The primary mission of TBSI is to make fundamental discoveries in biomedical research. TBSI is an environment where innovative and interdisciplinary approaches lead to scientific discoveries of biomedical importance, ultimately giving rise to better patient care. Occupancy began in 2011 and we now have over 550 researchers, working towards discoveries of direct relevance to human diseases in a multi-disciplinary environment. The past year has seen strong growth with research income of over €30m, important discoveries in areas such as cancer, asthma, Type-2 diabetes, Age-related macular degeneration, infectious diseases such as hepatitis C and motor neuron disease. Discoveries have been published in journals of the highest rank internationally, with six publications in Nature (three of which had TBSI principal investigators as lead), Science, Cell, Nature Medicine, Nature Immunology, Nature Neuroscience and The Lancet. Here we provide a snapshot of some of the key scientists working in TBSI. Contact us any time via our website [www.tcd.ie/biosciences](http://www.tcd.ie/biosciences)

Luke O’Neill, Academic Director, TBSI
TOM LYNCH

Working together to drive progress

Two heads are better than one, according to the old expression. So how about tens of heads, all working together to answer scientific questions and translate biomedical discoveries for use in the clinic?

A core vision of the TBSI is to encourage collaboration between scientific, engineering and medical disciplines, and the Institute’s Chairman (designate) Tom Lynch believes this is a key ingredient for success - to build on Ireland’s investment in science and engineering research to date, to develop new biomedical solutions of interest to industry and the clinic and to contribute to Ireland’s continued growth in the life sciences.

An economics graduate of Queen’s University Belfast, Lynch has built a stellar career in the biomedical area. To name but a few roles, he was Chief Financial Officer, Executive Vice President and Vice Chairman at Elan Corporation, he is a member of the Advisory Board of the Institute of Human Virology at the University of Maryland and he serves as a director of GW Pharmaceuticals plc. He is currently Chairman of the clinical research organisation ICON, of Molecular Medicine Ireland and of the Dublin Academic Medical Centre.

For 10 years Lynch also served on the board of IDA Ireland, where he could see the impact of the life sciences industry on economic development in Ireland, and he explains that this is an area where the country now needs to build on recent investment. “Pharmaceuticals and biotechnology have been absolutely vital to Ireland’s economic success, and will now hopefully contribute to its recovery,” says Lynch. “Over the last 10 to 15 years, funding through PRTLI and Science Foundation Ireland has built up the research capacity in Ireland. But now we really need to create a richer ecosystem for drug research, discovery and development.”

TBSI stands to play an important role in that ecosystem, building on a foundation of excellent science and translating it towards commercial and clinical benefit. “Through Luke O’Neill’s inspirational leadership and the team of researchers here, the TBSI already has a world-class and international reputation in many areas,” he says. “And I think TBSI has the potential to create a multi-disciplinary approach to pharmaceutical discovery and development.”

Collaborating on discovery and translation will drive progress, he adds. “Drug discovery is more than discovering something on the bench - there is a whole translational aspect to bring it into something that is suitable to be given to patients, and you just have to have all those parts working together.”

This ability to bring together academic and clinical experts with a common focus and the agility to work on innovative ideas is not lost on industry, notes Lynch. “Industry is now looking at university groups like the TBSI as fertile ground for drug discovery and development,” he says. “And this will help us to continue building on Ireland’s investment for the future.”
MARTIN CAFFREY (Membrane Structural and Functional Biology)

Life Form Follows Function

Think of a chair. It might be the standard issue four-legged variety with a straight back. Or it might be a suspended ‘egg’ hanging from the ceiling. Either way, it is shaped to suit its function. As soon as you sit on it, it works.

In the same way, molecules in your body are shaped for interaction, and through those interactions they carry out their functions - maybe signaling to your body to run from a sudden threat, or ‘telling’ your brain that the colour you are looking at is green.

Prof Martin Caffrey is particularly interested in how such form follows function, and his lab at TBSI focuses on the shapes of molecules in the membranes that envelope cells. Why membranes? Because they are one of the most critical interfaces in biology: bluntly put, they separate the insides of cells from the outside, and they are replete with molecules that are shaped for business, including many interactions that are of interest to pharmaceutical companies looking for potential drug targets.

“The membrane has two components, lipid and protein,” explains Prof Caffrey, who is Professor of Membrane Structural and Functional Biology at Trinity College Dublin. “We work with both lipids and proteins, and our approach to understanding how this very complex assemblage works is through structure.”

Prof Caffrey’s lab has developed methods to grow the delicate membrane components as crystals in a toothpaste-like viscous substance called a liquid crystal or mesophase. Once grown, the three-dimensional structures of the crystallized proteins can be examined using radiation-based technology.

But in a complex setup like a membrane, the trick is to tease out the structures one at a time, he explains. “We take a reductionist approach - we pull the complex membrane apart, we look at the components in isolation and then we build back up a view of the complex from those individual structures.”

By coaxing out the crystals, Prof Caffrey’s lab has enabled breakthroughs in understanding how important signals get passed across the membrane into the cell. They helped Stanford University biochemist Prof Brian Kobilka to crystallise an unwieldy molecule called the β₂-adrenergic receptor, which mediates the body’s ‘fight or flight’ reaction to a sudden threat.

Prof Caffrey’s group grew crystals of the β₂-adrenergic receptor protein, which were brought to the X-ray synchotron at Argonne National Laboratory in Chicago; The structure was worked out, the findings were reported in Nature, and in 2012 Prof Kobilka was awarded a Nobel Prize for his discoveries in this field.

Prof Caffrey and colleagues have also worked out the structure of a membrane protein, cytochrome oxidase, that helps our bodies release energy from food, and he is now planning to study membrane proteins involved in disease, including the CFTR protein that is mutated in cystic fibrosis.

“We know that CFTR is a chloride transporter, but how it actually does what it does is not completely understood because we don’t have the structure,” he says. “If we get the structure, then there is the prospect of designing a compensation for some of these mutations that are causing problems for people with CF.”
Going deep into the phenotype of motor neurone disease

This week, two or more people in Ireland will likely be diagnosed with motor neurone disease. Having the neurodegenerative condition means that these people will progressively lose muscle function, and over time they will no longer be able to walk, speak or eventually breathe.

There is currently no cure for MND, but Professor of Neurology and TBSI Principal Investigator Prof Orla Hardiman wants to change that. She has already made important discoveries about genetic links to the condition, and she hopes that understanding more about disease heterogeneity will point to new therapies to tackle it.

“The search for the causes of neurogenerative diseases feeds into the search for new therapies,” explains Prof Hardiman, a Clinician Scientist in Trinity College Dublin and Beaumont Hospital. “The idea is to understand mechanisms and to try and identify new therapeutic options.”

The Irish population, which historically has been genetically relatively isolated, offers a good cohort to study MND. Prof Hardiman and colleagues collaborate with international partners to correlate the clinical features of the condition with the genetic signature, and to identify new causative and modifying genes for this rapidly progressive disease, she explains.

For over 15 years, Prof Hardiman has been building up a register of clinical information and a biobank of DNA samples from consenting patients in Ireland, as well as ‘control’ samples and information from people who do not have MND. The resource allows many different types of research into the disease.

“We spend a lot of time characterising patient cohorts and investigating them very fully,” she says. “That includes looking at the family trees, neuropsychology, brain wave patterns and detailed imaging, and we can then correlate these with genetic signatures. We have some really exiting findings about the overlap between MND, dementia, and other types of neurological and psychiatric disorders. The goal is to both find markers of different subtypes of diseases, and to help to identify pathways of neurodegeneration.” The work has already led to a series of high profile publications in journals such as Nature Genetics, Lancet Neurology and Neurology.

From the banked information, Prof Hardiman and co-workers have now identified almost 1,000 candidate genes of interest, and they have also confirmed that a key genetic variant on chromosome 9 accounts for over 50 per cent of all familial forms of MND in Ireland. “One of the many interesting findings is that the frequency of known genes in Ireland differs from other countries,” she says. “One of the common genetics causes of MND in the US - the gene SOD1 - does not feature at all in the Irish population.”

And while it takes time to translate any scientific discovery into an effective treatment, Prof Hardiman says that in the shorter term, working how genetic signatures interact with the clinical phenotype of disease can help to understand disease heterogeneity, and this in turn can help to develop new and better treatments.
DANNY KELLY (Mechanobiology and Tissue Engineering)

‘Joint-up’ thinking for fixing knees and hips

If you have a problem with a knee or a hip joint, you probably don’t need too much reminding of it. Every step is likely to let you know it’s still hurting.

But the techniques that surgeons currently use to address knee and hip damage can be expensive, and they may not work in the long term. So TBSI PI Prof Danny Kelly is looking at new ways to promote high-quality healing of the joints using adult stem cells and also, for treating larger defects, how to ‘grow’ a replacement joint outside the body.

At the moment, surgeons can treat small defects in the knee joint by taking a biopsy of healthy, spongy tissue called cartilage from the patient’s joint, taking chondrocyte cells out of it in the lab and growing those cells outside the body before putting them back into the knee. It’s expensive, time-consuming and the chondrocytes tend to lose their ability to make new cartilage outside the body, explains Prof Kelly. A simpler option, he notes, is to surgically ‘microfracture’ bone in the knee joint, which kick-starts the growth of fresh cartilage - but that cartilage tends to break down over time.

Instead of using chondrocytes or the microfracture technique, Prof Kelly wants to use stem cells to repair joints. Already his lab has been able to harvest a patient’s own stem cells from fat tissue in the knee and show that they can grow good quality cartilage outside the body.

And now, with funding from the European Research Council, he wants to make the process more streamlined for tackling small defects. “We want to make it into a single procedure where the body is the bioreactor for growing the cartilage rather than growing it in the lab,” he explains. “So our ideal would be that the surgeon takes the stem cells out of the fat pad at the time of surgery, the stem cells are put onto a scaffold and then the scaffold and stem cells go back into the knee to promote healing.”

Bigger defects will probably need larger, more mechanically functional implants, and again Prof Kelly is looking at how to stimulate stem cells to ‘build’ more functional replacement tissues in three dimensions. “Our hypothesis is that we can do this by providing the appropriate cues to the stem cells in the scaffold,” says Prof Kelly.

With funding from Science Foundation Ireland he is now looking at how to grow an entire knee - cartilage and bone - outside the lab, and the construct could then be implanted to replace a whole joint. “We are working towards being able to take out the damaged knee or hip and replace it with an anatomically accurate scaffold seeded with stem cells from the patient,” he says. “The idea is that these stem cells would help form new cartilage and bone depending on where they are in the engineered joint.”
The biosensors that build themselves

Every moment, trillions of biochemical reactions are happening in your body. And some of those reactions can result in signals that give a status update on your health. Detecting clinically useful signals can help doctors keep track of how patients are faring, so Prof Thorri Gunnlaugsson is using chemical knowledge to discover and develop new sensor molecules to report on changes in the body.

“We are interested in generating compounds that can detect biological response and that can report on them,” explains Prof Gunnlaugsson, a TBSI Principal Investigator who heads the Supramolecular & Medicinal Chemistry Research Group. “And I am particularly interested in making sensors that can report back on activities, ions and molecules that are relevant to critical care analysis.”

His team works with colleagues in CRANN to make new ‘self-assembling’ materials, where small molecules get together in an organised fashion under the right conditions to build larger structures.

One chemical trick is to give them a level of ‘chirality’ or handedness. “Just like when we shake hands, we each shake with our right hands, not right hand to left hand, that doesn’t make sense to us,” explains Gunnlaugsson. “In the same way, molecules will find the right component to make a happy union.”

His lab also uses metals to encourage the molecules to assemble, and the researchers have observed how the molecules ‘grow’ structures that are new to chemistry. They are also exploring how custom-built biosensors can report changes in their environment by altering their luminescent properties.

“In these structures the metal will tell you, ‘I am in a different environment so my luminescence is going to be different’, and this could be applied for diagnostics,” he explains.

Some of the structures being developed in Prof Gunnlaugsson’s lab could be developed for situations where an individual patient needs continuous monitoring, such as during major surgery or in intensive care. Other chemical inventions could even act as nano-weapons that can target and kill cancer cells, and he has been working in close collaboration on this with TBSI PI Prof Clive Williams from the School of Biochemistry and Immunology, as well as other researchers from TCD and University College Dublin.

“We made metal ion complexes that can act a bit like a scorpion - it can grab on to a target structure, and it can change its luminescence, but there is also a sting in the tail,” says Prof Gunnlaugsson. “That sting in the tail is in a form of an electron transfer and it will damage DNA and cause cells to die.”

In practice, when the chemical ‘scorpion’ is introduced to cancer cells in the lab and activated by light, there’s a popcorn-like effect under the microscope as the individual cells start to die.

“What we are doing is really all about making these miniature chemical biosensors and novel therapeutics,” says Prof Gunnlaugsson. “And importantly, we are finding their application to biology.”
MAREK RADOMSKI (Pharmacology, nanopharmacology, nanopharmaceutical drug discovery)

Answering sticky questions about blood platelets

Why is traffic pollution bad for your heart? How can we deliver nanoparticles safely for medicine? And could blood platelets help cancer spread around the body? These are some of the questions that have exercised Prof Marek Radomski and shaped his research in recent years.

The TBSI Principal Investigator first became interested in the link between air pollution and heart problems when working in Houston, Texas. “People asked how come pollution is linked to myocardial infarction,” recalls Prof Radomski, who is currently Head of the School of Pharmacy at Trinity College Dublin.

That started him thinking about how particulate matter in the air might be linked with thromboses, or blood clots that can trigger heart attacks. A thrombosis forms when small cells called platelets in the blood become activated and clump together, or aggregate. If this clot travels to the heart it can trigger a heart attack. Could platelets be affected by the particulate matter that pollutes air? “We looked at the effect of particulate matter on platelet aggregation and thrombosis,” says Prof Radomski. “And what we found that particulate matter of size of 10 [which means 10 microns or less, the range found in smog] really activates platelets.”

By then, Prof Radomski had moved to Trinity, and as a PI in the Centre for Research on Adaptive Nanostructures and Nanodevices (CRANN) he also started to look at how the body responds to even smaller nanoparticles and nanomaterials. One strand of the research has been looking at whether nanomaterials can help keep blood in good condition when it is being treated outside the body during cardiac bypass surgery or kidney dialysis.

“The best surface for the blood is blood vessels,” explains Prof Radomski. “The moment blood is out of the body and it has contact with another surface it can start to clot, and you have got to do all the tricks to prevent the blood from clotting.”

More generally, research into the biocompatibility of nanoparticles will help to inform whether and how we can use them to deliver therapeutic drugs more effectively in the body, he adds. “The nature of the nanoparticle is to be very highly penetrative and reactive, and also some nanoparticles are technologically more friendly to use in a biological system,” he says. “So we are looking at various types of nanoparticles and their interaction with biological systems. You have got to answer the questions like this if you are trying to come up with the best nanoparticle-based drug-delivery system and optimise it.”

That’s not the only type of interaction that is igniting Prof Radomski’s interest: he has recently started looking at how blood platelets could be cloaking and protecting cancer cells as they spread or metastasise through the body in the blood.

“We have strong evidence that blood-borne metastasis may be facilitated by platelets,” he says. “They can aggregate around the metastasis and hide the cells from the immune system, and platelets may also be stimulating the cancer with growth factors. These questions about how platelets could be facilitating the growth of cancer - and how to stop them - is something I want to look at more in the coming years.”
LUKE O’NEILL (Inflammation Research)

What makes your innate immune system kick in?

Around the clock, cells of your innate immune system patrol your body for potential causes of trouble. That trouble might come in the form of bacteria or other infectious agents, or it might be an injury to tissues. And when it registers a threat, the innate immune system responds, triggering an inflammatory response that can kill off would-be invaders and promote healing. But how do those innate immune cells know when to swing into action?

Prof Luke O’Neill, Director of the TBSI, is looking at the cogs in that signalling process, working out the biochemical cascades that kick off when a signal arrives at the surface of an immune cell and eventually results in an inflammatory response.

“I have an obsession with innate immunity and inflammation,” says Prof O’Neill, who is Professor of Biochemistry at Trinity College Dublin. “So in my lab we are getting underneath the bonnet of this process and unravelling the component parts.”

Step one in that process can happen when a molecule binds to and activates a ‘Toll-like receptor’ on the surface of an immune cell, such as a macrophage in the blood. Prof O’Neill has discovered several key signals within the cell that get triggered when this happens.

“We found some of the cogs that get clicked and drive the host defence against infection,” he says. “But equally interestingly, this process gets activated inappropriately in conditions such as Type 2 diabetes, rheumatoid arthritis and inflammatory bowel disease - the same apparatus is dysfunctional in all these diseases.”

Prof O’Neill’s work has fed into Trinity spin-out company Opsona Therapeutics, which is looking to block Toll-like receptor 2 in patients who have had a kidney transplant, and so help reduce organ rejection. “This is clinical translation of the findings made through curiosity-inspired research,” says Prof O’Neill. “And we are continuing to look more into how these Toll-like receptor pathways work, because we still don’t understand all the mechanisms.”

With funding from the European Research Council, his lab is looking at how these signalling pathways are regulated by small molecules in the cell called microRNAs, and how the daily or circadian rhythms of the host can affect the innate immune response.

Prof O’Neill and colleagues have also recently discovered that macrophages switch the way they burn energy when they encounter a bacterial signal through a Toll-like receptor, and this change in metabolism is linked with an increase in a metabolite called succinate. In turn, the succinate seems to act as a ‘danger’ signal that activates pro-inflammatory molecules such as interleukin-1 in the macrophage, and so triggers inflammation.

“Importantly, we were also able to block this inflammatory switch in the lab with drugs that are already in use in the clinic, and this could point the way to new treatments for conditions where the inflammatory response is overactive,” says Prof O’Neill. “So we not only have a curiosity-driven discovery about this metabolic danger switch, but perhaps there’s a way to intervene that could be clinically useful.”
KINGSTON MILLS (Immune Regulation)

Balancing the immune system to a T

If something is out of balance, you soon know about it. If you work too hard and rest too little you feel exhausted, and even physically losing your balance can quickly cause you to fall.

Similarly, your immune system needs a certain balance to work effectively. If parts stop working in harmony, the overall system can be less effective at protecting your body from infection, or it may even turn tail and start to attack your tissues. Meanwhile there are times when we might want to actively tilt the immune system’s balance to help clinical treatments.

So Prof Kingston Mills is looking to understand how the immune system is affected by the balance of T-cells, which play important roles in recognising a threat or damage to the body and in telling the immune system to take action.

“The overall theme of my research is focused on T-cells,” explains Prof Mills, who is Professor of Experimental Immunology at Trinity College Dublin. “We are looking at subtypes of T-cells that are involved both in autoimmunity and also in immunity to infection and cancer.”

One approach his research group takes is to remove specific T-cells and see what happens. “We can artificially disrupt the balance in the types of T-cells using knockout mice,” explains Prof Mills, who heads the Immunology Research Centre at TBSI. “That means we can look at what happens in models of disease when they are missing the key parts of the system and so we can figure out the roles that these specific T-cells play.”

They have already seen some breakthroughs. In a lab model of multiple sclerosis, called experimental immune encephalomyelitis, the Trinity researchers found that ‘gamma-delta’ T-cells appear to be important for mediating damage to the nervous system. How? They recruit other immune cells into the brain and they produce molecules that trigger the breakdown of tissues. Now other groups are now finding evidence for parallel mechanisms in multiple sclerosis patients. “A lot of what we are seeing in the mouse model is translating,” says Prof Mills.

His group is also looking at how we might tweak the balance of T-cells to help make cancer treatment more effective. Tumour cells often have ways to avoid the immune system’s usual surveillance, but Prof Mills has discovered how to rev up the immune response by dampening down ‘regulatory’ T-cells that normally act as an immune brake. In effect this should help to put the tumour back into the immune system’s sights and allow ‘protective’ T-cells to respond to and kill the tumour cells.

The immune therapy showed positive results in models of melanoma (skin), colon and lung cancer and the discovery is now being brought towards the clinic through a start-up company, TriMod Therapeutics. Prof Mills reckons it could eventually offer a way to support cancer treatments: after surgery the immune system could be used to hunt down and target remaining or recurring tumour cells. “We are using an approach that specifically targets the tumour cells, and you are getting the immune system to do the work for you,” he says.
GAVIN DAVEY (Neurodegeneration)

Looking at brain disease ‘in a dish’

It almost goes without saying that the brain has critical input into keeping the body running smoothly. And if parts of the brain start to degenerate, whether through disease or ageing, the effects can soon turn up in functions such as movement, co-ordination and memory.

TBSI Principal Investigator Professor Gavin Davey is looking at the biochemical processes that underlie such neurodegeneration, particularly in the type of damage that occurs in progressive conditions such as Parkinson’s disease.

However, the living brain itself is not so easy to study biochemically in the lab. That’s why his group is using stem cell technology to grow ‘brain cells in a dish’. The process reprogrammes skin cells from mice so that they grow as brain cells, and particularly as brain cells that make a chemical called dopamine.

In Parkinson’s disease, this type of cell dies in the brain and the leads to symptoms, so Professor Davey wants to take a closer look at what is going on. He is particularly interested in structures within the cells called mitochondria, which act as energy powerhouses for the cells.

“In Parkinson’s disease in humans the mitochondria are defective, and the big question is why,” he explains. “So we use the stem cell technology as a model to look inside those brain cells in a dish in the lab, and we are particularly interested in a key enzyme in the process called Complex I.”

The work, which combines biochemical experiments with computational modelling, has identified several control points in the function of the brain cells and the ‘disease-in-a-dish’ stem cells also offer a useful test bed to test various potential drugs to combat neurodegeneration, adds Professor Davey, who is Head of the School of Biochemistry and Immunology at Trinity. “We work with existing drugs and we also synthesise new compounds with colleagues, and then we test them on stem cell models to see if they can reverse the neurodegeneration or slow it down.”

A more experimental arm is now looking to implant stem cells into the brain itself in a mouse model. “If you put stem cells into the brain, you may get an immune response against them,” says Professor Davey. “So if we encapsulate stem cells inside little spheres of inert material and transplant these encapsulated stem cells into the brain, the hope is that they will survive, grow and regenerate the damaged brain cells.”

Professor Davey and colleagues are also putting their understanding of metabolism to use in improving how certain drugs are produced, in particular protein-based ‘biotherapeutic’ drugs that are made by genetically engineered cells during bioprocess. As the cells make the proteins, they add various sugars to the structure, and Professor Davey is working with industry to make those sugar arrangements on the drugs more suitable for use in humans. “It might seem different to the neurodegeneration work we do,” he says. “But understanding the fundamental biochemical pathways can help us get to the root of all these problems.”
CLIONA O’FARRELLY (Comparative Immunology)

Immune differences point to potential treatments

Cows, chickens and humans obviously look different. But did you know that their immune systems are different too? Similarly, the immune system of a liver differs from that of a womb. And even individual people can have different immune responses to the same type of infection. Prof Cliona O’Farrelly looks closely at these differences to figure out specific immune responses, and how we might harness them to improve agriculture and medicine.

“I am interested in immune systems in different species,” explains Prof O’Farrelly, who is Professor of Comparative Immunology at Trinity College Dublin and a Principal Investigator at TBSI. “All multicellular organisms have to protect themselves against infection - viral, bacterial, fungal and parasites - so all those organisms are equipped with defence mechanisms. But because different species have evolved to occupy specific niches, they may have evolved different components of their immune system to protect against different threats, and we can learn a lot from them.”

One puzzle is why chickens can live happily with a bacterium called Campylobacter in their guts, but if the bacterium gets into a human gut it can cause food poisoning. While looking at this question, Prof O’Farrelly and colleagues saw that the birds had the appropriate immune toolkit to keep the bugs under control. “We discovered that chickens have antimicrobial peptides and a pathogen-detecting system that mammals don’t have,” she says. “And this could perhaps point the way to new vaccines and treatments to tackle these food-borne infections.”

Prof O’Farrelly is also working with Teagasc to look at how the immune system’s potential role in keeping the wombs of cows healthy - and the findings stand to inform breeding programmes. “We want to breed for healthier cattle that are not as reliant on antibiotics - we are looking for bovines that can produce meat and milk and resist disease naturally.”

In humans, her work has a strong focus on the immune system of the liver, particularly when the liver is challenged by a virus such as Hepatitis C. She has been working with samples from women who were exposed to hepatitis C through infected blood products. Some of the women were able to clear the virus, and Prof O’Farrelly wants to know what in their innate immune system is likely doing the job.

“We are trying to understand why some people are resistant to the virus,” she says. “We don’t have an effective vaccine against quite a number of viruses - that is because we don’t know how viruses interfere with the immune response - and we are hoping that by using information from the resistant patients it will help us discover why some people are more vulnerable to infection than others. Then from that we can inform potential new therapies and vaccines.”
Will a worm a day keep the doctor away?

The thought of being infected by parasitic worms is probably enough to put you off your next meal. But we can learn plenty about our immune systems from worms that like to live in humans. That's why TBSI PI Prof Padraic Fallon is analysing a type of flatworm called *Schistosoma* for clues about - and possibly even new treatments for - immune-based chronic conditions such as asthma, allergies and anaphylaxis. And he is particularly interested in how parasitic infections in childhood may prime the immune system to work more effectively.

The juvenile human immune system co-evolved with parasitic infections, including worms, explains Prof Fallon, who is professor of translational immunology at Trinity College Dublin. "Up until about 50 years ago they were still pretty common in Ireland, but today they are relatively rare, and when these infections do crop up we quickly address them with a trip to the pharmacy," he says.

But *Schistosoma* infection is still endemic in some regions of the world. And while those infections can be serious or even fatal in some cases, they are also linked with fewer allergies in those who have the live worms on board, explains Prof Fallon.

So what exactly does the worm do to its host's immune system? Prof Fallon and colleagues want to find out. They are looking at the immune interplay between worm and animal host during an infection in mouse models. So far, the work has already uncovered a new type of immune cell in the animal host, which they have called the 'nuocyte', and Prof Fallon believes this cell may have specifically evolved to tackle worms.

Plus it seems that there are upsides for the mouse hosts that can tolerate living with the flatworms - infection could offer some protection against the kinds of immune over-reactions seen in many chronic conditions in humans.

"We work with mouse models of anaphylaxis, and we found that if these mice are infected with live *Schistosoma*, it can prevent the anaphylaxis," says Prof Fallon. "We also found in mouse models that a live worm infection can reduce the severity of symptoms in allergic asthma, inflammatory bowel disease and a form of encephalitis that mimics multiple sclerosis."

Clinical trials with live helminth infections - though not *Schistosoma* - are ongoing for a range of inflammatory diseases. As there is a risk of adverse effects, Prof Fallon is looking at the potentially protective molecular events that are triggered by infection with *Schistosoma* with a view to informing new therapeutic regimes to mimic the positive side of a worm infection without the risk from the live parasite.

“Our aim is to determine how the immune system has evolved to tolerant helminths and use such insight to develop new therapies for inflammatory diseases,” he says.
MARY MEEGAN (Pharmaceutical Chemistry; Drug design and discovery)

Better anti-cancer drugs by design

Cancer cells are primed to grow, to divide and make more cancer cells, and that’s why many anti-cancer drugs look to target and block that cycle. But could we make even better drugs by looking closely at how the chemistry is working in this process?

Prof Mary Meegan, a principal investigator at TBSI, is taking a close look at where anti-cancer drugs can bind in cells, and the aim is to identify more effective and patient-friendly drugs of the future.

“We are interested in the design and synthesis and - in collaboration with our biochemist colleagues - in the evaluation of novel therapeutic agents that might be suitable for further development, or that would give insight into development for drugs,” explains Prof Meegan, who is Professor of Pharmaceutical Chemistry in the School of Pharmacy at Trinity College Dublin.

Breast cancer is one focus, and she has been studying the oestrogen receptor, which is implicated in around two-thirds of breast cancers. When the hormone oestrogen binds to the oestrogen receptor, it drives the growth of cells. Existing anti-cancer drugs such as Tamoxifen can act as an antagonist and block the receptor by binding to it, thus stopping oestrogen from giving the growth signal. But existing drugs are not without their own problems, explains Prof Meegan. “We want to design better oestrogen-receptor antagonists which would have fewer side effects and problems.”

Her research is also looking at binding sites on tubulin inside cancer cells. Tubulin is an important building block of microtubules, internal structures that cells need in order to divide. Existing anti-cancer drugs target tubulin and can block cell division in cancer cells, and now Prof Meegan is designing more effective drugs to bind to tubulin and inhibit cell division in several types of cancer.

The research uses X-ray crystallography and *in silico* computational modelling to examine the chemical binding sites involved and inform the design of chemical compounds that could do the job even better.

“The X-ray and computational approach helps us with the initial design and then as chemists we go on to modify the molecules to suit the purpose,” she says. “It’s really about focusing on the design of the molecule so it can interact in slightly different ways and produce very beneficial effects.”

Prof Meegan works with TBSI principal investigator Associate Professor Daniela Zisterer, a biochemist, to put the custom-built molecules to the test in cells in the lab. Their experiments have identified a number of molecules with interesting activities.

“We now have very potent compounds that are active in the nanomolar and sub-nanomolar activity concentration range and we are very excited about those,” says Prof Meegan. “And we would hope to interest pharmaceutical companies in their further development.”
MATHIAS SENGE (Organic, Medicinal and Biological Chemistry - SFI Tetrapyrrole Laboratory)

Better medicine through chemistry

What makes blood red? And plants green? They owe their natural hues to pigments that contain chemical compounds called porphyrins. And Prof. Dr. Mathias Senge is using this class of organic molecules as the basis of new compounds for medicine.

A synthetic organic chemist, the TBSI Principal Investigator and his colleagues look for ways to make porphyrin compounds and tailor them in the lab, then they work with researchers from other disciplines to put these customised chemicals to use.

“We develop synthetic methods, so we look at how to make these molecules, how to make them better and how to change them,” he says. “Then we look at the applications.”

Some of the porphyrin compounds developed in Prof Senge’s lab could be of use in making new materials, some could help to improve the function of solar cells and another arm of his work looks to apply porphyrin-based chemistry in medicine.

Porphyrins are already used to treat some cancers, most notably in the skin, he notes. “Porphyrin compounds, derivatives of the blood pigment heme, can be used for ‘photodynamic’ cancer therapy. The porphyrins go into the cancer cells and then if you expose them to light, reactive molecules are formed and they attack the cancer. It is a fairly established method and has a high success rate in skin cancer, but it is not widely used for other cancers.”

Prof Senge is now involved in a project with medical colleagues in St James’s Hospital to apply porphyrins in the treatment of oesophageal cancer. “We make the porphyrins and do the initial biological screening to assess the anti-cancer activity in our lab,” he explains. “Then the compounds go to the medical people, and they do the translational science.”

Porphyrins could also help to get drugs to where they need to go in the body. “It’s always a problem - how do you get your drug to the target cells,” says Prof Senge. “So we try to get better drug formulations, where by using chemical means you develop better targeting systems and get anti-cancer drugs to tumours.”

And if that weren’t enough, the porphyrin-based chemicals have another useful trick up their sleeve: killing microbes. “You can use these compounds as anti-microbial agents, and the application there would be in wound healing,” says Prof Senge. “You could potentially have a bandage impregnated with these compounds, then just because the bandage is in the light outside it would automatically disinfect the wound and help the body to heal.”

Prof Senge, who holds the Chair of Organic Chemistry and heads the Discipline of Organic, Medicinal and Biological Chemistry in Trinity College Dublin, describes synthetic organic chemistry as an important source of new tools for biological applications. “Biologists work on nice applications but the compounds have to come from somewhere,” he says. “The compounds come from people like me or the other synthetic chemists here in TBSI that make them.”
It’s a sobering thought, but right now there are trillions of viruses on and in you. And some of them could cause you harm if they get inside your cells and establish an infection. But your body is on alert, looking out for those attempted break-ins.

Prof Andrew Bowie and his group at TBSI have been analysing how cells and viruses interact, getting a ‘virus-eye view’ of how human cells can sense when a viral intruder is present, and the kinds of tactics that viruses use to avoid detection and capture.

Viruses present a particular challenge to the body’s immune system - not only are they smaller than bacteria or parasites, but they are also made of proteins and genetic material that look similar to our own, explains Prof Bowie, who is Head of Immunology at Trinity College Dublin’s School of Biochemistry and Immunology.

“That means our cells are trying to detect an entity that looks like quite similar to self and they are also trying to mount an appropriate response - one that won’t let the virus gain a foothold, but isn’t so vigorous that it will cause problems like inflammation or even auto-immunity,” he says.

To find out how cells react to viruses, Prof Bowie’s group introduces viruses or pieces of virus into human cells in the lab. These added molecules act like bait, and allow the scientists to fish out the human proteins that bind to those viral materials when they are in the cell.

That fishing approach led Prof Bowie’s lab to discover IFI16, a protein in human cells that appears to ‘sense’ the presence of DNA. The area of DNA sensors is exciting and emerging field, notes Prof Bowie, and plenty remains to be worked out about how cells ‘know’ the DNA is from a virus.

Meanwhile, viruses aren’t short of a few tricks either, and Prof Bowie’s group has been figuring some of them out in the lab. Again they add offending pieces of virus to cells and this time they take stock of the biochemical signals they can trigger, such as blocking the cell’s normal immune response to intrusion.

“When you start to examine the whole virus/host interaction, it’s like an arms race,” says Prof Bowie. “The virus is developing ways to infect host cells then the host is trying to develop ways to overcome the virus and then the virus develops new strategies to try and overcome the host.”

Teasing out those strategies could ultimately inform new approaches to help block viral infections, and it may even shed light on some aspects of auto-immunity, where the cell’s burglar alarms start to recognise its own components instead of actual intruders. And Prof Bowie believes that getting right down to the perspective of the virus offers important insights: “The virus-eye view is a very powerful way to find out what is going on.”
Some recent publications in www.nature.com

REVIEW

Metabolism of inflammation limited by AMPK and pseudo-starvation


Metabolic changes in cells that participate in inflammation, such as activated macrophages and T-helper 17 cells, include a shift towards enhanced glucose uptake, glycolysis and increased activity of the pentose phosphate pathway. Opposing roles in these changes for hypoxia-inducible factor 1α and AMPK-activated protein kinase have been proposed. By contrast, anti-inflammatory cells, such as M2 macrophages, regulatory T cells and quiescent memory T cells, have lower glycolytic rates and higher levels of oxidative metabolism. Some anti-inflammatory agents might act by inducing, through activation of AMP-activated protein kinase, a state akin to pseudo-starvation. Altered metabolism may thus participate in the signal-directed programs that promote or inhibit inflammation.

LETTER

Succinate is an inflammatory signal that induces IL-1β through HIF-1α

G. M. Tammahill1, A. M. Currie1, J. Adamik2, E. M. Falsomn- McDermott1, A. F. McGettrick1, G. Goel1, C. Frezza4,5, N. J. Bernard1, B. Kelly1, N. H. Foley1, L. Zhong1, A. Garder1, Z. Tong1, S. S. Jany1, S. C. Corr1, M. Haneklaus1, B. E. Caffrey1, K. Pierce1, S. Walmsley1, P. C. Beasley1, E. Cummins1, V. Nizer1, M. Whyte1, C. T. Taylor1, H. Lin1, S. L. Masters1, E. Gottlik1, V. P. Kelly1, C. Clish1, P. E. Auron1,*, R. J. Xavier1,*, & L. A. J. O’Neill1

Macrophages activated by the Gram-negative bacterial product lipopolysaccharide switch their core metabolism from oxidative phosphorylation to glycolysis1. Here we show that inhibition of glycolysis with 2-deoxyglucose suppresses lipopolysaccharide-induced interleukin-1β but not tumour-necrosis factor-α in mouse macrophages. A comprehensive metabolic map of lipopolysaccharide-activated macrophages shows upregulation of glycolytic and downregulation of mitochondrial genes, which correlates directly with the prolyl hydroxylase (PHD) inhibitor dimethylloxazolyl glycine, which stabilizes HIF-1α protein, also boosted LPS-induced Il1b mRNA (Supplementary Fig. 8). Conversely, pre-treating LPS-stimulated BMDMs with a cell-permeable α-ketoglutarate (α-KG) derivative, which increases PHD activity, depleting HIF-1α, significantly reduced LPS-induced Il1b mRNA (Fig. 2c). α-KG inhibited expression of both LPS-induced HIF-1α and IL-1β protein in a dose-dependent manner

LETTER

Viral immune modulators perturb the human molecular network by common and unique strategies

Andreas Pichlmaier1,2, Kumaran Kandasamy1, Gualtiero Alvisi3, Orla Mulhern1, Roberto Sacco1, Matthias Habjam2, Marco Binder1, Adriana Stefanovic1, Carol Ann Eberle1, Adriana Goncalves1, Ulfmann Rüekstimmer1, André C. Mittler1, Astrid Fauster1, Cathleen Hoze1, Kristina Lindsten1, Stephen Goodhourn1, Georg Koch1, Friedemann Weber1,4,5, Ralf Bartenschlager1, Andrew G. Bowie1, Kelyn L. Bennett1, Jacques Collinge1 & Giulio Superti-Furga1

nature.com
Crystal structure of the β₂ adrenergic receptor–Gs protein complex

G protein-coupled receptors (GPCRs) are responsible for the majority of cellular responses to hormones and neurotransmitters as well as the senses of sight, olfaction and taste. The paradigm of GPCR signalling is the activation of a heterotrimeric GTP binding protein (G protein) by an agonist–occupied receptor. The β₂ adrenergic receptor (β₂AR) activation of Gs, the stimulatory G protein for adenyl cyclase, has long been a model system for GPCR signalling. Here we present the crystal structure of the active state ternary complex composed of agonist–occupied monomeric β₂AR and nucleotide-free Gs heterotrimer. The principal interactions between the β₂AR and Gs involve the amino- and carboxy-terminal α-helices of Gs, with conformational changes propagating to the nucleotide-binding pocket. The largest conformational changes in the β₂AR include a 14 Å outward movement at the cytoplasmic end of transmembrane segment 6 (TM6) and an α-helical extension of the cytoplasmic end of TM5. The most surprising observation is a major displacement of the α-helical domain of Gs relative to the Ras-like GTPase domain. This crystal structure represents the first high-resolution view of transmembrane signalling by a GPCR.

Structure and function of an irreversible agonist–β₂ adrenoceptor complex

Structure and function of an irreversible agonist–β₂ adrenoceptor complex

Structure and function of an irreversible agonist–β₂ adrenoceptor complex

Structural insights into electron transfer in caa₃-type cytochrome oxidase

Cytochrome c oxidase is a member of the haem copper oxidase superfamily (HCO)². HCOs function as the terminal enzymes in the respiratory chain of mitochondria and aerobic prokaryotes, coupling molecular oxygen reduction to transmembrane proton pumping. Integral to the enzyme’s function is the transfer of electrons from cytochrome c to the oxidase via a transient association of the two proteins. Electron entry and exit are proposed to occur from the same site on cytochrome c³.⁴. Here we report the crystal structure of the caa₃-type cytochrome oxidase from Thermus thermophilus, contains a highly conserved glutamate residue in the sequence motif -XGHPEV-. In type A2, the gating glutamate has been proposed to be replaced spatially by a consecutive tyrosine and serine in a -YSHPXV- motif.⁵. The crystal structure of caa₃-type cytochrome c oxidase from Thermus thermophilus is the first for a type A2 HCO (Fig. 1). The structure was determined to 2.36Å resolution with crystals (Supplementary Fig. 2). grown by the in-nesto method using a synthetic, short chain (14 carbon) monoacylglycerol (7.7 MAG) as the hosting
Macrophage Metabolism

Slide courtesy of TBSI and Denis Klein www.denis-klein.de
Stem cells in a 3-dimensional hydrogels with microspheres

Danny Kelly, TBSI
Ovarian cancer cells aggregating blood platelets
Marek Radomski, School of Pharmacy

Neutrophils
Mark Little, School of Medicine
THP-1 cells stained LC3 (green)
Jim Harris, TBSI