behave? Professor Fleming has a specific interest in investigating the neuroanatomy of mothering with the help of functional neuroimaging. "To understand which brain areas are involved in mothering behaviour, it is necessary to look for the neuroanatomical correlates of the behavioural constituents", says Professor Fleming. Prior research, employing neuroimaging techniques, has provided insight into the anatomical counterparts of the reward system, regions handling emotion and affect, as well as the parts of the brain handling executive function.

Animal studies have identified a number of brain regions that are involved in maternal behaviour. Human behaviour is naturally far more complex, and a human mother taking care



THE MATERNAL BRAIN

The medial preoptic area (MPOA) of the hypothalamus is the brain's mothering centre – shaped by maternal hormones. The hypothalamus and pituitary produces oxytocin and prolactin. Oestrogen and progesterone also promote neuronal branching in hippocampus – an area crucial for memory and learning. The cingulate-, prefrontal-, and orbitofrontal cortices are regulating features such as empathy, impulse control and attention. Neural projections from cortical regions enter MPOA, along with input from sensory neurons and from amygdala – a region mediating affective states. From the MPOA neural projections run to the ventral tegmental area and to the periaqueductal grey, which are, along with the nucleus accumbens, lateral habenula and thalamus, also involved in mothering behaviour.

of her infant likely employs the greater part of her brain in the process. "A way to reduce this complexity while studying human mothering, is to focus on neural systems associated with social behaviour, emotion perception or regulation, action initiation and stimulus salience," says Professor Fleming.

In this way, Professor Fleming has built on discoveries made by colleagues (especially Michael Numan) who have identified a mothering pathway, involving a specific area of the hypothalamus, with neural projections going into the midbrain and hindbrain. Professor Fleming and her students have focussed primarily on Information from sensory, limbic, and cortical systems which project back onto the mothering pathway. They have explored in both animal models and humans the effect on the maternal system of limbic pathways that mediate affect, stimulus salience, and reward (especially amygdala and nucleus accumbens); as well as the prefrontal and cingulated cortical systems that mediate executive function, impulsivity, and attention. They have also explored, along with many other scientists (including Craig Kinsley, Liisa Galea, Frederic Levy, Joe Lonstein and their colleagues) how these structures in the maternal brain also show plasticity and can be changed by experience. While these neuropsychologic systems may be viewed as secondary in affecting the quality and intensity of mothering, the hypothalamus is viewed as imperative for mothering (in animal models), not least because it contains receptors for all the hormones involved in the activation of maternal behaviour.

HINDRANCES IN MOTHERING'S WAY

While the assumption that mothering comes 'naturally' when a baby is born is strongly believed, under certain circumstances there is a risk of mothering becoming compromised. The emotional ups and downs of the early postpartum period (the so-called 'blues') is a well-known phenomenon, with up to 85% of women experiencing mild to moderate lability with depressive symptoms postpartum. It has been hypothesized that the rapidly changing affect might serve as a way to heighten the early impressions and experiences of the baby, hence promoting attachment. When the depression is more serious and more long-lasting (in up to 18% of North American mothers), however, a less than optimal situation arises.

Depression in the postpartum period can have deleterious effects on cognitive, emotional, motor and neural development of the infant. These effects can be observed already after a few months postpartum, with noticeably less mutual attentiveness, vocal and visual communications, touching interactions and smiles in depressed mother infant pairs. More importantly, it is also associated with the development of psychopathology in the child later in life. There are many theories as to the hormonal and situational factors that increase risk of postpartum depression, however the causes are still little understood. Fortunately, in most mothers postpartum depression remits by 6 to 8 months after the birth and is amenable to supportive interventions and/or antidepressants.

Also, among the most influential factors for how a woman behaves when she becomes a mother, is how she herself has been shaped by early experiences. The qualitative aspects of mothering, such as warmth, vocal and visual exchanges, physical interaction and contingent responding, are extremely important for the healthy development of a child. Likewise, parental neglect, as well as physical, sexual or emotional abuse, has a strong negative impact on the attachment between a mother and her child, hence shaping the entire development.

Data from animal studies show a strong intergenerational effect of these qualitative aspects of mothering, and there is evidence for intergenerational transmission of parenting style and degree of bonding and attachment also in humans. In fact, the biggest risk factor for child abuse is a history of abuse of the mother.

Connecting these phenomena is evidence that both depression and early adverse experiences are tightly linked to a hyperactive stress response. This abnormal stress response in turn seems to contribute to the negative effects on maternal sensitivity and executive function. Early adverse experiences are also potentially interfering with mothering behaviour through psychopathology, since adverse experiences in childhood are strongly associated with the development of depression and anxiety later in life. Protective factors such as social support in the environment in the form of other relatives, community members, friends, or professional interventions can, however, break this potentially vicious circle.

Professor Fleming likes to think of mother infant interactions as a dance, and with this tender notion in mind, she enthusiastically continues investigating the steps and missteps characterizing mothering.

Researcher Profile

Professor Alison Fleming
Department of Psychology, University of Toronto, Missisauga and Fraser Mustard Institute for Human Development, University of Toronto.

As an undergraduate student, Professor Alison Fleming got hooked on psychology, choosing the subject over her English and history majors. This interest led to a lifelong research career trying to understand the biological basis of mothering behaviour. She is now the principal investigator of the Psychobiology of Maternal Behaviour Lab at the University of Toronto. Starting out by studying maternal behaviour in rats, she now focuses on animals and humans alike in her attempts to gain more knowledge about how physiology and the environment act and interact to enhance women's motivation to mother. Professor Fleming has received several prestigeous awards; the University of Toronto Excellence in Research Award in 2003, the UTM excellence in teaching award in 2005, a Canada Research Chair in Neurobiology in 2006 and in 2013 she received the Daniel S Lehrman Lifetime Achievement award from the Society for Behavioral Neuroendocrinology. She was also inducted into the Royal Society of Canada in 2004. Her passion for mothering goes beyond the professional, and her four daughters, two in-laws, and two glorious grand daughters are the recipients of that passion. In her spare time, she engages in her new avocation, perfect for retirement, as can be seen above.

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Audio-visual room perception

Acoustic scientist Dr. Hans-Joachim Maempel has long been interested in the interplay between hearing and sight. Here he describes his efforts to lay the groundwork for a unified theory of audio-visual room perception.

To start with, please could you describe what inspired you to start looking into the relationship between auditory and visual perception?

After receiving my diploma to become a tonmeister – a profession that combines the work of a music producer and a balance engineer – I composed or produced soundtracks for film and TV for some time. In so doing, you get a feeling for the effect of sound and vision on a semantic and aesthetic level. Within the framework of my PhD thesis I investigated the effect of the mixdown as a production stage of pop music, and as part of that I varied the presence of the corresponding video clip too. In the nineties music television was of special importance. Amongst other things I found that people prefer different mixdowns depending on whether or not there is a video clip. During my time as a postdoc researcher at the TU Berlin I was asked to develop and conduct a course on audio-visual perception, and I was invited to write a lexicon article. So I started to review empirical findings on different audio-visual tasks more systematically.

Why do you think acoustic research has historically failed to properly investigate the interdependence of the auditory and the visual systems?

Since acoustic research is not primarily interested in the investigation of audio-visual perception I think it is quite natural that it has first of all applied itself to its key subjects: for example sound propagation under certain conditions, auditory physiology, or basal perceptual abilities with particular regard to intensity, timbre, and localisation. There are several sub-disciplines in acoustics such as technical acoustics, room acoustics, electroacoustics or psychoacoustics. This is conducive to further differentiation rather than an extension of the scope of research questions. Particularly in room acoustics a physical perspective was predominant for a long time, though actually human perception is always the ultimate criterion for the evaluation of sound in rooms. Though emphasizing the psychological over the physical perspective was desirable, it still disregards the fact that hearing and seeing generally occur at the same time. So acoustic research should eventually start to investigate the optical and also visual conditions under which its diverse results are obtained. The localisation of sound sources is a good example. Auditorily it is quite accurate and reliable, but an additional corresponding optical stimulus in a slightly different position will result in the localisation of a fused percept close to this optical position. Experiments on time determination tasks show in turn that hearing may dominate seeing under certain conditions.

Why is there a need for an empirically founded theory of audio-visual room perception? What are some of the practical applications?

Generally, questions of empirical research are related to present knowledge in order to achieve connectable results. This knowledge is usually formulated in terms of theories that hold a certain degree of generality. But if a theory does not exist, its formation is the priority. Specifically, previous research into audio-visual perception of room acoustics can be characterised by a highly technical approach. This involved the use of room models and the use of artificial sound fields, for example presented by loudspeakers in anechoic rooms; the consideration of few, often highly specific independent and dependent variables; and by the application of different empirical paradigms and methods. Apparently this contributes to results that lack consistency and connectability.

Nowadays research is often required to legitimate itself by its immediate applicability. This criterion may, however, not apply to fundamental research. In fact, applications of our research are not really 'practical' at the moment. Results contribute to the understanding of multi- and intra-modal processes of speech and music perception in rooms; they provide criteria for the validation and/or interpretation of previous studies dealing with the perception of room acoustics under unimodal conditions; they add to the extension and the refinement of simulation techniques; and they are useful for the design of content for opto-acoustic environments.

Why is it so important to use consistent terminology when carrying out this kind of research?

The physical and the psychological realms must be properly differentiated. They need to be clearly differentiated in publications too, which has so far rarely been done. I try to introduce the terms 'acoustical' and 'optical' for denoting a physical representation and 'auditory' and 'visual' for denoting a psychological representation. Particularly with the acoustical terminology, I always struggle with the fact that in English both the physical and the psychological representation of a sonic event is called a 'sound'. It is easier in German – there are two terms, 'Schall' and 'Klang'. Furthermore, unimodal and multimodal perceptual and cognitive aspects should be differentiated. This would enable us to more clearly categorise the direction of effects, for example as 'cross-modal'.

Splitting the senses: creating a virtual environment to test audio-visual perception

Untangling the interactions between auditory and visual perception is a challenging task in the real world. That's why acoustic scientist Dr. Hans-Joachim Maempel turned to cutting-edge simulation technology to tackle the topic.

TACKLING ASSUMPTIONS

It seems intuitive that our perception of the world relies on a complex interplay between the senses, in particular sight and hearing. But in the science of acoustics, the impact of optical stimuli on how we perceive sounds has been largely ignored.

When reviewing the literature, however, acoustic researcher Dr. Hans-Joachim Maempel discovered that many studies assume such an interaction exists with little experimental evidence. This realisation encouraged him to set about developing a comprehensive experimental study of the interaction between auditory and optical stimuli on human's perception of rooms.

What research has been done on this topic has focussed on very specific questions and as a consequence results are not easily translated from one study to another. Inconsistent terminology has only exacerbated this problem, leading Maempel to the realisation that the field required a solid research strategy that encompassed easily reproducible methodology as well as a clear and consistent vocabulary. Under the framework of the German Research Foundation unit Simulation and Evaluation of Acoustical Environments (SEACEN) he commenced the project "Audio-visual perception of acoustical environments" in 2011.

APPLES AND ORANGES

As a starting point he realised there needed to be an obvious delineation between the physical and psychological aspects of both hearing and sight. This means distinguishing between acoustical and optical measures and auditory and visual ones, respectively. A problem with carrying out research on two very different sensory modalities, however, is that their measurements are not really comparable.

"Comparing the effect of the acoustical variation of sound pressure with the effect of the optical variation of illuminance is comparing apples with oranges," says Maempel. In addition, to properly tease out any interaction between the two modalities it is necessary to be able to vary them independently. In the real world this is clearly unfeasible – trying to make the sound from a speaker emerge from anywhere other than where it is optically located is very difficult.

To overcome these limitations, Maempel turned to cutting-edge simulation technology to present a virtual environment in which all the relevant audio-visual parameters could be tweaked independently. Using a combination of auralisation technology and stereoscopic projectors he and his fellow researchers created a virtual concert hall that allowed them to create the conflicting optical and acoustical stimulus that would help them reveal how the two modalities interact.

Solving the lack of comparability between the two modalities relied on a surprisingly simple trick. The team decided to record the optical and acoustic properties of six rooms, which could then be combined independently to create six environments with congruent stimuli and 30 with conflicting stimuli. This was no simple task though. "It was very hard to setup a low-cost optical virtual environment, every imaginable technical problem actually occurred and had to be solved," says Maempel.

IMMERSIVE ENVIRONMENTS

To start with the team had to take photographs for 360 possible head orientations to create panoramic stereoscopic images of each room. These were then projected onto a semi-cylindrical screen using five stereoscopic projectors and warping and edge-blending software that resulted in a nearly 180° field of view for the test subject. Mapping the acoustical environment was even more complicated though, as not only did the representation have to be highly precise, the simulation also needed to be able to respond to the subject moving their head to explore the panoramic visual display.

This required the team to rely on dynamic

binaural synthesis – a method whereby acoustic fingerprints are recorded using a 'dummy' head and torso with microphones in the position of each ear. By playing sine sweeps through loudspeakers located exactly where a performer would be positioned in each of the six rooms, the microphones on the dummy were used to build up the properties of the acoustical environment a human subject sat in the same seat would experience.

To cope with the fact that a human subject is likely to move their head, acoustic fingerprints were taken at various head orientations. Electromagnetic tracking technology built into the headphones human subjects subsequently wore for experiments, allowed their head orientation to be traced and the acoustical simulation to be compensatorily altered in real time.

Following the construction of the virtual environments Maempel and his team then made recordings in an anechoic room of four professional musicians playing Claude Debussy's 1893 string quartet and a professional actress performing the first paragraph of Rainer Maria Rilke's Duino Elegies. Both performances were then repeated in a green screen studio and recorded by a stereoscopic video camera. These optical and acoustical recordings were then blended with the virtual environment using chroma key compositing and dynamic binaural synthesis respectively.

This set up allowed human subjects to experience a fully immersive simulation of each room. The ability to turn their head without turning the virtual acoustic environment with it meant they could explore the virtual concert halls during each performance as they wished. It also allowed Maempel to independently vary acoustical and optical stimuli for the first time. To see what this could tell him about how the two modalities interact, he carried out a series of experiments where participants were exposed to each of the congruent and conflicting stimuli. They were then asked to evaluate their experience via an electronic questionnaire displayed on a tablet computer.

A SURPRISING CONCLUSION

Despite the long standing assumption of an interaction between auditory and visual perception, the group's first results indicate that there is neither significant interaction nor cross-modal effects between the two modalities.

To put it simply auditory perception relied on acoustic information and visual perception on optical information. An interesting additional finding was that the way the human brain perceives a room is relatively flexible. In a preliminary experiment with lower quality optical simulations distance and room size judgments relied predominantly on acoustic information. But in later experiments with the more sophisticated optical simulation the visual modality became dominant in making such judgements.

"Since I do not support a naïve-realistic conception of human perception I personally was not surprised about the flexible exploitation of available physical cues by the two modalities," says Maempel. "It took me, however, a little by surprise that we did not observe significant and practically relevant interaction or cross-modal effects. They have often been assumed, though one should take into account that thereby the term 'interaction' has not always been used in a strict methodological sense. Our findings indicate, anyway, that the modalities contribute to a percept (something that is perceived) in a straightforward and more or less additive way."

Refuting this commonplace assumption in acoustic science not only has major implications for research going forward, but will also allow academics to revisit previous studies to understand how this conjecture may have affected results. But as well as solving the question he initially set out to answer, Maempel's work has provided a valuable by-product. "The virtual concert hall is a quite flexible research tool allowing also for the investigation of more specific questions," he says.

The next phase of the project will look into a variety of more detailed research questions including whether humans can audio-visually match optical and acoustic room shapes, both when they are perceived and memorised. The team also wants to look at the role of participant's musical and acoustic expertise as well as their musical preferences in how they perceive audio-visual space.

Researcher Profile

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Dr. Hans-Joachim Maempel is head of the department for acoustics and music technology / studio facilities and IT at the State Institute for Music Research in Berlin, an agency of the Prussian Cultural Heritage Foundation. He started his career in the creative industry composing and producing soundtracks for film and TV before moving into academia. He received his PhD in Musicology at Berlin Institute of Technology in 2001.

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SEACEN

Understanding Psychological Consequences of Traumatic Brain Injury

Skye McDonald, PhD is a Professor of clinical neuropsychology, who has been interested in studying the social, emotional and communication disorders occurring following traumatic brain injury. Here we discuss her background, motivation and the outlines of her research and community service activities.

To start, what is your academic background and how did you pursue the early steps of your career in medical research?

I have a Bachelor's degree in science, with honours, and a Masters degree in clinical neuropsychology. Following my master studies, I worked as a clinician working with patients who suffer brain damage from a range of causes including stroke, dementia, and traumatic accidents. After several years, I became eager to understand the complex and subtle problems arising from brain injury, especially because of their immense impact on the ability of these patients to communicate. I enrolled in a PhD program, where I combined my research on patients with brain injury in the rehabilitation hospital with my clinical duties. After obtaining my PhD, I took up an academic position, through which I continued to perform research on the assessment and remediation of social and emotional difficulties arising from brain damage.

And what has been your motivation to choose neuropsychology as a field of specialization?

Understanding brain damage and its effects is a fascinating topic. Brain research has become a 'hot' topic in recent years, especially with the advent of modern brain imaging techniques that show the structures of the brain in detail, and indicate their activity during specific tasks. However, many facets of brain function remain difficult to reveal by these technologies. For example, there is a phenomenon known as unilateral neglect, whereby people suffering damage on the right side of their brain no longer notice anything to their left, despite having normal sensation. Why would this happen? What does it tell us about how the brain processes incoming information? We would not know the brain works in this way except by observing people with brain damage. So our understanding of the function and organization of the brain is extended by observing people with brain damage. It is also exciting to be able to pinpoint specific areas of brain damage or a particular neurological disorder, just from observing behaviour.

You are interested in studying the social and emotional disorders following brain injury. Can you explain to the readers the scope of these disorders and how do they influence the life of patients and their relatives?

Social and emotional processes can be affected by brain damage. For example, patients may lose their ability to recognize emotions in others, which can be problematic socially. If you are conversing with someone but you are unable to recognize expressions of boredom, irritation or even fascination, you will fail to guide your behaviour accordingly. This can be crippling socially when meeting new people, and can cause a huge strain on family members who find themselves unable to get the message across as to how they are feeling.

A second problem is the inability of these patients to put themselves "in another's shoes". We need to be able to see things from other people's perspective in order to understand conversational meaning. For example, when a person is being sarcastic they may say the opposite to what they mean. The only way we can understand their true meaning is to guess what is on their mind. Hinting, making small white lies, joking, using hyperbole are all instances where we need to guesstimate what the speaker intended.

A third major problem is related to disorders of emotional regulation. At one end of the scale is a disorder known as apathy, whereby the patient with brain damage cannot motivate

him/herself. Without external prompts the affected person may do nothing all day, every day. Another kind of disorder is losing control, where the patient may be over-talkative or tell bawdy jokes during job interviews for example.

All these social and emotional disorders have the sum effect of decreasing successful social interaction and increasing isolation and family strain.

Throughout your career, have you also collaborated or worked along with NGOs or patient support groups?

I am on the executive board of ASSBI, or the Australasian Society for the Study of Brain Impairment. ASSBI is a non-profit organization, and a vibrant society that offers clinicians and researchers the opportunity to come together in a cross-disciplinary forum to learn about the latest research concerned with people with brain disorders. Its cross-disciplinary nature is the key to its success. ASSBI holds an annual conference, offers a continuing education program, publishes a scientific journal, and operates a student forum. In addition, I developed a publishing arm 'ASSBI Resources', through which we sell evidence based resources for the assessment and treatment of conditions arising from brain disorders such as memory, language, communication, emotion perception, social skills, and anxiety.

Socio-emotional deficits in patients with Traumatic Brain Injury

Survivors of traumatic brain injury (TBI) suffer a multitude of social and emotional impairments, which negatively affects the quality of life of the patients and their families. Here we discuss the research conducted by Professor McDonald to unravel the nature and the underlying mechanisms of these disorders, and to develop diagnostic and treatment techniques.

Severe traumatic brain injury (TBI) arising from motor vehicle accidents, warfare and assaults is a leading cause of death and neuropsychological impairment worldwide. In the United States, it is estimated that around 5.3 million people are living with a TBI-related disability, while in the European Union the number is approximately 7.7 million. Survivors of TBI usually suffer physical, psychological and emotional deficits that prevent them returning to their former lifestyle. Relatives of these patients report lasting behavioural and personality changes such as childishness, self-centeredness, disinterest or dislike of others, quarrelsome, unreasonable or socially inappropriate behaviour, unhappiness and excitation. 'Such changes predict poor social adjustment and participation for the patients, and cause immense stress to their families and caregivers', said Professor McDonald.

A MATTER OF COGNITION

In 1978, an American neuropsychologist, Dr. Muriel Lezak, described impaired capacity for social perceptiveness as a key feature of the behavioural changes seen post injury. However, it is only recently that the research into the mechanisms underpinning poor social perceptiveness has commenced, fuelled by advances in the field of social neurosciences. A central element is social cognition— i.e. our ability to understand and predict the behaviour of others, share experiences and communicate effectively. As the human species relies upon cooperation and competition within groups to survive, social cognition is argued to be an evolutionary imperative that is modularly developed, independent of non-social information processing abilities (e.g. attention and memory).

THE BRAIN AND COGNITION

'The extent to which social cognition is mediated by unique brain processes, is hotly debated', says Professor McDonald. It does appear that the evaluation and interpretation of emotional and mental states represents a unique set of brain processes. Research involving the use of brain scanning technologies and behavioural assessment in patients with brain injury point to a system of interconnected networks within specific anatomical regions of the brain that mediate the automatic, often implicit, appraisal of emotionally salient information and mental states.

The brain structures thought to underlie social cognition are vulnerable to severe traumatic brain injury. TBI results in typical patterns of injury because of the way that acceleration/deceleration forces scrape the soft brain tissue across the bony floor of the skull. The frontal and temporal lobes of the brain are the most commonly affected regions. The brain structures in these regions are immediately affected by the contusions and bleeding, while more long-term effects can result from microscopic injury to the brain cells which disrupts the nerve connections. It is important to stress, however, that TBI is highly variable in its effects depending on both the severity and nature of the injury.

UNDERSTANDING COGNITIVE DEFICITS IN TBI

The research of Professor McDonald and her team focuses on understanding how social cognition is disrupted following TBI. Although the aforementioned changes in the personality and behaviour of the TBI survivors are not subtle, the early research has only described them in vague terms with no reference to the underlying mechanisms. Furthermore, no tools were available to pinpoint these disorders or to assess their severity. The early work of Professor McDonald focused on communication as a base to develop tests for the identification of social cognitive deficits. For example, in 2003 she developed a sensitive test to assess social perception in TBI patients called the 'The Awareness of Social Inference Test', better known as TASIT. TASIT is currently used on an international scale to not only pinpoint social perception deficit in TBI patients, but also in other neuropsychological disorders such as dementia, schizophrenia, autism, stroke. Even more, it constituted an important basis for the development of social cognition research. Additionally, Professor McDonald has developed theories to explain aspects of social cognition deficits in TBI and worked on methods to help the patient and their families circumvent misunderstandings. The following sections particularly discuss the research efforts of Professor McDonald in unraveling aspects of emotional and social impairment in TBI patients and their impacts.

Understanding the mechanisms underpinning social and emotional impairment in patients with TBI is a key element for developing techniques and treatments to improve the social interaction and life quality of these patients and their families

EMOTIONAL PERCEPTION

Emotional perception refers to our ability to recognize and identify emotions in others. During the last 15 years, Professor McDonald and her research group have proven that people with severe TBI have difficulties recognizing emotional facial expressions, especially negative expressions such as anger, sadness and disgust. In addition, they have established that people with TBI have significant difficulty recognizing emotion in audio and audiovisual displays. The reasons behind this impaired emotional perception have been explored by Professor McDonald in several studies. These supported the premise that people recognize emotions in others by simulating the same emotions in themselves. It appears that patients with severe TBI have problems with simulation but only for negative emotions. In several studies, these patients were able to mimic happy, but not angry faces of others and could express positive, but not negative emotions spontaneously and upon request. Similarly, they felt positive emotional changes when they were asked to assume happy postures, while no emotional changes were felt by assuming negative postures.

Based on their understanding of emotional perception deficits, Professor McDonald and her research team have recently developed treatments to improve emotional recognition, communication and social skills. These treatments can provide TBI patients with more positive opportunities for social interaction, leading ultimately to a better quality of life for them and their families.

THE THEORY OF MIND (TOM)

Another scope of the research done by Professor McDonald and her team is concerned with whether TBI patients are able to impute the thoughts and intentions of other people (an inability known as having a Theory of Mind, ToM). The ability to judge the motives of others is critical for understanding their behaviour and the meaning behind what they say. Professor McDonald has shown that some people with TBI have difficulty with this kind of judgement. 'This makes it very difficult for them to understand conversations. We have repeatedly demonstrated they can have a pronounced inability to understand sarcasm and, to a lesser extent, lies', said Professor McDonald. Professor McDonald and her team are currently in the process of developing treatments for ToM and broadly social cognition disorders.

THE CURRENT FOCUS

The current research of Professor McDonald is focused on two main thrusts; emotional regulation and empathy. Many people with TBI experience loss of emotional control. They may be under-aroused and fail to engage with the world, or, alternatively, over excited, for example, being quick to anger. Professor McDonald has recently received funding to explore three potential techniques for improving emotion regulation. Her first research project concerns the use of biofeedback to improve heart rate variability (HRV), which is reduced in cases of pain, anxiety and depression. Biofeedback refers to the concept of training an individual to change physiological activity for the purposes of improving physical and psychological health. Professor McDonald is testing whether improving breathing techniques can improve HRV and emotional control in people with TBI. The two other techniques are direct brain stimulation with a gentle electrical current, and self-control training, which involves doing tasks in a non-routine manner.

The second project involves the examination of the mechanisms underpinning empathy, including whether facial mimicry (i.e. mimicking other's facial expressions) and identification (i.e. identifying with others) influences empathy and how these processes are affected by TBI.

Researcher Profile

Professor Skye McDonald
Professor of Clinical Neuropsychology at the University of NSW

Professor McDonald is interested in studying social, emotional, and communication disorders as well as neuropsychological rehabilitation, more generally. She has developed novel approaches to assess and remediate emotion perception, social skills and communication in patients suffering traumatic brain injury. Her work extends to other neurological disorders such as dementia and developmental disorders such as Autism Spectrum Disorders. Skye leads a national Centre of Research Excellence "Moving Ahead" to address psychosocial rehabilitation after traumatic brain injury. With colleagues, she has also developed PsycBITE, a database freely available on the internet that indexes all research ever published in English that provides empirical evidence attesting to the efficacy of treatment for neuropsychological disorders arising from acquired brain disorders.

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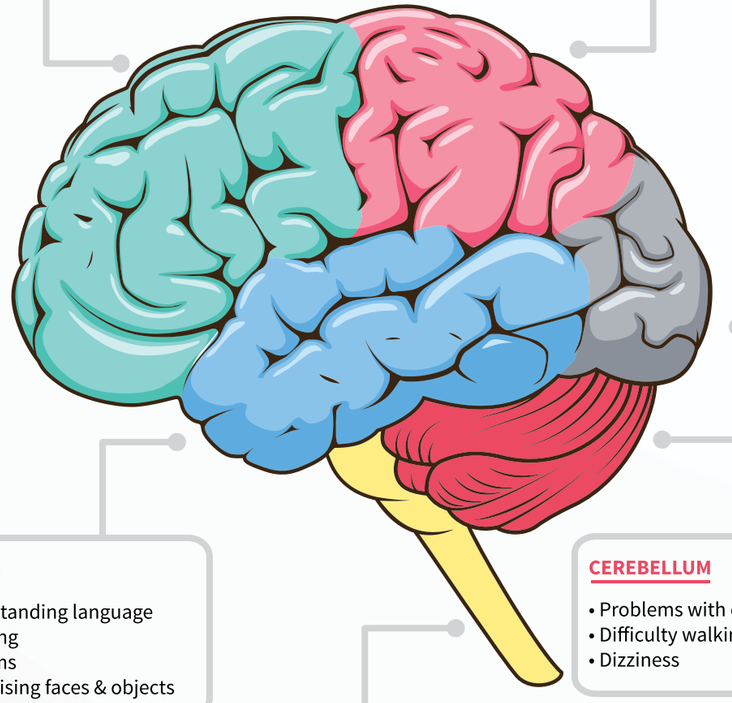
EFFECTS OF INJURY ON DIFFERENT AREAS OF THE BRAIN

FRONTAL LOBE

- Change in behaviour and personality
- Mood swings, irritability, impulsiveness
- Difficulty with language and problem solving
- Inability to focus
- Paralysis in severe cases

PARIETAL LOBE

- Difficulty distinguishing left from right
- Impaired hand-eye coordination
- Impaired special awareness
- Difficulty with reading, writing and mathematics



OCCIPITAL LOBE

- Vision problems
- Hallucinations

TEMPORAL LOBE

- Difficulty understanding language
- Difficulty speaking
- Memory problems
- Difficulty recognising faces & objects

CEREBELLUM

- Problems with coordinating movement
- Difficulty walking
- Dizziness

BRAINSTEM

- Breathing & heart rate changes
- Difficulty swallowing
- Dizziness and nausea

THE EVOLUTION OF GENETICS RESEARCH

In the middle of the 19th century, Gregor Mendel pioneered the field of genetics by studying inheritance traits in pea plants. At the time genes had not yet been discovered, and Mendel attributed the various traits he observed to discrete “units of inheritance”. His findings were published in 1966 but unfortunately received very little attention until the emergence of molecular genetics in the early 1900s. Scientists at the time were attempting to find out what cellular molecules were responsible for expressing inherited traits. In 1902, Theodor Boveri and Walter Sutton, who were working independently on different organisms using simple light microscopes, suggested that chromosomes (rod shaped structures in the nuclei of cells) may “constitute the physical basis of the Mendelian law of heredity”. Soon after, German biochemist Albrecht Kossel was awarded the Nobel prize for physiology for his work in determining the chemical composition of DNA, the genetic substance that makes up a chromosome. At around the same time, Hugo de Vries discovered genetic mutations, errors that occur in the replication of DNA molecules. This finding was furthered by Thomas Hunt Morgan in 1915, who elucidated the mechanism by which mutated genes could introduce new characteristics into populations, thus providing a means for new species to arise. This concept provided a genetic basis for Darwin’s theory of evolution. >

A defining moment in the history of genetics came with the discovery of the structure of DNA. In 1952, Rosalind Franklin collected x-ray diffraction data from an isolated crystal of DNA, which Watson and Crick then used to demonstrate the helical structure in 1953. In the years that followed, researchers began to understand how DNA controls the production of proteins. They discovered a similar molecule called messenger RNA, that carries genetic information from DNA in the nucleus of the cell to the ribosome, where proteins are synthesised.

In this section we introduce the research of Dr. Jonathan Wright, a molecular biologist who investigates how evolutionary adaptation occurs in the regulatory regions of genes. His research on zebrafish is helping to define the molecular evolutionary processes that gave rise to the structure of vertebrate genomes, in addition to offering insight into how the mechanisms that turn genes on and off may have evolved in our own species.

Understanding the basics of how genetics work at the molecular level has paved the way to develop a myriad of patient diagnoses and treatments. Currently, there are genetic tests available for diagnosing over 1000 diseases including sickle cell anaemia, Huntington's disease and cystic fibrosis. Predictive and presymptomatic tests are helpful for healthy individuals with a family history of specific diseases, such as genetic disorders and cancer, that may develop later on in life. This information can help people to choose healthcare that will either help to prevent illness or reduce its severity.

The second article in this section introduces Dr. Hilary Coon, whose research involves identifying the genes that predispose people to commit suicide. Not only will this work increase our understanding of the cellular processes that are involved in the tendency to become suicidal, but it may ultimately lead to the development of diagnostic tests and preventative treatments.

Secrets of Molecular Evolution in Zebrafish Genes

Dr. Jonathan Wright is a molecular biologist investigating how evolutionary adaptation occurs in the regulatory regions of genes after whole genome duplication events.

Increasing expression of an iLBP gene in the retina of a developing zebrafish embryo. FEBS Journal 275(12):3030-3040.

What drew you to the field of evolutionary biology?

Charles Darwin's theory of evolution by natural selection has always been vaguely in the background of my research, but I never thought in the early years of my career that I would land in the field of evolutionary biology. As an undergraduate in Canada, I had no great interest in biology and was considering a career in music, studying classical guitar and flute. That all changed in my 3rd year of undergraduate studies when my microbiology professor invited me to start an honours research project. By the end of the summer project, I was hooked on research and decided on graduate studies. I had no career goals – I simply enjoyed research, particularly the bench work. Curiosity was my sole motivation.

My research experience has focused on defining molecular mechanisms that control gene expression in bacteria, algae and fish. My early work also involved population and behavioural studies on a range of endangered wildlife species and developing some of the first DNA fingerprinting tools for genetic studies of fish. Today, these genetic tools are still widely used in conservation, population and behavioural biology.

How can your work on zebrafish help us better understand the diversity of life on the planet, including the origins of our own species?

Most vertebrate genomes contain ~20,000+ genes and the complexity of these animal genomes are the result of at least two rounds of whole genome duplication that occurred in vertebrates well before the fish whole genome duplication. The remnants of these two previous whole genome duplications in early vertebrates are barely detectable - the gene sequences have changed so much that duplicate genes are barely recognized as twins, if at all. Our work offers an opportunity to define molecular evolutionary processes that forged the structure of extant vertebrate genomes, including the human genome, in the crucible of natural selection.

What are the possible implications of your work for human medicine?

A class of regulatory proteins, now known to control the differential expression of vital gene groups in teleost fishes, has received increasing attention from the pharmaceutical industry. These peroxisome proliferator-activated receptors (PPARs) have been implicated in myriad human diseases such as hypercholesterolemia, obesity, arthritic inflammation, and diabetes. Currently, PPARs are under intensive study as targets for therapeutic treatment of these debilitating human afflictions.

What do you believe is the most significant outcome from your research career?

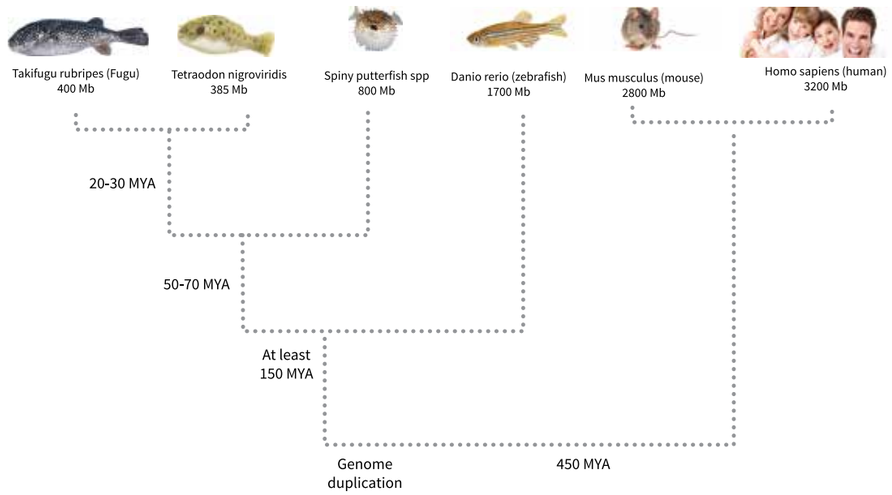
The students I have trained. I hope I've imparted to them the delight of curiosity, exploration, and an understanding of how scientific research is done. I hope they enjoyed the human aspect of science, the exchange of ideas, and playful discussions. I hope, too, they will pass these qualities on to their own students.

What is your assessment of the current state of scientific research funding? What legislation or policies would you change to improve how science in your field is done?

The general public and our elected representatives in government often view scientific research as a means to economic growth. This leads national science funding agencies to prioritize applied science leading to technological innovation while discovery science is increasingly underfunded. I think this is a mistake, as we cannot always predict where fundamental, discovery-based research will lead us. Science, like all of the arts, is an intrinsically human activity of seeking knowledge about the universe and ourselves. I believe few would argue against civic support to art museums or ballet companies. I ask myself, perhaps naively, why is 'curiosity-driven' science not government-funded simply for its intrinsic value to humanity? On rare occasions, scientific discovery leads to profound insight into the workings of the universe. New discoveries may also lead to creation of leading-edge industries generating enormous wealth or wondrous health benefits, or both. Let me briefly illustrate this point with one example: In the 1970's Werner Arber, Daniel Nathans and Hamilton O. Smith were independently studying DNA modifying enzymes in bacteria. In today's funding climate, this work might receive scant attention. But Arber, Nathans and Smith shared the Nobel Prize in Physiology or Medicine in 1978 for their discovery of restriction endonucleases, enzymes that cleave DNA at specific nucleotide sequences. These essential tools enabled the development of recombinant DNA technology, which in turn led to today's $400 billion dollar biotechnology industry.

The Evolution of Genetic Light Switches

Over 150 years after Darwin's seminal 'On the Origin of Species' was first published, biologists are still defining the molecular underpinnings of evolution. Dr. Jonathan Wright's zebrafish studies give us insights into how the mechanisms that turn genes on and off may have evolved in our own species.



ALL EVOLUTION IS MOLECULAR

On childhood fishing trips in England, Wright walked in Charles Darwin's footsteps around the naturalist's family lake at Maer Hall in Staffordshire, England. Perhaps it was that early brush with the great theorist that ultimately drew Wright, an aspiring musician, to study the molecular machinery of evolution.

The abstract notion of a gene as the fundamental unit of heredity was not coined until nearly 30 years after Darwin's death. Today, biologists know that evolution is rooted in molecular changes of genes. Genes are stretches of DNA, some of which acts as a blueprint a cell can read, transcribe into RNA and in turn translate into protein, generating the phenotype of an individual organism. Other stretches of 'non-coding' DNA do not contain protein recipes but instead interact with certain proteins that make nearby stretches of coding DNA either available or inaccessible to the cellular machinery. The result: portions of an organism's genetic blueprint is either closed (gene turned off), or opened to be read (gene turned on).

DNA sequence mutations in sperm and egg cells happen by exposure to environmental factors (such as, UV radiation in sunlight or natural or human-made chemicals), or spontaneously occur by random errors during DNA replication, processes that fuel the engines of evolution. When an essential part of the DNA is mutated, it will be removed from the gene pool through the pressures of natural selection. Mutations with adaptive benefit will spread throughout the population.

On very rare occasions, DNA mutation leaves little room for permanent inheritable changes in the genetic code with the catastrophic consequence of a lethal genetic disorder in the offspring of the next generation. Sometimes, however, mutation provides more raw material for genetic innovation. Before a reproductive cell divides and proliferates, it must create a full copy of its genetic material to pass on to each daughter cell. If this duplication proceeds abnormally, one daughter cell may retain both DNA copies. Such whole genome duplication (WGD), the doubling of an organism's genetic information, is believed to be one of the main forces underlying the increased complexity and diversity of life on earth. Susumu Ohno, the father of gene duplication theory, proposed in the 1960s that there had been at least two whole genome duplication events in vertebrates leading to humans.

While working on the genetics of fish species, Wright read about the many duplicated genes present in bony fishes. Theorists assume that such a WGD over 230 million years ago led to the high numbers of duplicated genes present in modern bony fishes. Using zebrafish as an experimental model, Wright set out to investigate why so many duplicated genes were still present in the modern fish genome. Evolution does not normally permit redundancy - an extra, unnecessary copy of a gene should be lost from the genome by mutational decay. Understanding the evolution of duplicated gene pairs in bony fish could provide insights into the origin of our own species.

THE FATE OF DUPLICATED GENES

With the zebrafish genome already sequenced, Wright quickly found that the intracellular lipid-binding proteins (iLBPs) gene family had retained over 60 per cent of its duplicates. This result was striking compared to the average duplicate retention rate of 3-6 per cent across entire fish genomes. iLBP genes code for transport proteins that carry fatty acids, vitamin A, and other essential lipids around the cell. These proteins convey important signals and are essential in cellular development, growth, and reproduction. Wright hypothesized that retention of more iLBP genes could allow for the development of more sophisticated cellular signalling networks.

Researchers have long been interested in the fate of duplicated gene pairs. If the ancestral gene function is maintained by one gene copy, the other copy can serve as raw material for evolutionary adaptation, free from selective pressure. Under the prevailing model of evolution following gene duplication articulated by Force et al. in 1999, a duplicated gene has three possible fates. In many cases, it will mutate into benign uselessness, leading behind evolutionary baggage. As Wright explains, "the process of evolution proceeds by happenchance, mistakes are made, and it is often a messy process leaving behind abandoned bits of life". Another possibility is that one copy of the duplicated gene will mutate to gain a new, adaptive function. This adaptive innovation will be preserved in the gene pool. The third possibility in Force et al.'s model is subfunctionalization, wherein each gene copy following duplication acquires through mutation only a sub-set of functions of the ancestral gene that are divided across the two duplicates. Framing his investigating with the Force's et al. model, Wright's curiosity about the duplicated fish genes led him to investigate how the iLBP duplicates had evolved since the teleost WGD.

REGULATING GENE EXPRESSION

Each cell in the human body contains over 20,000 genes. Yet at any moment, only a fraction of these genes will be active, readily available for DNA to be transcribed into RNA and then translated into protein. Gene expression, the switching on and off of gene activity, makes us who we are. Regulatory regions of the gene act as light switches, interacting with cellular signals to keep genes open or closed to the cell's transcription machinery. These genetic switches are sensitive to many factors, from the cellular environment to the organism's stages of growth and development.

Wright focused his evolutionary inquiry on regulatory regions of the iLBP genes and determined that the mechanisms that control many of these genes have diverged since the teleost WGD. Zebrafish iLBP genes appear to have developed different on-and-off switches that allow nearby coding regions to be activated at different times and in different body tissues. For example, one member of a duplicated fatty acid-binding protein gene pair is expressed in the zebrafish brain during development while the duplicate gene is expressed in the zebrafish swim bladder.

Wright's research reveals that dietary fatty acids have different effects on iLBP genes turning them on or off at the right time when needed whether in the brain, the heart, or the liver. The complexity of the iLBP multigene family allows for the essential transport and intracellular signalling of lipids by these proteins at stages of embryo or larval development, or under environmental circumstances that fit the zebrafish's changing needs.

NEW MOLECULAR MECHANISMS

Wright is currently working to define the precise molecular mechanisms controlling iLBP gene expression in different tissues. Recent studies have identified regulatory proteins called peroxisome proliferator-activated receptors (PPARs), which bind to specific response elements (PPREs) in the zebrafish iLBP genes. The binding action between PPARs and PPREs stimulates gene expression, opening up nearby genes to the cellular transcription machinery. Wright and colleagues seek to identify other proteins involved in the complex iLBP gene expression signalling pathway to understand how these interactions give rise to differential gene expression in different tissues at different times.

HEALTHCARE APPLICATIONS

Activities in the regulatory regions of genome appear to play a large role in common diseases such as cancer, diabetes, Parkinson's, and Alzheimer's. The PPARs that Wright is investigating in the context of zebrafish duplicate gene expression are currently under investigation as potential drug targets for the treatment of a range of human diseases. As research continues into understanding the cascade of molecular signalling events surrounding PPAR-meditated gene expression, Wright believes zebrafish can serve as an excellent experimental animal model. Elucidating these gene expression pathways and their behavior in diseased states could lead to the development of drugs that correct genetic dysregulation in many devastating human conditions.

Researcher Profile

Dr. Jonathan Wright
Professor
Dalhousie University
Department of Biology

Dr. Jonathan Wright received his PhD from Memorial University of Newfoundland. He studies gene and genome evolution with emphasis on the genesis and fate of duplicated genes. Dr. Wright's research deals with the mechanisms and evolution of gene regulation in zebrafish and other fishes, focusing on the multigene family of intracellular fatty acid- and retinoid-binding proteins. Among his many awards, Dr. Wright has received four UNESCO Biotechnology fellowships, has been a visiting research scientist at universities in Stirling, Scotland, Milan and Rome, Italy, and São Paulo State, Brazil and currently serves on the advisory board of the journal, Neotropical Ichthyology. He lectures on molecular biology and genetics at Dalhousie University.

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Dwelling on Suicide Genetics

Dr. Hilary Coon at the University of Utah is determined to find genetic risk factors predisposing people to commit suicide. Having access to DNA and phenotypic information from more than 4000 suicide victims, she is in an excellent position to fulfil her quest.

For most people, suicide is a topic they prefer to keep at arms distance. How did you become interested in studying the genetics of suicide?

The main focus throughout my research career has been the study of genetic risk factors contributing to psychiatric disease susceptibility. The study of suicide is a natural outgrowth of this interest, as most individuals who commit suicide struggle with mental illness. However, most individuals with mental illness do not commit suicide, which suggests that additional specific risk factors, some of which may be genetic, probably exist. Suicide has not yet been the focus of intense study in the field of psychiatric genetics.

I became aware that the University of Utah had a large, untapped resource of DNA from individuals who had committed suicide. Though these cases are de-identified to our research team, there are database resources in Utah that have allowed the cases to be grouped into high-risk extended family clusters. Knowing that cases are related allows us to search for genetic variation shared among these very distant relatives through their common ancestors. Their family relationships are distant enough to minimize the impact of shared environmental factors. However, since the genetic risk factors recur in each distantly related suicide case, the familial genetic risk is magnified and therefore easier to detect.

I have no illusions that the study of genetic risk factors for suicide will be an easy task. But each of us knows of a friend, relative, or co-worker whose life has been touched in some way by suicide. The repercussions of a suicide are severe and long lasting. Suicide is a potentially preventable tragedy that deserves urgent study.

You state that you wish to identify those who share phenotypic profiles with decedents with known sequence variation? How does this information strengthen your analyses?

Our database collaborators can match cases to electronic data that flags early life risk factors and co-morbid psychiatric and medical conditions. This additional data, combined with shared familial genetic risk, gives us an unprecedented opportunity to study familial genetic risk of suicide. One strategy is to use co-morbidity, a particular demographic characteristic, or particular environmental exposure as a way to select high-risk families and additional non-familial cases. For example, we have ongoing studies of a high-risk family where the proportion of women is unexpectedly high, and we are comparing this family to non-familial female suicides.

What light can the study of families at high risk for suicide shed on suicide in general?

We study the familial cases because familial genetic factors can be detected through their recurrence in families. It is however certainly possible that individuals who are not related, carry the same genetic risk factors. We intend to screen our top genetic findings in as many cases as we can afford to determine their frequency in the more heterogeneous non-familial sample.

What kind of interventions do you believe could spring out of your work?

We will make any finding where we have achieved appropriate scientific validation and replication known through publication and communication with local and national societies and support groups. Without knowing what our findings might be, it is impossible, at this point, to guess if any finding could be related to interventions. In the event a feasible intervention will be apparent, we are poised to take steps to advocate for this intervention. Nevertheless, I'd like to make it clear that our research group has formally declared that we will not seek to profit if a diagnostic test or treatment is developed from our work.

Do you think genetic tests will be part of suicide risk assessment in the future?

It is not certain if any of our findings would translate into genetic testing. From where we stand now, it seems that genetic testing may have a low impact if we are correct in our assumption that there is a high level of genetic heterogeneity, and that any one specific genetic risk factor likely plays out in the context of complex environmental exposures and other background genetic risk, and protective factors.

Our goal is rather to help identify some of the genetic risk factors for suicide to increase our understanding of underlying neurobiological and cellular processes that might be part of the undeniably complex risk landscape of suicide.

The Meticulous Drawing of a Neurobiological Suicide Map

Some people state that becoming a successful researcher requires the bright mind of the scientist, but then also depends critically on fortunate opportunities. For Dr. Coon this opportunity came in the form of access to a unique resource, that became the starting point of an exceptional project – Searching for genes associated with an increased risk of committing suicide.

UNTANGLING A KNOTTY SCENARIO

Studying the genetics of suicide is a "daunting task", to use the words of Dr. Coon. As opposed to genetically simple illnesses such as Huntington's disease, suicide is very heterogeneous. Suicidal behaviour, and more specifically, the completion of suicide, is dependent on a multitude of genetic factors, which are interacting with an unknown amount of environmental stressors. These factors differ between individuals, and many combinations of genetic and environmental factors can lead up to the same endpoint – Suicide.

Being lucky enough to get her hands on what must be one of the largest DNA collections from suicide victims in the world, Dr. Coon set out to do what she does best: studying the genetic risk leading to complex traits. Her research team first obtained ethical approvals from the University of Utah Institutional Review Board (IRB), in addition to IRBs at the Utah State Health Department and Intermountain Healthcare. Through these approvals, this DNA resource was made even more valuable by being linked to the Utah population database, holding medical, demographic and genealogic information. With the help of these data, Dr. Coon and her team hope to identify specific gene variants, while controlling for the influence of other factors such as psychiatric and physical disorders, hence being able to sort out the gene variants that are related to an increased risk of suicide per se.

Dr. Coon was soon able to identify several extended families where suicide was significantly more common than in the general population, providing a dream scenario for a researcher trying to identify genetic risk factors. "We study these familial cases because familial genetic risk factors are magnified through their occurrence over and over in extended families", says Dr. Coon. She is, however, underscoring that the research team doesn't have access to identities of her study subjects or their living relatives. "I'd like to emphasize that we study our data resource from a de-identified perspective; all identifiers are stripped from cases, and familial risk is given as an aggregated, family cluster statistic so that we have no chance of inadvertently identifying any cases or family members."

Suicidal behaviour, and more specifically, the completion of suicide, is dependent on a multitude of genetic factors, which are interacting with an unknown amount of environmental stressors.

Studying high-risk families is therefore a good start for understanding genetics of a specific trait, but findings from these family clusters will also be used to assess risk genes in the unrelated suicide cases. Using the top hits from her search within high-risk families, she also screens all the non-familial cases for the presence of a genetic variant. With the use of more comprehensive screening tools, such as whole genome and whole exome sequencing, Dr. Coon hopes to find variants that are shared between both related and unrelated individuals.

CO-MORBID COOPERATION

Realizing the huge potential of the resource she has access to, Dr. Coon has initiated collaborations with scientists and research institutions, ranging from her departmental colleagues to foreign universities. Among other factors, the joint ventures will be investigating the co-morbidity of suicide and other conditions, such as post-traumatic stress disorder, cardiovascular disorders and and opiate abuse. One of her collaborative efforts deals with the co-morbidity of suicide and asthma, two seemingly very disparate conditions. This research is based on observations that asthma sufferers are at significantly increased risk of suicide when compared to population suicide rates. Looking into the genetics of this co-occurrence will be an important contribution to resolving this medical conundrum.

Understanding how genes and environment interact is one of the most important issues a psychiatric geneticist is facing. Since the likelihood of developing a psychiatric condition is dependent on an abundance of both genetic and environmental risk factors, it is not enough to perform isolated studies of genes or environmental hazards. Therefore, in yet another collaborative project, Dr. Coon studies suicide victims exposed to specific environmental conditions. She believes they might carry genetic factors making them more vulnerable to the particular environmental impact, increasing the risk for suicide.

BRAIN CONTRIBUTIONS

Dr. Coon's close partnership with the Utah State Office of the Medical Examiner has given

her more than DNA samples. After obtaining additional ethical review board approvals, Dr. Coon has recently begun to collect post-mortem brain tissue and skin biopsies from suicide victims. Using brain tissue, it is possible to look for expression of the genes identified in the DNA samples. Gene expression analyses can conversely be used to further guide the DNA analyses, looking at specific genes or gene pathways that show abnormal expression.

Identifying gene expression changes that coincide with changes in DNA would make a result more solid. Given the heterogeneity of suicide, it is, however, crucial to look at the right sample subset. As brain collection from suicide victims is a slow process, Dr. Coon will have to bide her time for this part of the study, banking tissue until she can match tissue with DNA having a specific genetic profile, or when she manages to get her hands on DNA and tissue from the same individuals.

The value of the post-mortem brain tissue doesn't end here. Synaptic dysfunction is implicated in suicide, and studying synaptic characteristics in the brain from the suicide cases might further guide the search for genes involved in the increased risk of suicide. As with the gene expression data, this will be an important complement in the search of genetic variation, governing which genes to focus on.

GOING MORE THAN SKIN DEEP

With the recent advances in stem cell technology, cells from skin tissue can now be converted to stem cells, called induced pluripotent stem cells, or iPSCs. The technique, while still technically difficult and costly, is a huge step forward in medical science. Not only is it now possible to grow neurons from iPSCs but employing iPSC techniques might also answer questions on an individual level. As the study progresses, Dr. Coon plans to use skin fibroblasts from subsets of suicide cases with validated, high-risk gene mutations that have persisted through rigorous statistical and molecular tests, to produce neuronal cell cultures.

This approach, together with the post-mortem brain tissue, will open up a whole new avenue for functional studies. Having living neurons in culture, derived from individual suicide victims, allows studying the functional consequences of an aberrant gene, using electrophysiology and calcium signalling experiments. Also on the agenda are re-expression experiments, reversing a deficiency to study the functional outcomes. On top of that, neuronal cell cultures can also be used to test for potential pharmacological therapies, studying the effects of drugs on the cells.

"In short, we have found many opportunities for creative ways of looking at these data and have only begun to scratch the surface", says Dr. Coon.

Dr. Coon doesn't seem to be the kind of person that sits around waiting for opportunities to come her way. Like a hub in the middle of this suicide centred wheel, she has initiated studies that might answer many of our questions about why some people commit suicide.
It is obvious that it takes more than a lucky break to become successful in research. It also takes a brilliant intellect to realize the potential of a situation and transform ideas into action.

Researcher Profile

Dr. Hilary Coon
Department of Psychiatry, University of Utah School of Medicine

Dr. Hilary Coon is the principal investigator of a research initiative set out to identify genes associated with increased risk of suicide. Her work is focusing on high-risk families where suicide is frequent, and together with a broad network of both national and international collaborators, she also studies the co-morbidity of suicide with lung disorders, cardiovascular disorders and obesity. She also studies the genetics of autism and addiction. Dr. Coon's interest in research ethics has also led to long-term service on the University of Utah Institutional Review Board.

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FACULTY ACTIVITY REPORT (FAR)

BIOTECHNOLOGY

Biotechnology involves the use of biological systems for industrial processes. In this section we introduce two researchers with different goals, but with a firm focus on biological systems as tools to achieve them. While biotechnology may sound like a modern arrangement, humans have exploited biological phenomena for thousands of years. Records of ancient biotechnological processes include beer and cheese production, and selective breeding of animals and crops. While our ancestors learned how to utilise biotechnologies through keen observation and trial and error, our current understanding of biological systems has enabled us to address a plethora of complex problems across the entire spectrum of modern society. Increasing our understanding of complex biological processes will help us to better apply, or indeed discover novel, biotechnological approaches.

This is part of the ethos underpinning the Functional Diversity of Cofactors in Enzymes Research Training group, a collaborative effort to understand enzyme cofactors at a basic level. Professor Andreas Bechthold, who is the spokesperson for the group, explains how their study of the synthesis, structure and behaviour of these molecules could lead to breakthroughs in the discovery of antimicrobial agents and novel methods for chemical synthesis. These potential outcomes show the flexibility of biological systems for use in diverse applications. Dr. Yuichi Nodake and colleagues are investigating the use of bacteria commonly found on the skin as the active ingredient in a cosmetic product, which can be applied to the skin and act a moisturiser and an antimicrobial agent against harmful bacteria. This approach could lead to personalised probiotic cosmetic treatments that provide long lasting effects, exploiting the skin's own bacteria.

ENZYME COFACTORS – STRENGTH IN COLLABORATIONS

Cofactors in enzymes are like the second key in a two key lock – absence of a cofactor renders the enzyme dysfunctional. With a collaboration map more complex than a spider's web – the Functional Diversity of Cofactors in Enzymes Research Training group, is determined to deliver top-level science in the field.

Professor Andreas Bechthold, you are the spokesperson for the cofactor research collaborative group. How does the cofactors research training group differ from other Ph.D. programmes or research groups?

Firstly, and possibly obviously, the research focus is on cofactor dependent enzymes, and most conferences and lectures in connection with the research training group are focusing on this topic.

Secondly, the group is trying to set up a bridge between the academy and the pharmaceutical and biotech industry. We hold an 'industry lecture' for our students, giving them the opportunity to get to know people from the industry and to discuss future job opportunities. I am very impressed by the success of this lecture so far.

The group also has an updated way of handling gender equality, offering additional services (such as workshops) to women scientists. Why do you believe gender equality in academia is important and do you think women scientists need more support to be successful?

While the principle of gender equity in the workplace is generally accepted in the west, discriminatory practices persist in many organizations. At the University, more than 50 per cent of the undergraduate students and around 50 per cent of the Ph.D. students are female in subjects such as pharmacy. However, less than 10 per cent of the professors are female.

Most of the Ph.D. students are around 30 years old when they receive their Ph.D. Many Ph.D. students are planning to have a baby, and most of the time its women that take care of the baby – not getting enough time for research. Getting a permanent professor position at the University is very competitive. Many women do not even try to go for a scientific career, as they do not believe that it is possible while also raising children. We want to support women and men who are interested in science and who are also interested in starting a family.

Many of the projects of the research training group focuses on enzyme co-factors in natural products, was this a strategic approach, or is it merely mirroring the focus of the researchers composing the group?

The focus on enzyme cofactors in natural products is mirroring the interests of the researchers composing the group. When we applied for the funds to start this research collaborative group, we could count 65 joint publications about co-factors in natural products among the applying groups.

One of the outcomes of the co-factor research in natural products is the generation of novel antimicrobial substances. How is knowledge of enzyme cofactors aiding in achieving this goal?

I do not believe that the generation of novel antimicrobial substances is necessarily an expected outcome of the research collective. But there is a chance that findings will lead to novel drugs. The focus of the group is on basic science and the results might lead to future applications. For example, cofactor regeneration is an important issue in industry and some of our projects are focusing on this issue.

Describe how your protein engineering efforts merge with the focus on enzyme co-factors.

This is potentially an important issue. If you learn details about how cofactors are used by enzymes, how they bind to the enzyme and how the enzyme structure is determined by the cofactor, then protein engineering efforts will become much more effective. Conversely, protein engineering may also lead to new discoveries about enzyme cofactors and the processes in which they are involved.

What are the research training group's research goals for the next ten years?

Our goal is that the researchers composing the research collaboration will produce even more joint publications – mirroring increased collaboration within the group. We also want to contribute to producing well-trained scientists that successfully continue their career within the industry. Last, but not least, we hope to get a second period of the RTG granted or even to become an international research training group by 2019.

INTEGRATIVE APPROACHES TO COFACTOR BASICS

While enzyme cofactors are highly interesting out of a practical perspective, Professor Bechthold and his fellow colleagues in this outstanding collaborative effort have instead set their minds on scrutinising the basic properties and functions of these factors – making up the fine threads of the web of life.

Enzymes dependent on cofactors can be found in all areas of biology – human, animal and plant alike. Cofactors contribute to survival and maintenance of organisms and, if dysfunctional, can be the root of disease. However, these molecules – both organic and inorganic – transcend biology and are increasingly finding applications in other fields. But for such applications to become reality, someone first has to lay the foundations, providing detailed knowledge about which these factors are, and how they look and function.

Interdisciplinary focus

As academics know, and non-academics suspect, scientists within academia tend to be extremely specialized within their field, and knowledge of current research advances within neighbouring disciplines tend to slip by unnoticed. This is in part a prerequisite allowing the total focus on a subject that may lead to new discoveries. Biology is, however, not divided into faculties, and academic institutions increasingly realize the importance of collaborating across traditional departmental boundaries to produce state of the art research.

The Functional Diversity of Cofactors in Enzymes Research Training Group has taken scientific collaborations to a new level, forming a truly multidisciplinary team with contributing researchers from the Faculties of Chemistry, Pharmacy, Biology and Medicine and extensive partnerships outside academia. Using this approach, they hope to contribute to making the Institute of Pharmaceutical Sciences in Freiburg one of the top pharmaceutical institutes in Europe.

The 'training' part of the long name the group have chosen, witnesses of a part of academic life often overlooked by senior scientists. Traditionally, Ph.D. candidates within academia are trained to perform well within an academic context. A Ph.D. is, however, a gold mine in terms of transferable soft skills.

Unlike many academical institutions, the enzyme cofactor research-training group has a clear focus on producing excellent scientists that are capable of launching their

independent careers – within academia and beyond – once graduated.

Young scientists also have all the support they can imagine in terms of providing equal opportunities for both women and men. Researchers with young children are offered flexible work conditions and the University even have its own child care facilities – all to allow young researchers to continue doing what they do best.

"The most successful time of a researcher is when the scientist is young. Most young scientists are flexible enough to overcome conservative structures, and they are much better in creating novelty", says Professor Bechthold when explaining the generous support structures. As someone who successfully coached 38 Ph.D. candidates through their studies, he should know what he is talking about.

Enzymes for drug discovery

A large part of the projects within the collaborative group focuses on cofactors in enzymes related to natural substances. While drug discovery is not a specified goal of the research collective, work performed in the various labs sometimes lead to discoveries with a translational potential.

Mathematical models have predicted that streptomycetes – actinobacteria studied by several labs within the research collective – can produce approximately 100,000 antibiotics. Only about three per cent of them have been discovered so far.

By developing new techniques for culturing previously uncultivable bacterial species as well as using genomic sequencing, genome mining, high throughput miniaturized screening and combinatorial biosynthesis, the chances of identifying substances with antimicrobial properties radically increase. While big pharmaceutical companies have

lost their interest in the field, focusing on drugs with a bigger potential for economic gain, small biotech companies have plunged into the field.

Andreas Bechthold was not late to realize the potential of the serendipitously discovered substances. Together with eight colleagues, he started Combinature Biopharm, a small biotech that after merging with MerLion Pharmaceuticals successfully brought finafloxacin – an antibiotic for the treatment of otitis – to the market. The drug is also in clinical trials for a large number of other indications, including infections in patients with chronic obstructive pulmonary disease and cystic fibrosis, as well as hospital acquired infections such as MRSA.

A deeper understanding of the works

While drug development of substances discovered by the research-training group is a fortunate by product of their work, most of the efforts within the collective focus on basic research questions. A more thorough understanding of cofactors; their synthetic paths, their structures as well as mechanics and enzymology of the corresponding enzyme interactions, are a prerequisite for more applied research by researchers in neighbouring fields.

Professor Bechthold leads a project exploring cofactor-dependent luciferase–like proteins involved in the synthesis of natural products with antibiotic and cytostatic effects.
The knowledge of these enzymes allows for the manipulation of their characteristics. In the field of protein engineering, such knowledge can lead to the production of drugs with better properties, such as increased stability. In an innovative approach, Professor Bechthold uncovered what it takes to change an enzyme producing O-glycosidic bonds, to one that binds carbon by glycosylation instead. C-glycosylated proteins are valuable in drug discovery, because they mimic the features of the O-glycosylated factors, but are far more stabile. By introducing such a genetically engineered enzyme into a biosynthetic pathway, substances with more desirable characteristics can be produced in a process called combinatorial biosynthesis.

Professor Bechthold also studies the enzymes leading to the biosynthesis of mensacarcin and rishirilid. Mensacarin is an experimental drug with potent antitumor activity. It is, however, far too toxic to be used in humans. Knowledge of the biosynthetic pathways could nevertheless aid in producing compounds with more desirable characteristics.

Another group, led by Dr. Susana Andrade, is working on characterizing flavoproteins – in atomic detail – as she likes to put it. These proteins have the organic cofactor flavin adenine dinucleotide in common. Working together with Drs. Jung and Boll, Dr. Andrade is also investigating the medicinal and ecological potential of these FAD-dependent proteins.

Dr. Oliver Einsle's group (nitogenase) and Dr. Friedrich's group (NADH:ubiquinone oxidoreductase) are both working on cofactors of enzymes which are essential for life.

Dr. Boll's group, in turn, focuses on enzymatic ring reduction under anaerobic conditions –processes that are present in a large variety of cofactors. Yet others, such as Drs. Weber and Schleicher concentrate on the identification and characterization of paramagnetic cofactors in proteins by using continuous–wave and time–resolved magnetic resonance techniques, as well as transient absorption spectroscopy. Such paramagnetic species are involved in both light, and dark activated enzymes.

Cofactor mimicry

Co-factors have traditionally not been the main focus of drug development efforts. Drs. Günther and Jung, however, argue that the identification of cofactor mimicking inhibitors could provide a range of hitherto unexplored pharmaceutical targets. Such a search does not necessarily require laboratory work. Instead, they can predict biological effects of molecules using cheminformatics methods, such as structure-based prediction of molecular interactions and in silico screening techniques. Through the extensive collaborative network, the properties of molecules theoretically identified to have a biological activity can then be immediately validated in biological assays developed by Dr. Jung and others. "We believe that drug development will benefit from more knowledge about cofactors," says Professor Bechthold.

A biotechnological connection

When speaking of enzyme co-factors, people mostly think of biology and medicine. Enzymes, however, transcend the boundary between biology and technology, and the production of tailored enzymes for use in various technological applications is a promising field. Enzymes can, for example, be used in chemical synthesis, providing benefits such as milder reaction conditions compared to traditional methods.

Methyltransferase enzymes catalysing alkyl transfer have many potential technological applications. These enzymes use S–adenosylmethionine (SAM) as the crucial cofactor – transferring a methyl group to a target compound. In living cells, SAM is recycled in a complex, multistep process. By closely investigating these steps, Dr. Axender hopes to produce a toolbox to be used with methyltransferase catalysed alkyl transfer – offering biological solutions to technical problems.

The group, led by Dr. Michael Müller, is investigating a class of enzymes, known to catalyse oxidative phenol coupling. The focus is on understanding and hopefully to then use these enzymes in biotechnological approaches.

The research of the collaborative group continuously acts on levels close to practical applications, allowing other researchers to pick the ball up for translational applications. By joining forces, the combined knowledge and technical expertise of the research collaborative group lift the research to a level unprecedented in the field.

PROFESSOR ANDREAS BECHTHOLD

Meet the researcher

Professor Andreas Bechthold
Institute of Pharmaceutical Sciences, Pharmaceutical Biology and Biotechnology, Albert-Ludwigs-Universität Freiburg, Germany

Since graduating in pharmacy studies almost thirty years ago, Professor Andreas Bechthold has now an impressive list of engagements. He is a Professor of Pharmaceutical Biology and Biotechnology at the University of Freiburg, as well as the Dean of Study and member of the managing committee of the Faculty for Chemistry and Pharmacy at the University. He is also a member of both the German-French Ph.D. College 'Membrane Proteins and Biological Membranes', and the 'Spemann Graduate School of Biology and Medicine' at the University of Freiburg. Moreover, he is the spokesperson for the Cofactor Research Training Group and a co-founder of Combinature Biopharm AG.

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Designing Cosmetics From Your Own Bacteria

Dr. Yuichi Nodake studied a way to take Staph epi—a normal skin bacterium—and literally turn it into a probiotic cosmetic to aid in skin moisturizing and even repelling harmful bacteria like Staph aureus.

What attracted you to studying normal skin bacteria and making cosmetic products from them?

It is very difficult to find basic cosmetics that optimally suit each person's needs. Therefore, we wanted to produce more natural cosmetics for women.

The skin care effects induced by the normal skin bacterium *Staphylococcus epidermidis*—or Staph epi—have recently attracted attention in the world of cosmetics. Numerous preparations that facilitate the growth of Staph epi on the skin surface have been developed to exploit the natural benefits induced of Staph epi. We thought that an intentional and substantial increase in Staph epi on the skin would boost the levels of natural substances and improve skin health.

Most people know that yogurt is useful to improve the intestinal bacterial population and prevent various gastrointestinal problems. This is referred to as probiotics. In the same way, it might be possible to improve skin health by controlling skin bacteria with "probiotic cosmetics". There have been no previous attempts to develop skin probiotics like this. We sought to create such a product and focused on Staph epi as the candidate microorganism.

Your study dealt with *Staphylococcus epidermidis* taken from healthy subjects' skin. How is that bacterium different from the staph organisms we always hear about that cause serious infections, like *Staphylococcus aureus?*

Staph epi is a normal bacterial inhabitant of the human skin surface, with a density of up to 100,000 organisms per square centimetre on the face. Staph epi infections are restricted to people with compromised immune function or patients with indwelling catheters who receive various medical treatments. Normally people have Staph epi on their skin and it causes no problems. We figured that Staph epi could be suitable for use in a probiotic cosmetic.

Your study took bacteria from the patient's skin, multiplied it, and then mixed lyophilised (freeze-dried) bacteria with gel to apply to the skin to increase skin lipids and improve skin hydration. How would this be an improvement over simply mixing some type of oil and hydrating agent to the gel? Why are the bacteria better?

In this study, individual Staph epi samples from each subject were mixed for 30 seconds in a facial gel containing primarily water and minimal minerals. The subject applied the resulting mixture of the individual Staph epi sample on her face for 30 seconds. We don't know whether this specific strategy will ultimately be the most suitable way to achieve the desired results, but it's a start.

But the real point is, Staph epi has a unique symbiosis with humans—Staph epi provides not only a moisturizing effect by producing glycerine and related substances, but it also produces an active antimicrobial peptide that combats harmful bacteria like *Staphylococcus aureus* from attaching to the skin.

You applied for a patent based on the results of this study. What is the patent for and what will you do with it if it is granted?

Our skin care method using cultured Staph epi—augmentation with Staph epi—clearly differs from other basic cosmetics containing compounds that replenish moisturizing factors in the skin or increase the amount of Staph epi. Because we think our skin care method has unique novelties, we have applied for a patent. Our findings regarding augmentation with Staph epi may serve as a driving force to accelerate the development of a novel, personalized basic cosmetic that can provide long-lasting beneficial skin care effects.

Who were your collaborators in this research?

I had three collaborators in this research. Dr. Ryuzo Sakakibara, from Nagasaki International University, has a multidisciplinary research background. His current research is focused on understanding the bioactivities of fermented products by lactic acid bacteria. One of his current research interests is preventive medicine.

Dr. Itaru Dekio, of Tokyo Women's Medical University, is a foremost researcher in dermatological sciences. He analyses the relationship between skin bacteria and skin health and is interested in development of novel therapeutics for atopic dermatitis.

Mr. Hidetoshi Honda is a president of BIOGENOMICS Co. Ltd (Omura, Nagasaki, Japan). He has been interested in the importance of intestinal and skin microbiota. He has visions and methods to apply useful functions of bacteria to our health.

Do you have plans to extend this study in the future or focus elsewhere?

Because the growth of Staph aureus and pathogenic fungi is suppressed under low acidic conditions, because Staph epi produces antimicrobial substances to inhibit the colonization of Staph aureus, and because Staph epi contributes to skin defences by enhancing the activation of defensive chemicals in skin cells, the augmentation with Staph epi may be useful to prevent skin diseases probiotically. Staph aureus frequently colonizes the eczematous skin of patients with atopic dermatitis and is believed to be an important precipitating factor of atopic dermatitis. This means the elimination of Staph aureus is important for the treatment of atopic dermatitis. We hope that our augmentation with Staph epi can improve moisture retention, rough texture, and skin pH, which could be applied as an effective therapeutic method for atopic dermatitis.

Helping Mother Nature Do Her Job With Germs

The drive to find a better skin lotion leads researchers in many directions. Dr. Yuichi Nodake of the Department of Biochemistry at Nagasaki International University has taken a common skin bacterium and used it to produce a novel skin treatment that lubricates and hydrates the skin "naturally".

VANITY, VANITY, ALL IS (NOT?) VANITY!

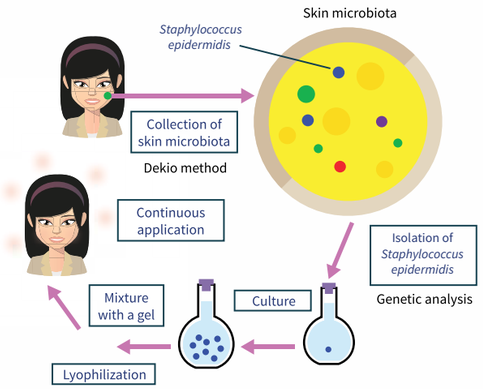
Women and now men, are constantly seeking better cosmetics to take care of their skin. Maybe this is vanity, maybe it's fear of aging, but it's certainly a fact. However, it is difficult to find good skin products that optimally suit one's personal needs. Is this product for oily skin or dry skin? Am I allergic to the components? Does it even work? And these days, there is always the push for "natural" products—the bias against "artificial" ingredients.

Dr. Yuichi Nodake has recently turned his attention to the science of cosmetics. His expertise in agricultural science—including the biochemistry and immunology of various food components and related bacteria—has led him to theorize that a common skin bacterium, *Staphylococcus epidermidis,* might be useful as the foundation for a novel type of cosmetic, a probiotic cosmetic, that is both natural and designed for the specific individual. And far from serving just vanity, Nodake thinks Staph epi can be used to better protect the skin against infection by dangerous pathogenic bacteria like *Staphylococcus aureus.* Taking a cue from the so-called probiotic treatments for stomach ailments that reinforce the "normal" microbiologic flora of the intestines, Nodake and his colleagues published a pilot study in 2015 in the Journal of Dermatological Science looking at the augmentation of normal skin bacteria to help moisturize the skin and perhaps inhibit Staph aureus.

THE GOOD, THE BAD . . . AND THE THEORY

Staph epi is a common and normal inhabitant of human skin. Recent research has shown that Staph epi is quite the beneficial bacterium, actually participating in the maintenance of skin health. Metabolic products produced by Staph epi, including glycerine and other organic acids, tend to improve skin moisture retention, help maintain a low pH on the skin surface, and also improve rough skin texture. In addition, Staph epi produces the enzyme superoxide dismutase, a known destroyer of reactive oxygen species. Since reactive oxygen species—free radicals—are associated with cell aging, Staph epi may actually help prevent wrinkles and other effects of skin aging.

Augmentation with Staphylococcus epidermidis



Most people know that yogurt is useful to improve the intestinal bacterial population and prevent various gastrointestinal problems. This is referred to as probiotics. In the same way, it might be possible to improve skin health by controlling skin bacteria with "probiotic cosmetics"

All these effects are good from the point of view of cosmesis. But more than that, certain antimicrobial substances produced by Staph epi actually help suppress the colonization of the skin by the pathogenic bacterium Staph aureus. Staph aureus is associated with a wide variety of conditions ranging from subclinical inflammation to severe infections like pneumonia, endocarditis and septicaemia. So the effects of Staph epi on the skin are beneficial both for cosmetic purposes as well as disease prevention.

There have already been some attempts to develop products to increase the growth of Staph epi on the skin to exploit the bacterium's potential benefits. However, the stimulating effects of these preparations on the colonization of Steph epi and other skin bacteria are often insufficient because of the differences in the skin characteristics of individuals and the gradual depletion of active substances in these products induced by the metabolism of the skin bacteria as they grow. Furthermore, a number of basic cosmetics contain oligosaccharides—short chain sugars—to facilitate the colonization of Staph epi. Unfortunately, they also have the undesirable property of promoting the growth of Staph aureus. In other words, if you feed skin bacteria, they all increase in numbers, both Staph epi as well as other, less desirable bacteria. What Nodake aimed to do is design a cosmetic to increase the numbers of Staph epi—and only Staph epi—on the skin surface. That way you get a pure increase in the good bacterium and no parallel growth in any bad bacteria. Of course, using "good" bacteria to promote health like this is the aim of probiotics.

BYOB: BRING YOUR OWN BACTERIA

Nodake's pilot study consisted of 21 subjects—all adult women with normal skin—who were

recruited in 2012 and studied for approximately three months. Swabs were taken of the subjects' forehead skin and tested for various organic acids, pH and moisture, as well as used to isolate colonies of Staph epi from each individual subject. Those isolates of Staph epi from each patient were cultured in the laboratory to get large numbers of bacteria—ultimately concentrations of 1,000,000,000 cells per millilitre. Those individual lots of bacteria were then lyophilised—freeze dried—and preserved for later use in the study.

The 21 subjects were randomized in a blinded fashion into a group of 13 who were inoculated with their own bacteria and a group of 8 who constituted the control group. The freeze-dried bacteria were mixed with a facial gel that was made primarily of water with minimal minerals. Gel with bacteria was used on the 13 subjects in the active group and gel with powdered milk instead of bacteria was used in the control group. The women rubbed the gel into their foreheads twice a week at bedtime and over time swabs were taken to measure bacterial count, levels of the various organic acids, pH and moisture retention. The subjects' skin was also examined and tested for signs of irritation, such as redness. Then, after four weeks, the groups were switched and the first group got the powdered milk gel while the second group got live bacteria.

The results of the study were exactly what Nodake expected. Innoculation with the person's own concentrated Staph epi was associated with a 15-fold increase in Staph epi on the skin, first of all. But this caused increased levels of organic acids, in particular glycerine, propionic acid and lactic acid, as well as a decrease in pH from 5.5 to 5.0 and an increase in water content. There was no difference in redness or other evidence of irritation, so it was apparent that these increased numbers of Staph epi did not cause any obvious problems on the skin. In fact, Nodake had originally wondered if the subjects would complain about "stickiness" from the increases in organic acids and water content, but none of the subjects had any complaint in that regard. All in all, the results were precisely what Nodake predicted based on his knowledge of Staph epi and the underlying science. Probiotic skin treatments made with a person's own Staph epi are possible and they work.

LOOKING TOWARD THE FUTURE

Nodake and his colleagues clearly showed that a skin care method using cultured Staph epi to augment the numbers of a person's own bacteria worked as expected. This treatment clearly differs from other cosmetic strategies that used compounds that replenish moisturizing factors in the skin or increase the amount of Staph epi (and other bacteria) by using sugars or other nutrients. Their findings regarding augmentation with Staph epi from the person's own skin may serve as a driving force to accelerate the development of a new, personalized probiotic cosmetics that can provide long-lasting, beneficial, and natural skin-care effects by making the person's own bacteria do the work.

What Nodake is planning for the future is showing that augmentation of the skin flora with a person's own Staph epi is actually protective against colonization by harmful bacteria like Staph aureus. There are a number of conditions, such as eczema, where Staph aureus can cause dangerous complications. If using the person's own Staph epi can probiotically prevent such Staph aureus infections, the next step in the development of probiotic cosmetics will be achieved. It's not all just about vanity and looks, but there is health to be considered, too. And your own bacteria may be a key component in achieving both.

Researcher Profile

Dr. Yuichi Nodake
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Department of Biochemistry, Faculty of Pharmaceutical Sciences

Dr. Yuichi Nodake received his Ph.D. from the Division of Agriculture, Graduate School, Kyushu University. He has been interested in a variety of scientific areas, including biochemistry, agricultural chemistry, cosmetic science, and functional food science. He has published papers on the topics of "hot dog fold" proteins, the immunogenicity of cow's milk, crystallographic and biochemical analysis of a variety of important bacterial enzymes, and thermostability factors of the heat-loving bacterium Thermus thermophilus. One of his research aims is the contribution to preventive medicine. He is focused on understanding the bioactivities of probiotic cosmetics containing skin microbiome species and functional foods fermented by lactic acid bacteria.

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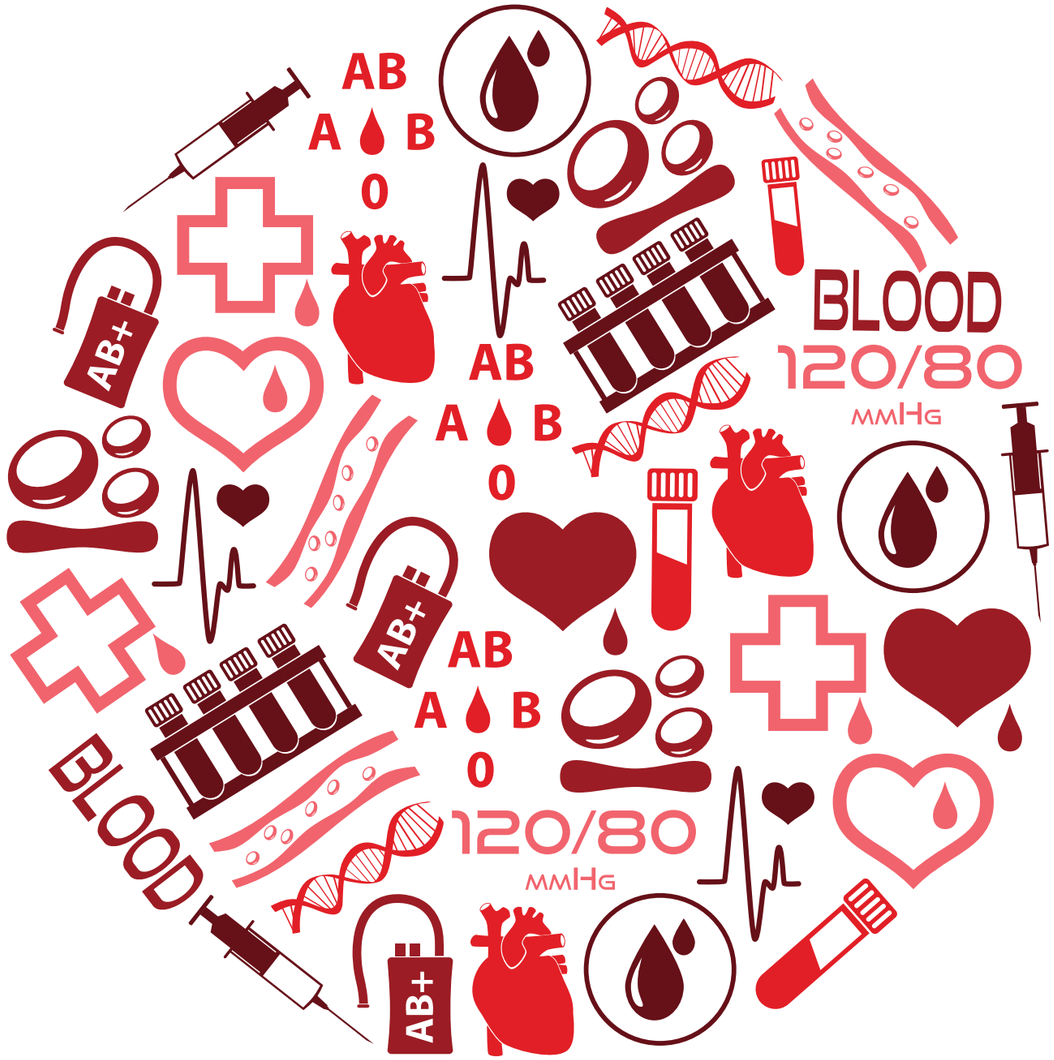
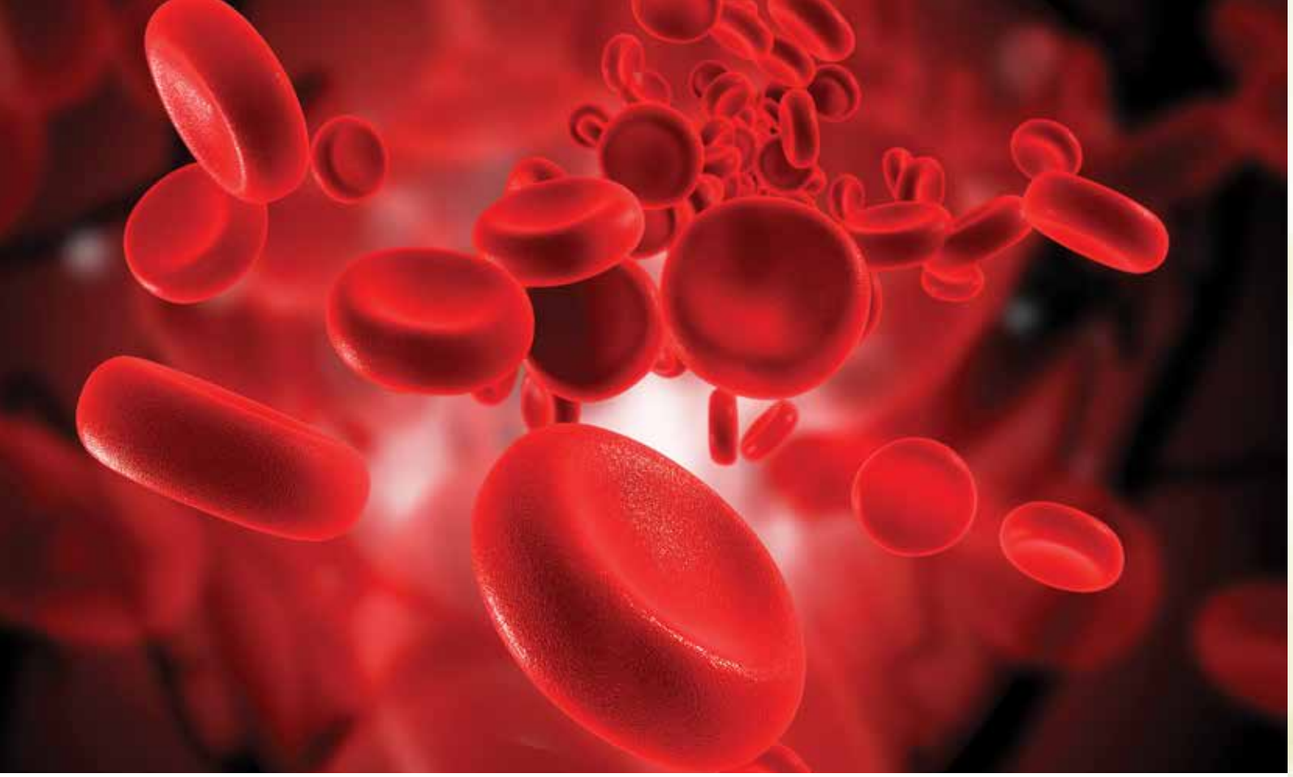
いつも、人から。そして、心から。
長崎国際大学
Nagasaki International University



BLOOD AND HEALTH

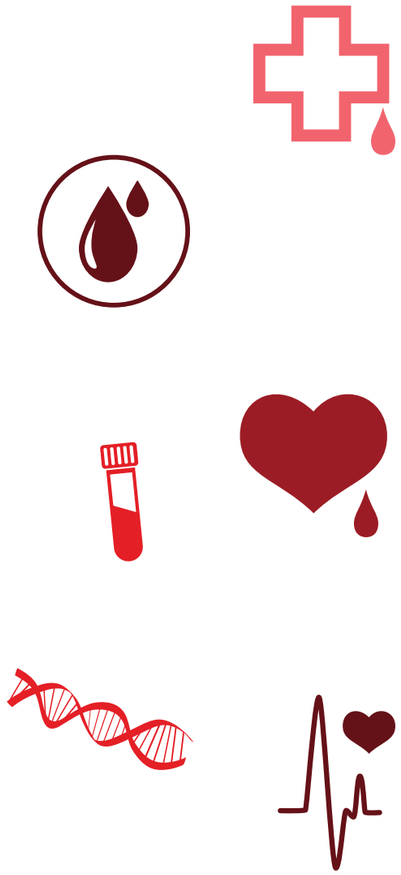
Blood is essential for the transport of nutrients and oxygen to every cell of the body and the removal of waste. It is also a means by which cells, tissues and organs communicate and interact through the release and transportation of hormones and other signalling molecules. The cardiovascular system through which blood travels is complex and elegant, precisely controlling blood pressure and adjusting blood flow to muscles or organs to accommodate physical exertion or resting activities such as digestion. As such, blood can be seen as a conduit for mammalian life and a physiological fundamental. However, what happens when things go awry in the blood? In this section, we introduce three investigators who look at disease processes in the blood or help the public to keep levels of essential nutrients in their blood at healthy levels. >



> Dr. Roi Gazit is looking at ways to reprogram blood cells into hematopoietic stems cells (HSCs), a regenerative cell type which can differentiate into several different types of blood cell. The HSCs can be transplanted into patients without immune rejection issues. The idea is that HSC transplants could help to replenish levels of blood cells after the aggressive chemotherapy required to treat leukaemia, a form of blood cancer.

The blood can also act as a means by which other types of cancer cells can travel throughout the body and form new tumours, at sites that are distant from an original solid tumour. This process, called metastasis, is the focus of Professor Nicola Aceto, who looks at large clusters of tumour cells that circulate in the blood and are key mediators of the metastatic process. The idea is to characterise the clusters and develop therapies that could help to break them up, making them more vulnerable to destruction by the immune system.

Malignant disease is not the only problem that can manifest in the blood. Blood is a medium for the transport and storage of minerals and nutrients that are essential for good health. Dr. Lynn Riddell is interested in helping women to maintain healthy levels of iron, essential for the transport of oxygen in the blood, through the development of an educational app for use on smartphones. The app aims to educate users about nutrient-rich foods, helps them to set nutritional goals and provides reminders. A clinical trial is underway to see if the app can positively affect levels of iron in users.



Novel Inroads From Hematopoietic Stem Cells to the Treatment of Leukemia

Dr. Roi Gazit is a biomedical scientist interested in improving the success rate of current treatments of leukemia. His research has focused on understanding Hematopoietic Stem Cells, the precursors of all blood cells. This understanding will create patient-compatible cell grafts for transplantation.

Can you discuss how your research background led to your interest in Hematopoietic Stem Cell Research?

My interest in Biology started early on childhood, and grew during high school. I have always been interested in how living organisms develop and regenerate. This natural curiosity led me to pursue a B.Sc. degree in life sciences, which developed into studying brain development for my M.Sc. I then turned to Immunology, focusing on the study of Natural-Killer (NK) cells for my PhD. Hematopoietic Stem Cells (HSCs) have attracted me by their unique combination of being the continuous source for all blood and immune cells. The rapidly developing field of adult stem cells presents amazing opportunities for young scientists, and combine multidisciplinary methods to advance understanding and develop novel therapies.

Your research interests are focused on exploring the role and functioning of Hematopoietic Stem Cells. Why these cells and why now? Where does this research fit in the larger context of current biomedical research?

Hematopoietic Stem Cells (HSCs) are saving tens of thousands of lives every year, thanks to bone-marrow transplant. However, this requires an adequate match-donor that is not always available. As the stem cell field is rapidly developing, HSCs are leading both basic understanding and translational studies. Understanding fundamental principles of adult stem cells has major implications for regenerative medicine as well as for cancer biology.

Have you experienced any obstacles doing your research and how did you overcome them?

Cutting-edge research is the unpaved road towards the unknowns, so you better enjoy overcoming obstacles if you are to pave this road for others. I have encountered, and keep encountering, both technical and conceptual obstacles; some of which I have overcame by hard work, some by working together with good colleagues. It is most helpful to foresee the road ahead to overcome obstacles, no matter what technical, conceptual or personal troubles you run into, you always get ahead easier if you know what you aim for.

Has your work revealed any significant findings to date?

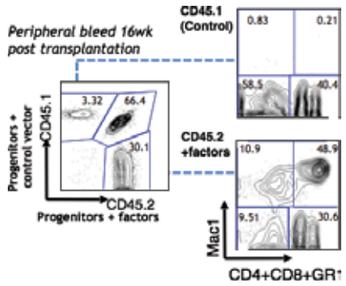
Some of my major findings include (1) finding role of NKp46 against influenza virus in-vivo, by generating the first NK cell specific knockout and knock-in. (2) Molecular understanding of Hematopoietic Stem Cells (HSCs) transcriptome (3) Reprogramming of committed blood cells directly into HSCs (4) Novel HSC-reporter mouse (5) Leukemia-models.

Your investigation of Hematopoietic Stem Cells is motivated in part by its role in providing a cure for leukaemia. Do they play any other roles in the organism? Have you worked with any other researchers for this study? If so, how did they contribute?

HSCs are needed throughout normal healthy life, their role being to generate the blood and immune cells required for homeostasis. A healthy human generate about one million new blood cells every second, which translates into an astronomic number of cells every day! HSCs are further essential for regeneration from insults, especially in leukemia that severely impairs the normal blood system.

Do you envision any type of Hematopoietic Stem Cells-based treatments and how they might be implemented?

HSCs are the functional unit of bone-marrow transplant. Dr. Donnall Thomas' pioneering studies of bone-marrow transplant are now applied worldwide, and constitute the leading clinical utilisation of stem-cells.



REPROGRAMMING inot HSCs

What implications might this study have on future work and potentially on healthcare, society and policy?

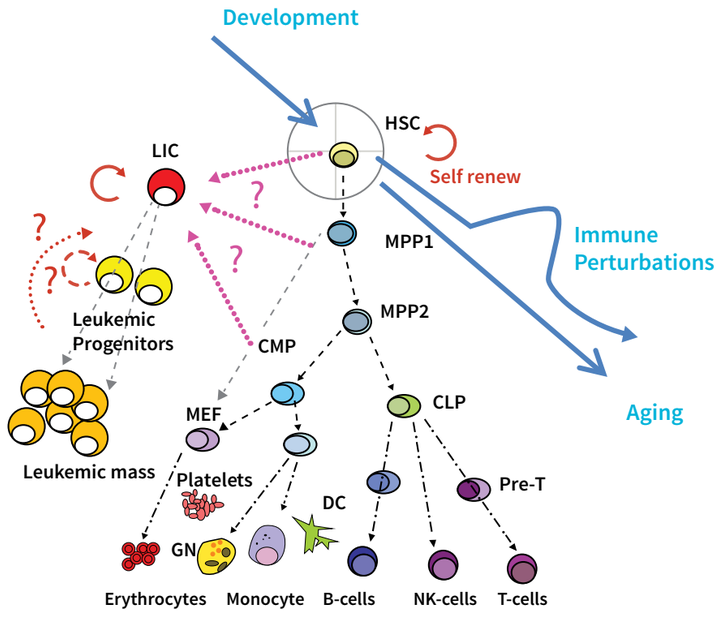
Once the ability to reprogramme blood cells directly into HSCs would be translated into humans, and robustly validated for safety, we will have a novel source of perfectly matched own cells for transplantation. This might actually be a very rapid implication, as bone-marrow transplant is well established. Nevertheless, we must take all caution and carefully ensure safety first. A major advantage of working with adult stem cells, such as HSCs, is the potential rapid implication for healthcare on the one hand, and the avoidance of any ethical issues that other embryonic stem cells may encounter.

Are you planning to extend this research further? Where might you focus your attention and why?

I will keep working on reprogramming of HSCs. We made the first discovery of specific factors- and I want to understand how they work. This will help progress in this field, and might suggest ways to increase the efficiency of this novel reprogramming. At the same time, we are also using our system for the generation of novel leukemia-models that can be tailor-made and propagate in immune-competent mice.

Hematopoietic Stem Cells and Leukemia

Leukemia is a disease of the white blood cells, which leads to hematopoietic and immune system dysfunction. Current leukemia treatment research, such as Dr. Roi Gazit's work on Hematopoietic Stem cells offers new perspectives on curing leukemia and furthering understanding of the relevant fundamental biology.



STEM CELLS: WHAT THEY ARE, AND WHY THEY ARE IMPORTANT

Stem cell research has received a great deal interest in the last decade. Stem cell research is currently at the forefront of biomedical research, and holds great promise towards the development of new treatments for some of the deadliest diseases.

Stem cells are undifferentiated cells that can divide to produce more stem cells and can differentiate into specialised cells. The focus of Dr. Roi Gazit's research interests is hematopoietic stem cells (HSCs). They are a class of somatic, adult stem cells that can differentiate into any of the blood and immune cells (including red blood cells, and various types of white blood cells). HSCs are located in the bone marrow, and they are the functional unit enabling bone-marrow transplant. Since HSCs have the potential to develop into healthy blood cells, they have been used in the treatment of leukemia.

LEUKEMIA: A STEM CELL APPROACH

Leukemia was the first disease to be treated with stem cells, by performing bone marrow transplants. Leukemia is a cancer of the blood and of the bone marrow, in which the white blood cells of the patient abnormally accumulate. Since the hematopoietic and immune systems' role in the organism is to protect the body against infection and disease, the symptoms of the disease are bleeding problems, feeling tired, fever, and an increase risk of infections. The excess of white blood cells in leukemia patients perturbs the circulatory system, and supresses normal red blood cells that are needed to supply oxygen, and platelets that prevent bleeding. Leukemia can also come to a lethal conclusion in those patients who contract illnesses such as pneumonia, as one is unable to fight the infection.

Being a form of cancer, leukemia is caused by a series of mutations. These mutations may also be genetically inherited, which makes predisposition to leukemia an inherited factor.

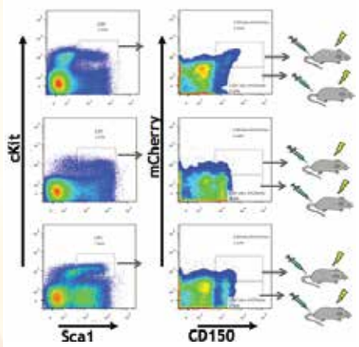
Alternatively, exposure to radiation, certain types of chemotherapy, and accumulation of acquired mutations are all possible causes of leukemia. Many types of leukemia originate in the HSCs, before they have had a chance to differentiate into a specific type of blood cell.

Treatment with stem cells involves first treating leukemia with chemotherapy, which often is successful in killing leukemic cells, but it also severely damages the normal HSCs in the blood marrow. These can then be replaced by HSC transplantation from a healthy donor, whose immune system type must match the patient's. The procedure is risky because it can have a range of unwanted side effects: infections and graft-versus-host disease (occurring when the donor's blood cells attack the patient's tissue). There is a great deal of work in the field of stem cell research aiming to "reprogram" cells so as to make them compatible with the host's immune system, which would possibly eliminate the risk of rejection.

ADULT STEM CELL REPROGRAMMING

Dr. Gazit is using a multi-pronged approach to studying HSCs. Thanks to the ImmGen consortium Dr. Gazit has gained unprecedented data of gene expression across the hematopoietic- and immune-system. This allowed identification of HSC-specific genes and prediction of key regulators, some of which are being validated and explored. During his postdoctoral studies at Derrick Rossi Lab, Dr. Gazit took part in the identification of HSC's transcription factors and established an experimental system for functional demonstration of reprogramming in-vivo. This allowed him to define six core factors and two facilitators that can turn blood cells into "induced-HSCs", which can transplant and reconstitute all types of blood and immune cells. This discovery paves the way for making the stem cells needed for bone-marrow transplants out of the patients own blood cells, an area now being extensively researched. Dr. Gazit has additionally developed a new model which expresses a fluorescent reporter gene in HSCs specifically, allowing for direct identification of these cells. This model further allows us to follow and study HSCs upon stimulation; while other markers lose their specificity, this novel model seems to reliably keep track of the cells. Finally, continuing with the reprogramming study, Dr. Gazit discovered the robust ability to generate leukemia-models using defined oncogenicdrivers in an immune-competent mouse. These novel models allow examination of new treatments in-vivo against various leukemia types. At the same time they may shed new light on basic biology of cancer, and on the presumable identity of "Leukemia-Initiating-Cells".

Dr. Gazit is also interested in the immunology aspect of HSCs. The hematopoietic cells are the source of virtually all the body's immune cells as well as the blood cells, and there is mutual dependence between the two, Gazit explains. "Somehow there's feedback between the stem cells and immune cells—it makes sense that the body has a regulator mechanism to tell the stem cell that more immune cells are needed, or that there are too many. One great interest is to uncover the activity and relationship of the stem cells with the whole immune system, which will affect the treatment of any infection. That's a long term dream—we are having amazing discoveries already, and hope to keep busy with this broad field for many years.



Identify Hematopoietic Stem Cells during Immune Stimulation

HEALTHCARE APPLICATIONS

"We dream of reprogramming hematopoietic stem cells (HSCs) to make them stronger and more capable of transplant, and maybe even generating them from a patient's own cells," Dr. Gazit says. "If you can reprogram blood cells back to the HSC state, you have an unlimited resource for adult stem cells ready for clinical utilisation. That's a big dream—and we have reason to believe we can do it!"

Dr. Gazit wishes to understand the basic biology behind adult stem cells. Understanding the differences between adult stem cells and other adult cells at a molecular level may then aid the researcher to turn adult blood cells into HSCs, which can then be used for transplants. Since the stem cells thus reprogrammed come from the patient who will receive the transplant, there is presumably no risk for rejection. Somatic cell reprogramming back into the stem state is not new. Somatic cells have been reprogrammed before into a pluripotent state by defined transcription factors (TFs), and Dr. Gazit believes that the expression of a minimal set of factors can induce blood cells back into their proximal adult stem cell state of HSC.

"My goal is to understand how specific genes regulate adult stem-cells, and use this understanding to help patients as soon as possible" says Dr. Roi Gazit. "We have succeeded already in turning blood-cells directly into such stem-cells that may cure multiple diseases, including leukemia, lymphoma, anaemia and more. Our results from animal studies require translation into humans and expand our basic understanding of both normal and malignant stem-cells".

Researcher Profile

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Dr. Roi Gazit is a Senior Lecturer (Assistant Professor) at the University of the Negev, Be'er-Sheva, Israel. He is an Ilze Katz Career Development Chair in Health Sciences Research and a member of the National Institute for Biotechnology in the Negev (NIBN) and of the Centre for Regenerative Medicine and Stem Cells at the Ben-Gurion University. He has completed a post-doctoral research at the Immune Disease Institute, Harvard Medical School University with Derrick J. Rossi and also collaborated extensively with the ImmGen Consortium. He received his B.Sc. and M.Sc. in Life Science from the Hebrew University of Jerusalem, and did PhD studies at the laboratory of Ofer Mandelboim, Hebrew University Haddasah Ein-Kerem.

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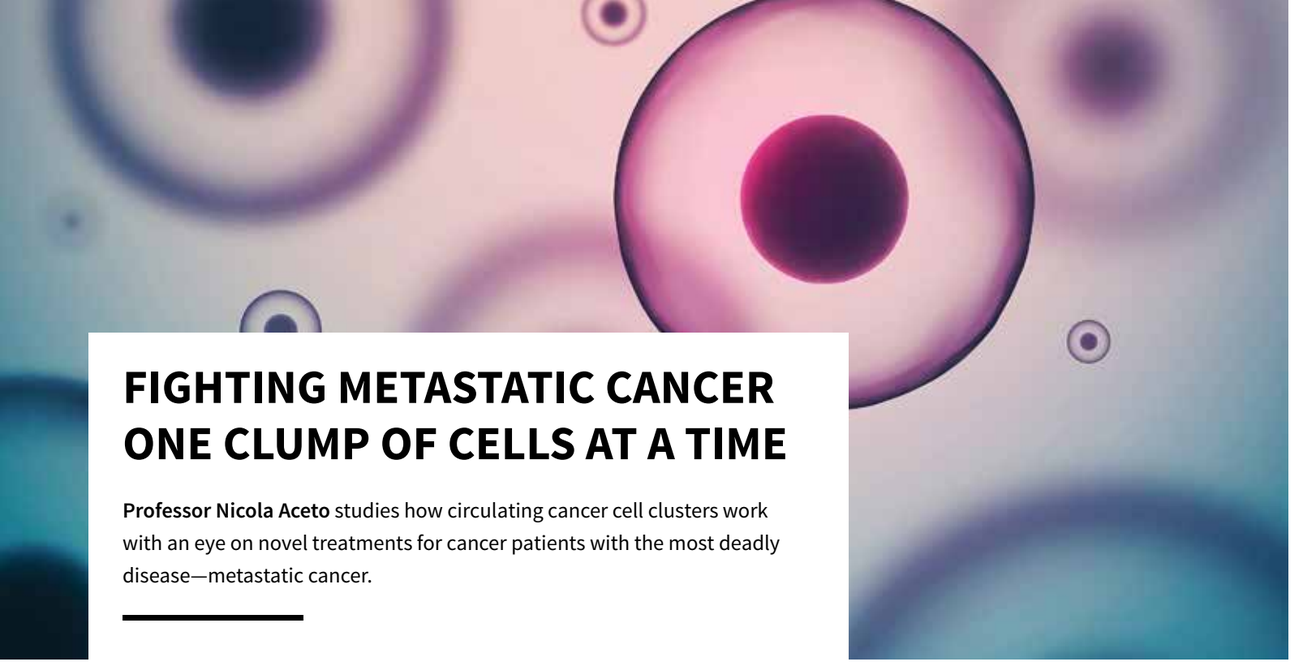


FIGHTING METASTATIC CANCER ONE CLUMP OF CELLS AT A TIME

Professor Nicola Aceto studies how circulating cancer cell clusters work with an eye on novel treatments for cancer patients with the most deadly disease—metastatic cancer.

How did you come to work at the Cancer Metastasis Lab at the University of Basel, Switzerland? In other words, what got you interested in the topic of cancer metastasis in general—and cancer cell clusters specifically—and how did you come to head the Lab at Basel?

Over 90% of cancer-related deaths are due to the development of a metastatic cancer. This corresponds to more than seven million deaths per year, worldwide. Clearly, we do not know enough about how human cancer spreads, and we do not know how to block the development of metastasis in cancer patients. To dissect the mechanisms that orchestrate metastasis in humans is an extraordinarily important challenge. The solution may greatly impact the life of several million people worldwide affected by this disease. This is why I am interested in this topic.

During my postdoctoral training in Daniel Haber's lab at Harvard, we understood that cancer cell clusters in the blood of cancer patients represent highly dangerous metastatic precursors. This finding highlighted a previously unappreciated aspect of how metastasis occurs. More importantly, it now provides an outstanding opportunity to target these metastatic precursors to block the metastatic process. With this goal in mind, I took the position at the University of Basel in Switzerland. We are embedded within an outstanding academic environment here and collaborate very closely with medical oncologists, as well as experts in genomics, bioinformatics and biomedical engineering worldwide. This environment and collaborative spirit allows us to pursue very ambitious research goals.

You are studying cancer cell clusters and their role in cancer metastasis. Where did the idea of cancer cell clusters come from and why is it important in cancer metastasis?

Cancer cell clusters in the blood of patients with cancer were observed for the first time several decades ago, and often again as an incidental finding during autopsy of cancer patients. Yet, compared to single cancer cells in circulation, these clusters represent a minority, and their isolation has always been dependent upon technological constraints. It is only very recently that microfluidics technology allowed us to isolate and characterize viable cancer cell clusters from the blood of cancer patients, allowing their detailed characterization.

Understanding that cancer cell clusters are not only present, but also functionally connected with the development of metastasis, is now a fantastic opportunity to block a main route of cancer dissemination. Further, we have already characterized gene expression of such clusters in patients and are now testing several strategies to eliminate them.

Do you have a plan on translating your laboratory findings about cancer cell clusters and metastases into actual human cancer treatment?

Yes, absolutely. Currently, metastatic cancers

are usually treated as a localized tumour. No strategies are available that block the mechanisms that support the spread of cancer cells throughout the body. For this reason, too many patients die because of metastasis and we are very anxious to translate our findings into clinical practice as soon as possible.

We are working to identify cellular and subcellular targets that are required for cancer cell clustering. We plan to move rapidly into testing the efficacy of inhibiting such targets in preclinical models and then, with our collaborators, transition into clinical studies with the best candidates.

How is your cancer cell research funded and what expectations do you have for any self-generated funding?

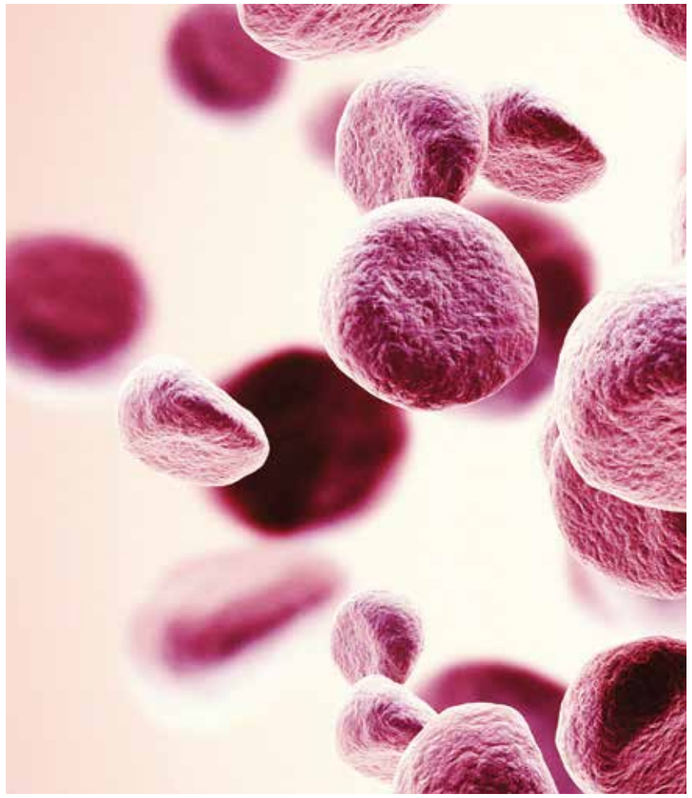
We are grateful to several funding agencies that funded our work. During my time at Harvard, I was awarded funding from the Human Frontier Science Program, the Swiss National Science Foundation, the European Molecular Biology Organization, and the American-Italian Cancer Foundation of New York City. Upon starting the Cancer Metastasis Lab in Basel, we have been awarded a prestigious European Research Council Starting Grant, as well as grants form the Swiss National Science Foundation, the Basel Cancer League, and the L.&Th. La Roche Foundation through the University of Basel.

The expectation from our work is that we identify critical mediators of cancer cell clustering to pave the way to the development of new pharmacological agents tailored to suppress the spread of cancer. This is a very ambitious goal, but we are confident it will be feasible in a short time frame given the tools we have available and the knowledge we already developed from the analysis of several patient sample.

What long-range plans do you have for this research and do you intend to focus on other topics in the future?

Ultimately we aim to translate our findings into clinical practice as soon as it can be done. However, from a certain perspective, research on cancer cell clusters has just begun. We now understand their importance in the metastatic process. Yet there are so many open questions to answer about their biology, composition, heterogeneity, and physical properties. Our research is also focused on addressing these questions since their answer may lead to new findings with potential to shape the way we treat patients.

What is also important in the long run is that circulating cancer cell analysis may develop into a real-time diagnostic method to show how cancer cells evolve in a patient in response to a given treatment. Further, it may provide a way to predict in individual patients the particular organs that would be in danger for a possible development of metastasis and whether or not a certain therapy will be successful. Our lab is highly interested in these aspects, too, and we have already generated exciting preliminary results in this regard.



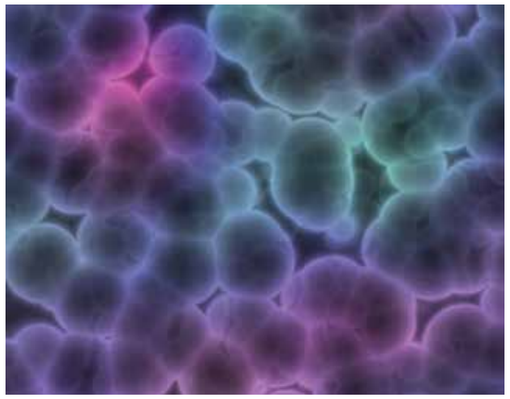
FIGHTING AN INVASION BY IDENTIFYING THE INVADERS

To understand how cancers metastasise through the body, Professor Nicola Aceto and his colleagues at the Cancer Metastasis Laboratory of the University of Basel study not just individual tumour cells, but circulating tumour cell clusters, in an effort to understand and fight cancer metastasis

A Deadly Invasion by Two Routes

A deadly force arises from a local population. It grows, pushing out or killing the locals and robbing them of their food and resources. When it gets large enough, it sends out individuals disguised as migrants or refugees to other locations where they revert to their true identity and start a new camp, growing and dispossessing the local population. Even worse, larger groups of invaders brazenly band together and travel down major highways to establish satellite camps, wreaking havoc on the native populations wherever they decide to stop.

Who are these malignant invaders? These are cancer cells, spreading from the original tumour as either single cells sneaking through the body via a special disguise, or travelling down major blood vessels in groups bound together by cellular adhesion forces. Either way, either as single circulating tumour cells (CTCs) or circulating tumour cell clusters (CTC clusters), Professor Nicola Aceto and the scientists at the Cancer Metastasis Laboratory in Basel, Switzerland, want to find ways to identify these traveling invaders to enable physicians to more effectively prevent or treat cancer metastases in their patients.



How Cancers Metastasise and Why It's Important

Actual identification of CTCs was first reported in the Australian Medical Journal in 1869 by Thomas Ashworth. Ashworth found CTC in the blood of a man with metastatic cancer and theorized that cells from a cancerous tumour circulated through the vascular system and caused a new tumour in a distant site. This supported the theory proffered by the British Royal Society award winner Ludwig Virchow as early as 1858, that metastases were caused simply by cancer cells breaking away and embolising through the bloodstream. Then, in 1889 Sir James Paget published his observations in The Lancet, that there were higher rates of metastases to bone and ovary in women who had died of cancer. Paget reasoned that metastases were not just a random seeding of distant tissue by tumour cells, but that the tumour cells had to somehow be compatible with the target tissue before a metastasis could take root. The subsequent "seed versus soil" debate—whether cancer cells simply embolised where they willed or whether particular distant organs were providing a more favourable environment than others—has persisted since. But is that important? And why is it important even to know much about metastases other than that they exist?

Cancer is a scary word and a terrifying condition to have. But many cancers, especially when found early, are eminently curable. But when there are metastases, the odds are much worse. Cancer that has spread to distant organs, usually resulting in a label of "stage IV", reduces survival rates dramatically. For example, stage I breast cancer—cancer confined to the breast—has a survival rate at five years of about 99%, according to Cancer Research UK. The American Cancer Society quotes 100%. However, for stage IV breast cancer—breast cancer that has spread to distant organs—the survival rate is 15% according to CR-UK, 22% according to the ACS. The difference is obviously remarkable . . . and disturbing. Aceto and like-minded scientists believe that we need to learn all we can about the process of cancer metastasis to find better ways of preventing or treating deadly metastatic cancer.

Finding CTC Clusters In Live Patients

Current research by Aceto and others have determined that CTCs spread through the body both ways, as individual CTCs and as CTC clusters. Individual CTCs are thought to travel through the body in disguise, so to speak. Individual cells of epithelial cancers, like breast cancer for example, can transition into mesenchymal-like cells—cells that usually make up connective tissue—and then transition back to their native epithelial cell type after they wander through the body and arrive at a suitable destination. There, they proliferate into a new tumour if conditions are right. The problem with individual CTCs is, individual cells are easier for the body to eliminate, if they survive at all.

On the other hand, CTC clusters—groups of cancer cells bound together by intercellular adhesive molecules—are more resistant to the body's defences, giving them more metastatic potential than individual CTCs. In other words, CTC clusters are the most dangerous type of metastatic cells. This is why Aceto and his colleagues are especially focused on CTC clusters and how to find and destroy them.

In terms of identifying CTC clusters, Aceto and collaborators have isolated CTC clusters in the blood patients with metastatic breast cancer, prostate cancer and melanoma with newly developed specialized technologies. Their results were published in Cell, Science and Nature Methods during the past two years. The ability to actually detect CTC clusters in cancer patients may be very useful to stratify patients that might have more severe disease. It also could identify patients who might benefit from cell-cell junction therapy, a new strategy Aceto is pursuing specific to CTC clusters.

Aceto has done molecular analysis of human CTC clusters and found that these metastatic precursors rely upon the expression of specific cell-cell junction components such as plakoglobin and other cell-cell junction markers. In other words, certain junction molecules keep the cells in CTC clusters stuck together. These molecules—cell adhesion molecules—are similar to the molecules that keep adjacent normal cells together in a tissue. The strategy would be to find specific pharmacologic agents—drugs—that would attack junction molecules in CTC clusters without harming similar molecules in normal tissues. This would theoretically break up the CTC clusters, making them vulnerable to the body's own defences and other therapies. Additionally the ability to isolate CTC clusters from individual patients and analyse them could lead to individualized patient-specific therapy, therapy to use in combination with cell-cell junction therapy, depending on the characteristics of that specific patient's CTC clusters.

Looking Toward The Future

This is Aceto's dream outcome—to achieve a therapy that suppresses metastasis by targeting CTC clusters in live patients. According to mouse models, such therapy could have a phenomenal impact in reducing the spread of cancer. A lot of work still needs to be done in this direction, including the identification of the best therapeutic targets in the CTC clusters. What will be needed is to find those molecular targets that are required for cancer cell clustering, but not required for cell-to-cell attachment of healthy cells within the body. Once these targets will be identified, the dream outcome is to implement a therapy and to readily test it in patients, aiming at the suppression of their metastatic disease.

Beyond a therapy to suppress cancer cell clusters, the analysis of circulating cancer cells holds the extraordinary potential to dissect the molecular drivers of cancer metastasis, and to achieve precision medicine for each patient in real time. Future studies will be key to transform the potential of circulating cancer cell analysis into clinical practice.

PROFESSOR NICOLA ACETO

Meet the researcher

Professor Nicola Aceto
Group Leader, Cancer Metastasis Laboratory
Department of Biomedicine, University of Basel, Switzerland

Professor Nicola Aceto received his Bachelor of Biotechnology and Masters in Medical and Pharmaceutical Biotechnology from the University Amedeo Avogadro in Novara, Italy. He received his PhD in 2011 from the Friedrich Miescher Institute in Basel, Switzerland. He was a postdoctoral fellow in the Haber Laboratory at Harvard Medical School and Massachusetts General Hospital Cancer Centre in Boston, Massachusetts. He has also been an active member of the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, and a visiting scientist in the Clevers Laboratory at the Hubrecht Institute in the Netherlands. Professor Aceto has authored several peer-reviewed publications in leading journals in the cancer field, including Cell, Science, Nature Medicine and Nature Methods, and he is an inventor on four patents related to the diagnosis and treatment of cancer. He has been an invited speaker at a number of congresses, academic and industrial organisations that are leaders in the life sciences field.

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Seeking answers from iron and blood

Dr. Lynn Riddell of Deakin University's Centre for Physical Activity and Nutrition Research (CPAN), has made a career out of studying nutrition and public health. Here we talk to her about her latest venture, an app to improve iron nutrition in women.

To begin with, tell us about yourself. How did you get to this point in your career?

I began my studies in food and nutrition science at the University of Otago straight out of school and have never really looked back. I loved learning about food science along with learning about nutrition and the impact of food on health. After working for a couple of years as a food chemist I wanted to further explore the relationship between compounds in food and their influence on health and so returned to the University of Otago looking at the impact of folate on health. I greatly enjoyed the opportunity to work in a research area that was at the interface of micronutrient intake, the impact on health and potential implications for national food policy. This was a time where the debate around fortification of the food supply with folic acid was a hot topic. Following the completion of my PhD, undertook postdoctoral research training at Drexel University where I further developed my dietary intervention skills and since joining Deakin University's Centre for Physical Activity and Nutrition Research (CPAN) over a decade ago I have been able to continue my work investigating the impact of micronutrient intake and health outcomes. The primary focus of my work currently is iron and zinc but I also collaborate with colleagues such as Professor Caryl Nowson and Dr Carley Grimes also from CPAN on sodium and iodine.

Why did you decide to get into the field of nutrition?

I can't really say with any certainty – I was always fascinated by food and its relationship with health. As an adolescent I remember experimenting with new foods (tofu – a novelty in NZ in the 80s!), and different eating patterns and it was a natural progression to move into tertiary studies in food and nutrition sciences. My interests started to focus more on the nutrition sciences mid-way through my PhD and this is the field that I have stayed in since. With the rise in dietary related chronic diseases and the overwhelming challenges facing our population at the moment with abundant, dietary energy and increasing opportunities for sedentary lifestyles, we aren't running out of work anytime soon.

A lot of people are taking iron/multivitamin supplements at the moment. What are your thoughts on this?

Iron supplements are recommended for individuals who have been diagnosed through blood tests to have iron deficiency anaemia. Thus, in the presence of a diagnosed micronutrient deficiency then iron or multivitamin mineral supplements are important. For the general population however, vitamin and mineral supplements are not necessary. There is good evidence from a number of studies from a range of different countries that individuals who use supplements have better diet quality simply from food alone than those that don't use supplements. There are a number of phytochemicals present in foods that aren't included in supplements and studies have shown that individuals who consume diets more closely aligned to national and international dietary guidelines have better health outcomes. The concerns with taking unnecessary supplements are many: the cost; the waste; potential excess intakes; and potentially a sense of complacency that nutrient needs are met through the supplement.

The WIZE app, developed to help women with avoid Iron/Zinc deficiencies, is currently the centrepiece of a clinical trial. How do you feel about its progress?

With the rise of mobile phone technology and the increasing proportion of the population owning a smart phone, moving traditional dietary intervention materials into an accessible and interactive platform appeared to be a natural progression for our research. Dietary trials have indicated that when women with low iron stores increase the amount of iron they eat and increase the bioavailability of the iron in their diet they are able to improve their iron stores. These trials are typically very resource intensive, requiring repeat appointments with nutritionists and individual dietary planning. We are interested to see if we can achieve similar outcomes using a platform that has the ability to reach a larger number of women. Within economically developed countries, there are very few trials looking at dietary strategies aimed at improving zinc status in women so we have less to go on for the dietary recommendations to improve zinc status. Increasing bioavailable forms of iron in the diet should also increase the bioavailability of zinc and if we combined these recommendations with recommendations for increasing other sources of zinc, such as milk, we hope to see an improvement in both zinc intake and zinc status. So far we are only about half way through the trial so it is too early to tell if the app is working and too early to tell if we can initiate dietary change to a level that can result in improvements in iron and zinc stores.

Smart phones, smart nutrition

The Centre for Physical Activity and Nutrition Research is an Australia-based world-class institute devoted to improving public health by researching preventative measures such as good nutrition and exercise.

Iron and zinc are two of the most commonly used metals in modern society, providing us with products ranging from corrosion-proof building materials to the batteries in our homes. They are also immensely important to us as living beings, acting as essential metal ions for many, many enzymes within the body. Iron is easy to observe, the red colour of blood and muscle is due to the iron locked into haemoglobin and myoglobin, carrying oxygen to where it is needed. Zinc is more subtle, appearing in over one hundred different enzymes as a structural or catalytic element. The importance of both leads to the body stockpiling stores for later use – indeed each of us have over 3 grams of iron and 2 of zinc scattered between our various organs.

But where do these metals come from in the first place? Both tend to occur in the same food types, coming in particular from two main sources, namely meat but also cereal grains such as wheat. Meat, being basically muscle, acts as a concentrated and readily bioavailable source of both micronutrients, and thus vegetarians often have lower zinc intake and lower iron levels than others (although we can also take 'cereals' to the literal extreme and note that Cheerios® have very high zinc and iron levels). Iron and zinc levels in food often correlate to each other, although there are naturally exceptions to this rule – e.g. dairy foods are high in zinc but low in iron, dark chocolate has more iron than zinc.

To ensure that their communities have enough of these minerals, several countries are actively engaged in fortifying flours with added metals. Thus residents of the US will find that their wheaten baked goods contain added iron, while Indonesians and Mexicans have fortified levels of zinc. The levels vary around the world, however, as do the regulations – thus Australia has no additional minerals while somewhere such as Canada will only have iron fortification. Making this more complicated is the fact

that iron/zinc uptake and secretion is heavily dependent on the form in which it is presented (meat iron is simpler to absorb than plant) and the presence of other molecules in the same meal (polyphenols from tea will inhibit uptake, while the ascorbic acid from an orange will boost it). The variation across the globe in both micronutrient supply and absorption means that it is remarkably difficult to determine when people are getting the right amount of both.

This is a particular problem for women, as the blood loss during menstruation means that they require higher iron intake compared to men. Indeed, studies have shown that around 12% of women have depleted iron stores, as compared to only 1-2% of men. Insufficient iron has been linked to reduced physical capability (particularly tiredness and weakness) and has also been shown to affect some mental skills as well. Testing for deficiency is also difficult, while most iron can be easily measured as it floats around in the blood as haemoglobin or ferritin, there is no equivalent biomarker for zinc levels. Thus a lot of recent research focuses on both determining correlations between the two as well as encouraging women to consume sufficient amounts of each.

Setting out to answer these questions are scientists such as Lynn Riddell, currently the Deputy Head of the Deakin University School of Exercise and Nutrition Sciences. Her long career in nutrition research has recently come to focus on iron and zinc metabolism within the greater population, in particular how these levels are affected by nutrition and each other. A recent publication from their group examined the eating habits and blood mineral levels of a number of women, both blood donors and volunteers from university staff and students. Their work supported the importance of encouraging micronutrient consumption, as over 30% of those studied had low iron intake, and almost 19% low zinc (the flip-side of this is that 20% of those interviewed were taking some form of iron/multivitamin supplement, although as she points out “for the general population, however, vitamin and mineral supplements are not necessary”). As expected, their study showed that women who consumed more iron had higher zinc levels, but were unable to show that low zinc could be detected by a corresponding low level of iron in the blood. This lack of success in finding a simple biomarker for zinc deficiency meant that the research and public health focus would remain on prevention rather than diagnosis.

To support the prevention of iron/zinc deficiency, Dr. Riddell has also been involved in the development of public-health mobile apps, with their latest creation being known as Women’s Iron, Zinc, and Energy (or WIZE, for short). This app has been designed so as to inform women as to the importance of iron/zinc, teach them which foods provide the highest nutrition, and help support higher nutrient uptake. Information is provided in the form of facts and games, while the app also uses goal setting, monitoring and feedback reminders as a way to encourage better health. Initial testing was positive, and a number of suggestions by the first set of users was incorporated to make the new, improved version which is currently undergoing clinical trials. As Dr. Riddell comments “mobile phone technology, when combined with well communicated public health nutrition recommendations, has the potential to help people make healthy food choices.”

WIZE joins a growing list of health-related applications, with health apps accounting for 10-15% of all downloads in the last few years. The personalised feedback and information provided by these apps has been shown to increase several health-related outcomes, and their role in the new world of ‘personalised medicine’ is drawing in groups from business, academia, and government. Given the importance of iron and zinc to our well-being, apps such as WIZE could make a significant difference to public health. As such, it will be very interesting to see the outcome of Dr. Riddell’s clinical trial when it finishes next year.

Dr. Riddell also plans to continue her research investigating strategies to help young adults improve their diet quality and improve their nutrient intakes. Without going into too much detail, she plans to work on an app that helps provide young adults with real time nutrition and food advice to help with meal decision making. If more people were able to follow dietary guidelines for good health (without the confusion of mass media on what makes up a healthy diet), Dr. Riddell believes we would see fewer micronutrient deficiencies, improvements in body weight and decreased dietary related chronic disease rates. It is a matter of figuring out how best to empower people to make these changes.

Researcher Profile

Lynn Riddell, PhD
Associate Professor, Centre for Physical Activity and Nutrition Research and Deputy Head of School, Exercise & Nutrition Sciences, Deakin University

Lynn Riddell has long been interested in nutrition, majoring in the field for her Bachelor of Science degree, then continuing on with a PhD from the Dept. of Human Nutrition at the New Zealand University of Otago. A stint as a post-doc and then Assistant Professor at Drexel University, US, led to further success and eventually her current role as Deputy Head of the School of Exercise & Nutrition Sciences, at Deakin University. During all of these travels she has managed to find the time to write over 40 publications and become a recognised expert in the field of nutrition and public health.

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ENVIRONMENTAL HEALTH

Challenging times lie ahead for the health of our environment. With the human population now in excess of seven billion people, our impact on the planet has become irreversible. Since the Industrial Revolution, the concentration of carbon dioxide in the atmosphere has increased from 0.028% to over 0.04%. This might not sound like much, but carbon dioxide is a potent greenhouse gas that absorbs infrared (heat) radiation released from the surface of the earth, driving global temperatures up. Upsetting this delicate balance is causing icebergs to melt, species to become extinct, and violent weather systems to form. A warming climate can even increase the prevalence of certain pathogens, as we will demonstrate in this section.

Carbon dioxide is just one of a plethora of pollutants that we are dumping into the environment at an alarming rate. These pollutants not only wreak havoc on the environment, but also directly and indirectly damage human health. Coal burning releases noxious gases and particulates into the atmosphere, causing an increased instance of respiratory and cardiovascular disease. The release of mercury is also a by-product of coal burning, which enters the ocean through rainfall and assimilates into our diet through the fish we eat.

In this section, three research groups will be discussed, each covering a different problem challenging the health of the environment, and in turn, the health on humankind. First, we introduce the work of Dr. Celia Chen and her team, who examine the concentration of methylmercury in estuaries, and its biological accumulation in fish. The occurrence of this toxic compound in our food poses a significant problem for public health, and therefore understanding how it enters and accumulates in the food chain is of great importance. Next, the research of Dr. Elke Genersch is presented, who investigates infections in bee colonies at the molecular level. In particular, her work involves Nosema ceranae, a fungal parasite believed to have become more prevalent as a result of the warming climate. Because an enormous percentage of our food, wildlife and biodiversity relies on the pollination of plants by bees, Dr. Genersch’s work is of huge significance. Finally, we introduce Professor Pamela J. Lein, who studies how environmental toxins affect the development and progression of neurodegenerative and neurodevelopmental disorders. This will hopefully lead to the development of methods that identify environmental risk factors and approaches to prevent exposure. In addition to her research, Professor Lein is also the Program Director for the Advanced Training in Environmental Health Sciences program at UC Davis, where she is currently training up the next generation of environmental health experts. As the demand for highly skilled environmental health scientists is now bigger than ever, this program is making a significant contribution to the longevity of environmental research and protection.

EFFECTS OF COAL COMBUSTION ON PUBLIC HEALTH

Mercury in Seafood: What the Madhatter didn't know

A childhood spent between smokestacks and alongside beaches led Dr. Celia Chen to a long and distinguished career investigating marine ecosystem pollution.

Tell us about yourself, what brought you into this field?

I wanted to be an environmental scientist since I was very young. I grew up along the metropolitan corridor of New York City and New Jersey where there were lots of industrial facilities spewing air and water pollution. It made a very deep impression on me. At the same time, the beaches of New Jersey gave me my love of marine ecosystems. As a result, I came to be interested in contaminants in aquatic ecosystems, particularly at the margin between freshwater and saltwater, i.e. estuaries.

How did you end up in the Toxic Metals Superfund Research Program?

In the year that I finished my Ph.D, a group of Dartmouth scientists got together to develop and submit a program proposal for the Superfund Research Program. We were awarded the program grant in 1995 and have had it ever since. The program requires a combination of biomedical and non-biomedical projects and I became the Co-leader of a non-biomedical project on metals in aquatic ecosystems.

The program has scientists from many different backgrounds. How do you feel this affects the research you can do?

I believe that in order to solve the complex environmental problems in our world, we need to take interdisciplinary approaches, not just within the sciences but the social sciences as well. It definitely expands my range of knowledge and allows me to examine my own scientific questions in different ways. Even within my own project, I work with biogeochemists and trace metal chemists who have taught me so much about the physical/chemical environment of the estuaries we work in and the intricacies of metal speciation.

You are also the leader of the Research Translation Core. Can you tell us a bit about this role?

As the leader of the Research Translation Core, I am responsible for communicating and translating the research in our Toxic Metals Program to our stakeholders (governmental and non-governmental entities) and the public. This requires that I become a "translator of science" in fields of study outside of my own; the other projects in our program involve epidemiology, plant genetics, and molecular biology – all far from my expertise in aquatic ecology. Some of our main Research Translation projects have involved making short films for the public on arsenic in drinking water and mercury in fish. We have also brought together mercury scientists to summarize and synthesize mercury science relevant to policy makers and the recently signed Minimata Treaty. We are now doing the same for the science associated with arsenic in food.

What should society be doing to minimise methylmercury pollution?

The only thing we can do is to reduce sources, both atmospheric sources (especially coal-fired power plant and artisanal small-scale gold mining) and industrial point sources. The former requires technology for removal of mercury (Hg) from power plant emissions and the latter involves educating the artisanal small-scale gold miners found mostly in the developing world. The Minimata Treaty, when fully ratified, will help to reduce Hg sources.

Where would you like to take your research from here?

I think there is still a lot of work to do on predicting the effects of climate change on the fate and bioavailability of Hg particularly the interactions of environmental factors (nutrient loading, temperature, salinity, pH). I am also interested in the co-occurrence of contaminants (e.g. organic contaminants and mercury) in fish and the benefits and risks of eating fish. For the latter, I am interested in the factors that control the fatty acid composition of fish.

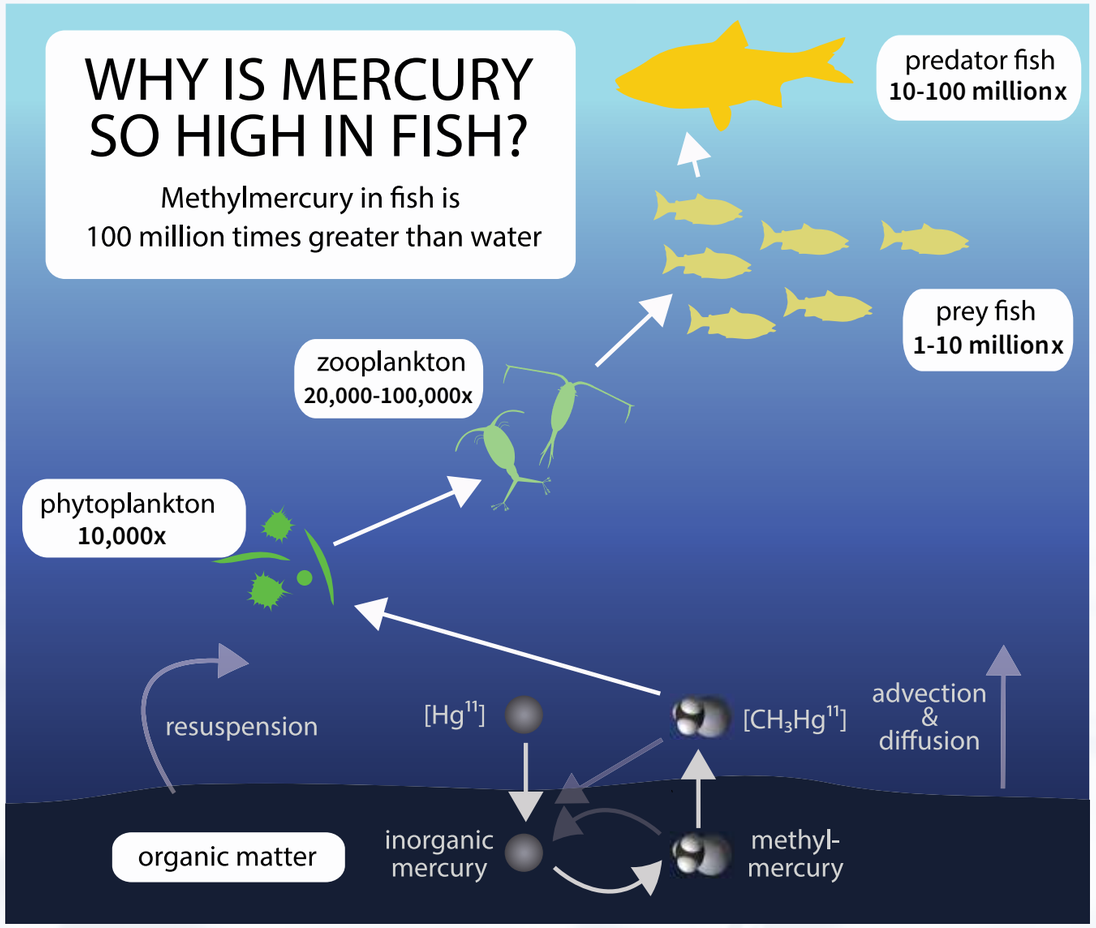
If you could perform one experiment, regardless of cost or difficulty, what would it be?

I would conduct a large mesocosm experiment (Ed: a mesocosm is a controlled section of the natural environment) on the interactive effects of pH, temperature, and organic carbon on the production, bioaccumulation, and trophic transfer of MeHg. It would require a larger mesocosm system than we have available and would likely need to run for the better part of a summer. These larger scale controlled experiments are important since they capture environmental realism but allow for controlling important environmental factors as well.

And lastly, every mercury-related article needs a question involving the Mad Hatter…so why do you think a raven is like a writing desk?
Ha ha! I like the answer, "Poe wrote on both of them."

Mercury Rising

The Dartmouth Toxic Metals Superfund Research Program comprises an interdisciplinary group of experts investigating the effect arsenic and mercury have on the environment and human health.



Be it mad as a hatter, suffering from the Danbury Shakes, or showing severe mercurialism, humanity has known for many years that mercury poisoning has long-reaching dangers. But mercury is no longer the concentrated poison which drove hat-makers mad, it now occurs in a more dangerous form – concentrated in aquatic food-chains, and is now known to have a wider range of health effects.

Mercury is particularly problematic in the marine food web, as the highly bioavailable methylmercury (MeHg) is readily taken up by marine organisms such as plankton in a process known as bioaccumulation. These organisms are then eaten by predatory fish, who in turn are fed upon by higher predators, each in turn accumulating the mercury already present in their prey. Thus high-level predators such as tuna and swordfish will eventually end up with potentially harmful levels of mercury, a process known as biomagnification. This in turn means that humans who feed frequently upon these higher predators can give themselves mercury poisoning, with all of the neurological symptoms that implies.

This is important because fisheries and farmed fish provide tens of millions of tonnes of protein to consumers worldwide, protein which in many cases cannot be replaced by other sources. In addition, seafood has important nutrients that are also not found in other foods. The accumulation of mercury in both wild and farmed species is thus a significant problem for public health, and thus understanding the manner in which mercury enters, travels through, and accumulates in the food web is of vital importance.

Methylmercury is both toxic and easily bioavailable, and enters marine ecosystems via several sources. Estuaries sit at the interface of fresh-water rivers and salt-water coastal systems, making them an intersection between land-based sources and ocean sources of pollution. Because of this central location, estuaries tend to collect mercury from contaminated sites on land, from river inflows, and from the ocean itself. Despite this knowledge, very little research has been performed on how exactly estuarine food webs and mercury sources actually link together.

So what do we know? Methylmercury, the toxic form of mercury, is formed in underwater sediments, from which it can diffuse out into the water – here it joins MeHg brought in by river inflows or ocean currents. In the water, it is taken up by microscopic plants and animals. Sediment MeHg can also be picked up during feeding by benthic infauna (e.g. worms and clams burrowing through the sediment). Transfer of MeHg from sediments into the water is particularly important, although the nature of this process in coastal and estuarine systems is not well understood. Further factors complicate this process: for example, organic carbon molecules can bind to Hg and reduce its availability to bacteria and fish, while other factors like temperature will encourage the uptake of Hg by certain organisms.

MERCURY STUDIES IN THE FIELD

To shine further light on this process, Dr. Celia Chen of Dartmouth College, and her collaborators have recently been examining the amount of MeHg present in estuaries across the northeast US coastline. Essentially, they have been measuring sources and stores of mercury within individual estuaries in the region, attempting to determine which environmental factors (temperature, organic carbon, salinity) influence MeHg production and bioaccumulation and thus provide a possible conceptual map of mercury transformation and movement.

Interestingly, they did not observe any correlation between the amount of methylmercury in sediments where most of the mercury is stored and that found in fish. However, there was a strong link between the amount of mercury in the water, be it completely dissolved or as particulate matter, and the amount found in the fish themselves – and MeHg levels were noticeably lower in fish which fed in the sediment. This all suggested that the direct source of mercury contamination in the food web was coming from the water, and that this pollution was coming not just from the sediments in the estuary.

So where was it coming from? The group performed further research to try and answer this question, showing that water methylmercury levels were not related to sediment mercury levels across a range of sites– completely surprising given the amount of mercury stored in sediments. Estuaries are intersections of multiple different mercury sources, and it seemed that a number of complex external sources were interacting to create the final polluted mixture of mercury in the water and sediments.

MERCURY STUDIES IN THE LABORATORY

One challenge facing researchers in this field is the sheer complexity of the problem – when dealing with an entire ecosystem, how do you decide which variables are the most important? One way in which complexity can be simplified is via the use of model systems, for example in the use of cultured cells to help answer questions covering an entire human patient. Part of Dr. Chen's research involves the development of model systems for mercury bioaccumulation, in particular the use of killifish and amphipods in the laboratory.

Killifish, specifically the gloriously named Mummichog (Fundulus heteroclitus), are an exceptionally hardy species, living happily in waters with differing salt, temperature and oxygen levels and in pristine to polluted ecosystems. Due to this, their widespread distribution, and their position towards the bottom of the food web, killifish are a good model for examining the accumulation of mercury within an ecosystem.

Dr. Chen's research has already shown the value of these fish, with recent work having shown that higher water temperatures are linked to increased mercury accumulation in the mummichog both in the tank and in the wild. This is a concerning discovery, as the steadily increasing global temperatures are thus likely to be matched by an increase in mercury within the ecosystem – bad news for those who enjoy tuna frequently.

The group plans to use model organisms and their field research to further identify these complex sources and pathways of mercury. This is particularly important nowadays when other environmental conditions are changing with climate and the international community has recently committed to control global mercury sources through an international treaty, the Minimata Convention on Mercury. Though there is as yet no real way to extract methylmercury from the environment once it is there, their work holds out the hope of understanding these puzzling processes. And from understanding, we can predict how, when and where mercury pollution will end up in our seafood.

Researcher Profile

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Dr. Celia Chen has spent the last 20 years unravelling the ways in which metal pollutants travel through and contaminate freshwater and marine food webs. Using both laboratory and field studies, her work on biological accumulation of mercury forms a core component of the Toxic Metals Superfund Research Program at Dartmouth College. Alongside her research she also works to communicate the program's discoveries to both the wider community and government agencies.

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Molecular perspectives on bee pathogens

With a solid career in human molecular medicine in her back pocket, Dr. Elke Genersch decided to put her skills to the test in another organism – the honeybee.

Almost 15 years ago you decided to change the focus of your research from human to bee diseases. What circumstances led you to choose bee disorders over the human counterpart?

At the time, I was working with molecular medicine and cancer research in Lund, Sweden. Because I wanted to come back to Germany, I started to look for an attractive position in academic research in and around Berlin. In this situation, I was offered the position as Head of Department for Bee Diseases and Vice Director of the Institute for Bee Research. After short meditation I accepted the challenge to switch from humans to bees and from tumors to pathogens because principally the way of scientific thinking stays the same. My solid background in molecular biology and my previous experience in virology helped me a lot and I habilitated 5 years later with a thesis on American Foulbrood and became an Associate Professor for Molecular Microbiology with the Faculty for Veterinary Medicine at the Freie Universität Berlin.

What do you find most rewarding about studying bee pathogens?

When I started working in this field, very little was known about bee pathogens on a molecular level. This was – and still is – the most rewarding part for me. There were so many open questions regarding pathogens and pathogen-host-interactions that every idea could potentially lead to a new project – and many did.

Since the questions were new, most of the results were also novel and changed the view we previously had on the pathogens. An example is the reclassification of the etiological agent of American Foulbrood, *Paenibacillus larvae,* and our finding of the existence of distinct genotypes, which have evolved different virulence strategies.

These results were highly relevant from a practical point of view and were almost immediately incorporated into the laboratory-, and clinical diagnostics procedure of American Foulbrood. Our results really made a difference! However, working with these pathogens is much more difficult than working with established model organisms. There are no molecular tools easily available and you cannot just order your reagents, kits, or antibodies from a catalogue. Therefore, to work with bee pathogens on a molecular level always feels like being a pioneer; there are no quick and easy solutions to experimental problems.

You have been involved in the recent startup of the Smart Bees project. Describe your role in the consortium.

My group will be involved in studying the triangular interactions between honeybees, deformed wing virus and the ectoparasitic mite Varroa destructor; V. destructor acts as a mechanical – and sometimes also biological – vector of deformed wing virus.

We and others have previously shown that *V. destructor,* acting as a biological vector of deformed wing virus, can be an evolutionary bottleneck for the virus, selecting for more virulent variants. We will further analyze this finding, together with the immune response of the honeybee to Deformed wing virus infections.

What practical implications do you hope your research will have in the future?

In order to combat a disease, you first need to understand the pathogen, its mode of action, its virulence mechanisms, its spread, and the factors influencing the success of the pathogen. By working on these topics and by furthering our understanding of all these pathogen-related topics I hope to contribute (i) to cures against bee diseases and (ii) to preventing the spread of bee diseases – not only between honeybees but also to other pollinators. I believe that our results will contribute to determining pathogen threats, and to enhance honeybee resistance mechanisms to parasitic disease.

Advancing virulence research

Leading an ambitious program of bee research, Dr. Genersch's molecular outlook is likely to alter the way we view the diseases of bees and other insect pollinators. Her novel approach to understanding an old problem is fast-forwarding the understanding of key factors mediating a rapidly spreading decline in the world's pollinator populations.

A PIONEER IN AN OLD FIELD

Beekeeping is an ancient pursuit, but as with many other chores we have brought into our modern times, beekeeping is now surrounded by a range of problems. Most of the issues are health related. While the demand for honey has led to a worldwide increase in honey bee management, bee diseases have been also on the rise for several decades. These diseases cause extensive problems with winter losses of bee populations.

Dr. Genersch's knowledge in molecular medicine turned out to be an invaluable asset for bee research, but not out of the bee perspective. Instead, Dr. Genersch has answered many important questions regarding bee diseases focusing on the molecular secrets of the pathogens. The molecular interactions between bees and their pathogens are also under her looking glass, and she is hence taking a novel approach in a field dominated by researchers focusing on the bees.

THE SECRETS OF A GENE SEQUENCE

American Foulbrood is the name of the most devastating of diseases affecting bee larvae (going under the technical name 'brood'). Initially described in terms of the foul smell accompanying the infection, the disease is lethal for the infected larvae and eventually kills the whole colony. The radical treatment of disease outbreaks includes the destruction of infected hives – a costly measure for beekeepers.

American Foulbrood is caused by the bacterium *Paenibacillus larvae.* The disease has been studied for decades; yet, the classification of the causative agent has been under constant revision since its identification in 1906. Prior to Dr. Genersch's engagement in the field, researchers believed the causative agent was divided into two subspecies.

Using repetitive element sequence based-polymerase chain reaction, a molecular technique optimal for studies of microbial subspecies, Dr. Genersch's group managed to reveal that what was previously considered as two species subspecies, was actually one species encompassing four different genotypes – named ERIC I-IV.

The key idea that allowed Dr. Genersch's group to succeed where others had failed was the comparison of the genotyping data to phenotypic observations of the bacteria. Differences in virulence – the strategy the pathogen uses to infect its host – accounted for a majority of these phenotypic differences. Dr. Genersch hence set out on a path to molecularly characterise the virulence factors of the different ERIC genotypes.

Using suppression subtractive hybridization and comparative proteome analysis in combination with gene inactivation experiments, they identified two toxins specific for ERIC I, and a protein specific for ERIC II, involved in the pathogenesis of the respective genotypes.

They also found a chitin-degrading enzyme, common to all *P. larvae*, which is crucial for the infecting process. The gut of bee larvae is lined with a chitin-rich layer, being one of its main barriers towards intestinal pathogen infection. By first destroying this layer, the bacteria create a route to entering and kill the larvae.

Further analysing the gene sequence of *P. larvae,* Dr. Genersch also predicted that the bacterium likely produces substances with antimicrobial or cytotoxic properties. Many antibiotics, or cytostatic drugs used in cancer medicine, are products originally isolated from bacterial strains producing similar substances.

The prediction turned out to be correct and in a close collaboration with Professor Roderich Süssmuth, she managed to isolate and characterise two novel substances having antimicrobial activity; paenilamicin and sevadicin.

This discovery undeniably opened up new avenues in Dr. Genersch's research: "On the one hand, we are now interested in understanding the mode of action and the biological role of these secondary metabolites. On the other hand, we are of course interested in determining their potential for human and veterinary medicine", she says.

CLIMATIC IMPACTS

The effects of a changing climate can be spotted in all areas of life – beekeeping being no exception.

The microsporidian *fungus Nosema* – an obligate intracellular pathogen – was until recently not viewed as a great threat to honeybees. The *Nosema fungus* harbours two subspecies; one infecting the European honeybee *(N. apis),* and one used to be known for infecting only the Asian honeybee *(N. ceranae).* A couple of decades ago, however, European beekeepers started reporting losses of their colonies due to infection with *N. ceranae.*

It is now known that *N. ceranae* can indeed infect both bee species, and the infection is often more severe when European bees are infected with the Asian form of the fungus. Unlike its local cousin, *N. ceranae* namely has the ability to suppress the immune system of the European bees.

Looking further into the issue with colony deaths caused by *N. ceranae*, Dr. Genersch noticed a clear regional pattern of infection. Death of colonies had been reported mainly in Spain or other southern European countries, while a thorough investigation of Nosema strains in Germany revealed that *N. ceranae* could not be held accountable for colony deaths in this temperate region.

Suspecting a climatic influence on the virulence of *N. ceranae,* Dr. Genersch investigated the spore germination of the two subspecies, finding that *N. ceranae* lost its spore germination ability at temperatures below +4°C – a temperature not affecting *N. apis.*

"Warmer winters and hot summers are obviously beneficial for *N. ceranae*", says Dr. Genersch. "Thus, any climate change in this direction will be advantageous for *N. ceranae;* this pathogen will become more prevalent and will possibly replace the rather benign species *N. apis.* If the climate continues to change, colony losses due to *N. ceranae* infection may pose a new threat to the beekeeping and pollination industry", she states.

THE BENEFITS OF CELLS IN A DISH

Studying intracellular pathogens, such as the *Nosema* subspecies, requires living cells. Bee cells are notoriously difficult to culture, leaving researchers to examining infected bees – a tedious practice considering that the bee season is rather short in the northern parts of the world.

Again, using her ability of thinking outside the box led her to find a solution where others found none. Since all previous attempts to produce a permanent bee cell line had failed, Dr. Genersch turned her gaze to cells originating in the order Lepidoptera; including butterflies and moths. The Lepidoptera cells turned out to be susceptible to infection with the *Nosema* subspecies, and Dr. Genersch's determination led to the development of the world's first cell culture model for studying *Nosema* subspecies. And since obligate intracellular bee pathogens were believed to be impossible to culture, this is, in fact, the first honeybee pathogen ever grown and studied in cell culture.

The model, extremely valuable for molecular investigations of virulence factors, can also be used as a screening assay that allows testing substances for activity against *Nosema* subspecies: "With our publication, we wanted to draw the attention to the fact that we now have a cell culture-based medium throughout screening system, available for quick identification of substances with activity against Nosema", says Dr. Genersch, inviting any parties interested in testing substances against *Nosema* to establish collaboration with her group.

SYNERGISTIC INTERACTIONS

First found in Southeast Asia at the beginning of the previous century, the parasitic mite Varroa destructor has spread from its native region with the help of modern beekeeping practices and is now present worldwide.

Varroosis is the most widespread infection of honeybees and it is blamed for a majority of bee colony winter losses. Recent research from Dr. Genersch's lab has, however, made it clear that it is not the feeding activity of the mite in itself that results in the death of bee colonies.

Deformed Wing Virus is a close companion of the Varroa mite, infecting almost all colonies where a mite infection is present. Researchers still argue whether the virus existed in the European bee population prior to the arrival of the mite from Asia in the 70's, or if the virus and the mite spread together. Be that as it may – they now coexist in bee colonies around the world.

The virus has been associated with the appearance of bees with deformed wings – a sign that colony collapse was imminent. It was not until the thorough investigations by Dr. Genersch that it became clear that the death of bee colonies ascribed to the *Varroa* mite was actually a result of a synergistic coexistence of the mite with the virus.

Deformed Wing Virus doesn't cause any symptoms in infected bees, unless the virus replicates in the mite prior to transmission to its bee host, turning the mite into a biological vector. Mechanical transmission, with mites acting as transient hosts spreading unreplicated virus, doesn't pose any apparent threat to bees.

"When we started to work on Deformed Wing Virus, its replication in mites and the relationship between the replication and the occurrence of overt infections was unknown. We were the first to prove Koch's postulates for crippled wings", says a proud Dr. Genersch.

Indeed, Dr. Genersch has all the right to be proud. Pioneering the field of molecular bee pathogen research, in a short time, she has contributed to findings that have changed the view of several of the diseases, providing knowledge that might ultimately also help saving other pollinators.

Researcher Profile

Dr. Elke Genersch
Deputy Director, Institute for Bee Research Hohen Neuendorf and Associate Professor, Department of Veterinary Medicine, Freie Universität Berlin, Germany

Following an educational background in molecular biology, virology, biochemistry, and molecular microbiology, Dr. Elke Genersch research career took the route over human molecular medicine before she joined the field of bee pathology in 2001. She is now a key player in the German Bee Monitoring project, she participated in the European Bee Monitoring efforts, and has been leading the working group "Pests and Pathogens" within the COLOSS network – an association for honeybee research. Dr. Elke Genersch is a member of the Editorial Board of Applied and Environmental Microbiology and an Associate Editor of the Journal of Invertebrate Pathology.

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CONTRIBUTIONS TO ENVIRONMENTAL HEALTH THROUGH RESEARCH AND TRAINING

Professor Pamela J. Lein is a neurotoxicologist and current Program Director for the Advanced Training in Environmental Health program at UC Davis. She investigates the potential roles of environmental contaminants as risk factors for neurodevelopmental disorders.

Your contribution to environmental research is impressive. What initially peaked your interests in toxicology and environmental health?

My interest in toxicology and environmental health was initially sparked by three phenomenal researchers and teachers at Cornell University: Paul Feeny, who taught an introductory course in Ecology and Evolutionary Biology; Tom Eisner, who taught a course in chemical ecology that focused on how insects use chemicals to protect themselves from predators and to entrap prey; and John Kingsbury in the School of Veterinary Medicine, who taught a course on poisonous plants. These three courses really solidified my interest in merging the two fields of biology and chemistry to study how chemicals interact with biological systems. I also loved these courses because they involved field studies – I have always loved being outdoors.

How crucial is it to discover environmental toxins and make the appropriate public health recommendations regarding their use?

There is now credible evidence that environmental contaminants, including chemical contaminants, interact with genetic susceptibility factors to determine individual risk and/or severity for a number of neurodevelopmental disorders and neurodegenerative diseases, ranging from autism and ADHD to Parkinson's disease and Alzheimer's disease. Collectively, these diseases exact a huge toll on individuals, their families and society. Currently we do not have pharmacological interventions that prevent or cure these diseases – the best we can do is slow the progression of the disease. So, our best bet is prevent or minimize the severity of disease by identifying the environmental chemicals that influence risk because, in contrast to genetic risk factors, which are currently irreversible, environmental factors are a modifiable risk variable.

In addition to your role as a researcher, you are also the Program Director for an environmental health training program. Why did you pursue this role?

I have always enjoyed teaching – it is really gratifying to see the students you are working with grow and succeed as academicians and researchers – and I have always believed in giving back. I was extremely fortunate to have had some truly amazing teachers and mentors who provided support and encouragement for me at every stage of my career, and I really wanted to return that favor to the generations following me. I also felt that taking on the role of Program Director for the Advanced Training in Environmental Health Science at UC Davis would enable me to reach more students than I would be able to in just my own lab, and it would allow me to provide tangible support in the form of fellowships. Training research scientists in today's world is an expensive endeavor, and these training programs are a very important piece in the network of support available for graduate students and their faculty mentors.

As the demand for environmental health experts is growing, so is the need for training. What are some of the highlights of your program?

The highlights include financial support for graduate students performing research in environmental health sciences, mentored research training laboratories performing cutting-edge research, access to world-class research facilities, and a unique course developed for trainees focused on emerging concepts in environmental health that engages trainees in critical thinking about complex issues in a modern society.

Can you elaborate on the impact of the faculty on training?

The faculty are at the core of the training program – they are the ones who oversee the research progress of the trainees. Each trainee is affiliated with the laboratory of one of the training faculty members, and this faculty member will work with the trainee to teach them the skills needed to perform their predoctoral research as well as develop the conceptual and technical aspects of their research project.

As Program Director and a scientist, what are your goals for the improvement of environmental health overall?

Our goals are to develop better methods for identifying the "bad actors" and the "neutral or good players" in the environment so we can more efficiently utilise resources to protect the public; to understand the mechanisms by which genetic susceptibility factors interact with environmental risk factors to determine the risk and/or severity of disease, which will hopefully improve approaches for identifying specific environmental risk factors, and possibly provide insight on novel preventive and therapeutic approaches; and to develop more effective approaches for communicating to the public the value and importance of environmental health research in public health.

TRAINING FUTURE ENVIRONMENTAL HEALTH EXPERTS

The Advanced Training in Environmental Health Sciences program provides a didactic and student oriented curriculum, collaborative research opportunities, faculty mentorship, and career development. It prepares future scientists with critical thinking skills, multidisciplinary expertise, and the ability to apply scientific knowledge to complex environmental health problems.

The Commitment to Environmental Health

There is increasing concern regarding the potential role of the environment in the development and progression of human diseases. This has consequently increased the universal demand for environmental health experts. To meet these critical demands, it is necessary to train scientists to identify and study environmental factors that are contributing to disease. These complex factors require scientists to be equipped with sharp critical skills and intellect in a comprehensive range of scientific disciplines.

The UC Davis Advanced Training in Environmental Health Sciences program is the field's second oldest training program in United States and has been operating since 1968. The National Institute of Environmental Health Sciences (NIEHS) grant, which sponsors 6 graduate level trainees per year, has been a key funding source in the training of aspiring environmental health experts. Approximately 150 trainees, which come from a diverse spectrum of scientific backgrounds, have been supported by the NIEHS funded program. Graduates have gone on to utilise their expertise in the environmental health field. The program remains highly dedicated and motivated to continue this long tradition of training.

A Curriculum Geared Towards Training

The two year Advanced Training in Environmental Health Sciences program incorporates didactic teaching and research training in the core principles of toxicology and methods of quantitative analysis. The curriculum is comprised of key requirements which includes didactic coursework, student centered learning activities, and research. A fundamental course called Emerging Concepts in Environmental Health offers a solid foundation for trainees in their first

year. Students are expected to complete laboratory rotations and elective coursework designed to support their research interests. In addition, trainees gain teaching experience in their roles as teaching assistants.

There are student led experiences designed to train the students in applying and integrating basic and clinical sciences. For example, student groups are assigned complicated environmental health problems with the goal of working together to formulate proposals and solutions. The groups are expected to review relevant literature and hold weekly brainstorming sessions with faculty. Students then present their final projects to the class and submit a written proposal for publication.

First year trainees are responsible for identifying a faculty member to mentor their thesis projects. As students work on their mentored research studies, they are required to present chalk talks, in which they discuss their projects in terms of successes, challenges, and future steps. This approach allows trainees to receive feedback from faculty from various disciplines. This additionally serves as preparation for doctoral dissertation.

Another component of the training program is the annual retreat in which trainees give formal presentations to the environmental health science community. These presentations are expected to meet the high standards of professional scientific presentations. Faculty members work with trainees prior to the retreat and guide their presentation skills.

Since the curriculum is one of the main elements of the training process, the program relies on trainees themselves to deliver critical feedback and help shape the structure. The NIEHS program officer is also influential in the progression of the training program by setting guidelines and standards.

There is the External Advisory Committee composed of environmental health experts at outside institutions who review the program and offer suggestions for improvement. All of the above recommendations are taken into account to help the program evolve in a way to meet global needs.

How Research Collaboration and Mentorship Play a Vital Role in Training

The 53 distinguished training faculty members in this program are involved in five major research areas, which are 1) Cancer, 2) Endocrine and Metabolic Mechanisms of Toxicity, 3) Genotoxicity and Epigenetics, 4) Neurotoxicology, and 5) Respiratory Toxicology. Multidisciplinary research opportunities exist because many faculty members incorporate numerous focus areas into their research. Therefore, the trainees have a myriad of options when choosing and developing their thesis projects. Faculty encourages trainees in their collaborative efforts.

There are countless research projects which integrate multiple focus areas. An example of a multidisciplinary research project is a joint study between Professor Pamela J. Lein of the neurotoxicology group and researchers of the respiratory toxicology group investigating the mechanisms of how organophosphates cause hyperreactivity of airways. The cutting edge research conducted through this program demonstrates the critical role the faculty play in training graduate students.

Faculty members also participate in graduate groups and other training programs. They serve as mentors on dissertation committees guiding students through their research projects and training. Students cross train in other laboratories as well. UC Davis promotes professional and academic relationships.

The extensive research opportunities are supported by the multitude of grants that UC Davis researchers have secured. In addition to the funds from the NIEHS grant, there are funded projects by other institutions such as the Center for Children's Environmental Health, the Western Center for Agricultural Health and Safety, the Center for Nanotechnology Health Implications Research, the Superfund Basic Sciences program, the Center for Neuroscience, and UC Davis MIND Institute.

As a prominent research university, UC Davis provides trainees with the access to world class facilities including the National Primate Center, the Mouse Biology Program, the Genome Center, the Comprehensive Cancer Center, and others as well. It also hosts other centers including the USDA Western Human Nutrition Center as well as three neuroscience institutes. Main academic departments include the School of Medicine, School of Veterinary Medicine, and various colleges in the sciences. UC Davis awards more than 200 PhDs in the life sciences yearly and remains a leader education.

Career Development and Opportunities for Environmental Health Scientists

The training program is committed to mentoring trainees in their pursuit of careers. Assigned mentors are available to guide trainees through career planning. Furthermore, trainees participate in career oriented seminars in which they select and invite a leader in the environmental health industry to speak about career development. There is also emphasis on curriculum vitae writing and interviewing skills. Other parts of career training include seminar speaking, teaching, and grant writing.

Graduates of the program have been very successful in their post training careers. They heavily contribute to environmental health by using the skills and knowledge acquired at UC Davis. Approximately 60 per cent of graduates are working in regulatory positions in government and private sectors. Many graduates have appointments with the California Environmental Protection Agency (EPA). Others are working in consulting firms, pharmaceutical companies, or the manufacturing industry. In fact, Chevron and Chlorox are two well known employers of environmental health scientists. The remaining 40 per cent of graduates are in academia serving as faculty members and investigators. Some are involved as faculty for this program training.

Dedicated to excellence, the Advanced Training in Environmental Health Sciences aims to: 'Train future scientists with the tools needed to solve complex problems in environmental health', says Program Director Professor Lein. With the emergence of a new generation of experts, there is much promise for their overall impact on identifying modifiable environmental factors and their role in complex diseases. This, in turn, can make a significant difference globally.

Meet the researcher

Professor Pamela J. Lein
Professor, UC Davis Department of Molecular Biosciences, School of Veterinary Medicine Chair, UC Davis Pharmacology and Toxicology Graduate Group
Program Director, UC Davis Environmental Health Training Program

Professor Lein is a developmental neurobiologist and neurotoxicologist with a Masters degree in Environmental Health and a PhD in Pharmacology and Toxicology. Her research is focused on investigating the cellular and molecular mechanisms by which environmental contaminants play a role in the development and progression of neurodevelopmental disorders and neurodegenerative disorders. One of her ultimate goals is to identify these modifiable environmental factors and stressors in hopes of contributing to preventative and therapeutic approaches for diseases. Professor Lein is involved in many national and international collaborative studies which are funded by numerous grants. She also pursues her passion for teaching in her appointments as Program Director and faculty member for the Advanced Training in Environmental Health Sciences program at UC Davis. Throughout her accomplished career, Professor Lein has contributed her expertise while serving on advisory groups and regulatory panels. When not working, she enjoys the outdoors.

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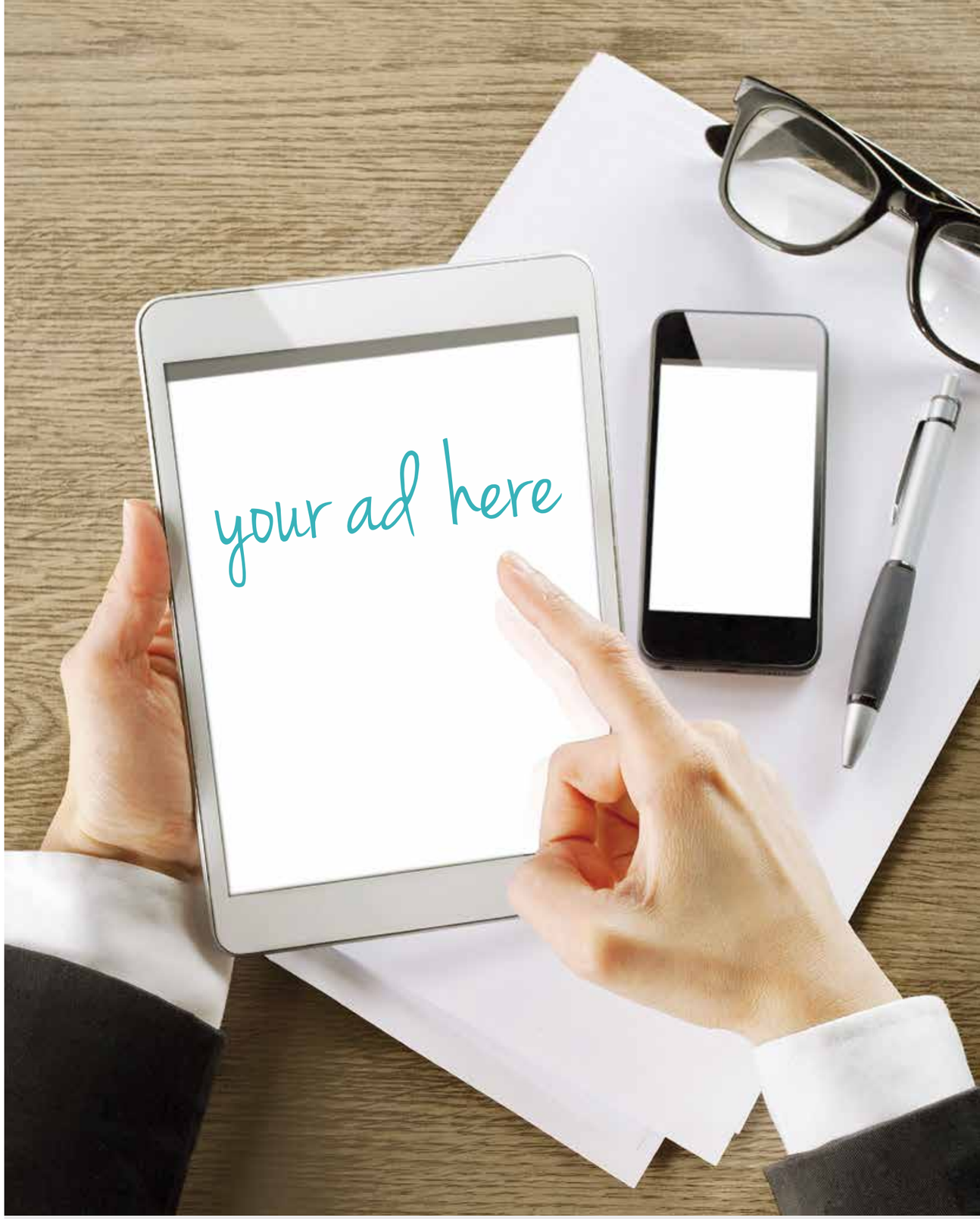

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