A fascination for thyroid diseases

Dr Terry F Davies describes how combining clinical and research roles has underpinned his career in endocrinology and driven his work on thyroid translational medicine.

You have had a long career exploring the many aspects of thyroid diseases. How has the field progressed since you entered it, and what contribution has your lab made to these developments?

The impact of thyroid diseases is huge because they are so common. It is amazing how one gland can occupy an entire career, and in fact I have been mostly focused on just one molecule; the thyroid-stimulating hormone (TSH) receptor. It comforts me to know that I am not alone. I have worked with Dr Rauf Latif, a researcher who is equally addicted to the strange ways of the TSH receptor, for the last 15 years. During this period I am pleased to say that we, and my friends from across the USA, UK and Europe, have made good progress in advancing our understanding of how the TSH receptor works.

Our own laboratory has made important contributions, we think, in producing the first monoclonal antibody to the TSH receptor that stimulates the receptors as seen in Graves’ disease, a condition caused by an overactive thyroid. We have also found that TSH receptors group together in complexes called multimers, which appear to be important in the normal workings of the receptor. In addition, we have recently characterised a form of TSH receptor antibody that binds and kills thyroid cells.

How did you initially become interested in this area of medicine?

Endocrinology is a cerebral and logical subspecialty. My attraction to the field began when I was lucky enough to meet a wonderful person, Professor Reginald Hall, while I was an intern in medicine at Newcastle University, UK. Professor Hall was the Chief of Endocrinology and he recruited me directly to join him when I finished my residency, showering me with projects and experience that set me up for life. From the day I met him I have been enthralled with thyroid physiology and disease.

What have been the major technological advances that have facilitated your current research efforts?

X-ray crystallography and molecular modelling have changed the entire endocrine research field. Having the ability to model the TSH receptor and see how it may form dimers and where antibodies can bind is just incredible. To be able to do it in my own laboratory still amazes me.

The advances in fluorescent visualisation of the cell have also been remarkable, and have been a great aid to cell biology.

High-throughput screening has been another significant technical advance. The ability to screen hundreds of thousands of molecules within a reasonable timeframe is a fantastic asset, and a major advance in searching for new and interesting compounds.

Your work stretches from basic research to applications in the clinical arena. How does such a holistic approach benefit your studies?

I strongly believe that you cannot do translational research without clinical expertise, because you have no idea what the needs are and where the field is standing. Similarly, you cannot be a great clinician if you don’t know what the cutting edge is and what is advancing. This is evidenced by observing how well MD- and PhD-trained scientists work together – both bring a different perspective and the cooperation is synergistic. My mentor, Professor Hall, first pointed this out to me and I have worked closely with PhD colleagues ever since.

I think that endocrinology is one of those subspecialties where it is still possible to be successful in both the research and clinical arenas. There are many shining examples of great clinical endocrinologists who have strong funded research programmes.

How would you like to see your work developing in the future?

Right now, we are focusing on better methods of developing human thyroid cell lines from stem cells and understanding the transcriptional regulation of thyroid cell development. In the small molecule programme we are using our potent agonist to help stem cells become thyroid cells, which is a good blending of two projects. More importantly, we are searching for more potent TSH receptor antagonists which may have therapeutic potential in the treatment of Graves’ disease.

We also have a strong interest in the other roles of the TSH receptor in the body and have devoted a number of years to examining the effects of TSH on bone cells, where it turns out to be osteoprotective. I expect some important new insights to come from there in the future.
A vital gland

Pioneering projects at the Icahn School of Medicine at Mount Sinai and the James J Peters VA Medical Center in New York are transforming understanding of thyroid diseases and suggesting an array of potential treatments for these serious conditions.

Thyroid Diseases Affect 5-10 per cent of the population, most commonly resulting in an over- or underproduction of the hormones that regulate the body’s metabolic rate and therefore influence how it uses energy. Other thyroid conditions can involve the development of thyroid nodules, which can be malignant, albeit rarely. These can be debilitating diseases, and current treatments tend to consist of lifetime courses of drugs or thyroid hormone replacement.

A better understanding of thyroid development and function will be critical in developing more effective treatments in the future. Dr Terry F Davies from the Icahn School of Medicine at Mount Sinai in New York has dedicated his career to the thyroid, and specifically a protein expressed on its surface termed the thyroid-stimulating hormone (TSH) receptor, which is involved with many important signalling processes in the gland. He has pioneered the development of new approaches for investigating how thyroid function is altered in disease, and discovered potential opportunities to establish more effective treatments for thyroid dysfunction.

Differentiating Stem Cells

Stem cells are undifferentiated cells that have the potential to develop into mature cells with a variety of specialised functions. Davies and his colleagues have been employing these cells for a number of years in their studies of the thyroid. This work began by attempting to programme mouse embryonic stem cells to differentiate into thyroid cells, but progress was initially slow due to a lack of funding for the project, which many believed to be impossible. Despite this, the Davies group eventually succeeded by inducing the cells to first form endoderm, an early embryonic tissue from which the thyroid tissues develop, and then overexpressing two critical developmental transcription factors (Pax8 and Nkx2-1) in the cells, which induced thyroid follicle formation.

Translating this work from mouse embryonic stem cells to human embryonic stem cells was not straightforward because human cell cultures are far less receptive to genetic manipulation. However the Davies group, with Dr Risheng Ma as the lead investigator, was able to overcome this obstacle by using viral vectors to induce the stable overexpression of PAX8 and NKX2-1. These modified cells then expressed the TSH receptor, but not thyroglobulin, the protein required by the thyroid to produce its metabolic regulatory thyroid hormones. The researchers rectified this by treating the cells with TSH, which induced thyroglobulin production and caused the cells to form functional 3D thyroid follicles. The team was thus the first to succeed in differentiating human embryonic stem cells into thyroid cells, although Davies believes there is still a lot more work to be done: “Of course, once you have a system that works it all seems very easy and straightforward, but it was difficult to get the recipe right. We are still not satisfied with our methods and are planning new approaches,” he reveals. Davies hopes to find a way to develop thyroid cells without having to overexpress transcription factors – a process that could have long-term negative impacts on the cell.

This pioneering research provides an important model for the study of thyroid development, with the potential to show where cellular function can go wrong during normal development as well as in disease. In addition to roles in physiology research, these cells can also be used to screen small molecules that may be beneficial in treating thyroid problems. Ultimately, Davies hopes that cells from a patient could be used to make fully functional thyroid tissues or an entire gland, which could replace the diseased tissue of the same patient, totally avoiding any transplantation rejection. He and his team are currently taking the first steps towards making this a reality, using...
In Graves’ disease, the TSH receptor is targeted by autoantibodies in the blood, which act like TSH and cause the thyroid to overproduce its metabolic hormones. Davies is currently looking for compounds to combat this disease, with the knowledge that small molecules that bind to the TSH receptor and stop it from signalling to the cell, called antagonists, could potentially be very helpful for Graves’ patients. All currently reported antagonist molecules are lacking in potency, and more work needs to be done to achieve significant therapeutic potential.

**TARGETING THE TSH RECEPTOR**

TSH is produced by the brain’s pituitary gland, travels through the blood and activates the TSH receptor on the surface of the thyroid, as well as a variety of other cells. The TSH receptor is involved in a number of roles; signalling to the thyroid cells either to grow and divide or to begin making and releasing thyroid hormones: “This receptor is so complicated we could write an entire book about it,” Davies explains. “But suffice to say, the TSH receptor not only serves important physiologic roles, but can be abnormal itself or can be the subject of attack by the immune system.” Crucially, the TSH receptor is a major player in both over- and underactive thyroid diseases, and also in thyroid cancers.

In recent years, there has been a significant effort to find novel small molecules that can target the TSH receptor in patients with thyroid dysfunction. These compounds are particularly appealing as therapeutics because their small size enables them to cross cell membranes easily, and they can be administered orally and produced cheaply. The molecules reported to date that were able to target the TSH receptor have lacked sufficient potency, so in response Davies and his colleagues joined the effort and developed a new high-throughput system for screening compounds in order to find new candidates. Using this novel approach, they screened over 48,000 compounds and found two that target the TSH receptor with a high specificity and potency. These small molecules can stimulate the receptor to signal in the absence of TSH, leading to the upregulation of thyroglobulin and TSH receptor expression in mice, and significantly increased thyroid hormone levels. This could be developed into a cheaper treatment for patients, particularly those with thyroid cancer who are currently relying on expensive recombinant TSH for testing and treatment. “We use human recombinant TSH in clinical practice in a variety of ways, but it is expensive and difficult to produce,” Davies continues. “Instead, we now have small molecules that have the potential to substitute for TSH if developed for human use in the future.”

**REVOLUTIONISING TREATMENT**

Treatments for the thyroid diseases are in need of an overhaul: “The treatment of the overactive gland hasn’t changed for 50 years,” points out Davies. Current methods include using anti-thyroid drugs with serious side effects, killing the gland with radioactive iodine or removing it with surgery. There is oral thyroid hormone therapy to treat a failing gland and, while this is very straightforward, it does mean taking thyroid hormone for life. The work being done by this team has yielded several promising new avenues for developing treatments, while also enabling major advances in the understanding of thyroid development and function: “It is a very exciting time in thyroid cell biology,” Davies concludes.

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