ePathWay
THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

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Issue #068

In This Issue

- Immunotherapy steps up as Tasmanian devil's advocate
- Zika virus is still a hot topic for the world's medical community
- Is pathology ready for a digital makeover?
- Future digital trends could make pathology the ultimate App for medicine

Interesting Facts

3 to 12 days

The typical incubation period for the Zika virus.

4 to 7 days

The timeframe in which the acute symptoms of Zika virus are typically resolved.

Welcome to the April 2017 edition of ePathWay

We're still covering topics presented at Pathology Update in February, with one exception. A breakthrough in treating a transmissible cancer that has devastated Tasmanian devils was announced. We're excited because immunotherapy and a Fellow of the Faculty of Science (RCPA) are at the forefront of this great news.

Our other articles (all from Pathology Update) cover:

- An update on Zika virus.
- Future digital trends in pathology.
- Using digital imaging in pathology.

As always, check in to our Facebook page, review the latest tweets from our CEO Dr Debra Graves (@DebraJGraves) or the College (@PathologyRCPA), to keep up to date with the RCPA and new about pathology.

Immunotherapy steps up as Tasmanian devil's advocate

32 to 41 days

The longest reported period between symptom onset and sexual transmission (based on an incubation period of 3-12 days).

Source: Australian Government Department of Health

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Dr Eric Glassy

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An international study involving multiple institutions[1] over six years has shown that immunotherapy can cure Tasmanian devils of an infectious facial cancer that has ravaged the species for 21 years. This is a significant breakthrough because this unique Aussie animal was listed as Endangered in 2009, mostly due to the deadly effects of devil facial tumour disease (DFTD).

Prof Greg Woods is a Fellow of the Faculty of Science (RCPA) and Professor of Immunology at the University of Tasmania where he led the DFTD team at the Menzies Institute for Medical Research. He said their research demonstrates that the Tasmanian devil's immune system can target DFTD cancer cells, and that a vaccine is achievable.

"This is almost a eureka moment for us because it's the first time we can say for sure that it was immunotherapy that was making the tumour shrink. It is also an important step along the way to developing a vaccine to protect against DFTD, and potentially for immunotherapy to cure devils of established DFTD," Prof Woods said.

DFTD is a fatal condition characterised by cancers around the head and neck. It is spread through biting, and this impacts its particularly pervasive effect because biting about the face and neck is an integral part of the devils' mating ritual. Once infected, the animal dies within a few months. The only other types of known transmissible cancers are found in soft-shell clams and in some domestic dogs.

"DFTD has been unstoppable because its cancer cells are totally invisible to the Tasmanian devil's immune system. This is because the cancer cells don't express major histocompatibility complex (MHC) proteins that serve as beacons to alert the animal's immune system that there is a foreign invader to attack," Prof Woods explained.

"When we cultured the cancer cells with special cytokines the MHC 'beacon' was turned back on. By immunising devils with these cytokine-treated cells, the animal's immune system was able identify and destroy the cancer cells."

He said this breakthrough confirmed that the devil's immune system is actually its best ally against DFTD.

"It also shows there is a path forward for these animals in terms of a vaccine to protect future generations and potentially treating existing cases. We have now released about 50 vaccinated and microchipped Tasmanian devils into the wild, and we will follow them as best we can to see how they go."

Tasmanian devil fact file

- Its scientific name is *Sarcophilus harrisii.*
- It is the world's largest extant (living) marsupial carnivore.
- It disappeared from the Australian mainland about 400 years ago, but populations still live in the wild in Tasmania.
- DFTD was first seen in 1996, and devil numbers are estimated to have declined by over 80% as a result of this cancer.

[1] The research was led by the University of Tasmania's Menzies Institute for Medical Research with input from the School of Medicine. It also involved the Walter and Eliza Hall Institute of Medical Research, CSL Ltd, and the Universities of Sydney, Southampton, Southern Denmark and Cambridge.

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Zika virus made global headlines after outbreaks in French Polynesia and Brazil. What is the situation now?

The number of cases in the Americas has peaked and fallen, probably because people infected by Zika virus have developed immunity to it and are therefore unlikely to become infected again. Having said that, the effects of the virus will still be there for the life of a baby born with abnormalities associated with their mother being infected by Zika virus. There is still cause for vigilance because there are always babies being born representing a large non-immune population who could potentially become infected in the future.

Is there a proven link between Zika virus and birth abnormalities in babies?

Yes. If a pregnant woman is infected with Zika virus during pregnancy, data has shown that she has a high chance of delivering a baby with a significant birth abnormality, especially if the infection occurs during her first trimester. In fact, the newest data from the past two months shows that over 40% of babies born to mothers infected with Zika virus have some kind of neurological birth abnormality, but not all of them have microcephaly (a condition in which the baby's head is significantly smaller than expected, often due to abnormal brain development.). They are being born with abnormalities that affect their eyes and hearing as well. These neurological birth defects are the reason there is such heightened concern about this virus, as is its ability to be transmitted sometimes through sexual contact and potentially through a blood transfusion.

Can you elaborate on its transmission through sex and blood transfusions?

Sexual transmission causes anxiety in the community, especially in the context of pregnancy or potential pregnancy. It drives

a lot of requests from GPs and obstetricians for testing. There are studies to find out how long the Zika virus stays in the semen and vaginal fluids of infected people, and the time frame in which it can be passed to sexual partners. Current research shows that the Zika virus can remain in semen longer than in other body fluids including vaginal fluids, urine, and blood. As with any transmissible disease, preventive measures such as abstinence or using condoms are advisable if a person suspects they may be exposed to the virus in this way.

Blood transfusion risks are always a concern. However, the Australian Red Cross Blood Service and the New Zealand Blood Service have precautions in place to protect their blood supplies.

What advice would you give to people who may be worried about contracting Zika virus in Australia or New Zealand?

We don't have a local spread of Zika virus in Australia, even though the particular mosquito that transmits the virus – the Aedes species – is present in North Queensland. There are no Aedes mosquitoes in New Zealand. The Zika virus is only a threat when a person returns from a country already infected with the virus, is then bitten by an Aedes mosquito in North Queensland, and that mosquito bites and infects another person. You'd have to say the chance of this happening is quite low, especially when you consider that the person infected with Zika virus is only infectious for a week or so. For these reasons, the risk of transmission by other means in Australia and New Zealand, such as through sexual contact, is also very low. However, if there is a chance of infection, mostly due to sexual contact with a person who has returned from a country where Zika is endemic, then preventive measures should be used.

Zika fact file

- Zika is a Flavivirus, as are Yellow Fever, Dengue, Japanese encephalitis and West Nile viruses.
- It can be transmitted through mosquito bites and from a pregnant woman to her foetus. Less commonly it can be transmitted through sex, and potentially through a blood transfusion.
- Most people infected with Zika virus have no symptoms, or their symptoms – which might include a rash, joint pain and red eyes - are mild.
- There is a strong association between Zika virus and Guillain-Barré syndrome (GBS), which is an autoimmune condition in which a person's nerves are attacked by their body's own immune system.
- Diagnosis of Zika virus is based on a person's recent travel history, their symptoms and pathology results. A blood or urine test can confirm a Zika infection.
- Zika virus was first identified in monkeys in Uganda in 1947.

Professor Dwyer spoke about Zika virus at the RCPA's Pathology Update Conference in Sydney in February, and at the Australasian Society for Infectious Diseases Annual Conference in April.

Zika virus was covered in the February 2016 edition of ePathWay.

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In summary, Dr Glassy said digital pathology could be used for:

1. Multidisciplinary Case Conferences (MDCCs) where pathologists present whole slide image[1] presentations rather than still photographs of regions of interest to clinicians and surgeons.
2. Image analysis including finding rare events that might be missed with analogue technology; quantifying what is seen under the microscope such as the number of cell divisions (mitoses); and simultaneously testing two or more substances on the same tissue sample (multiplexing).
3. Digital consults including sharing cases electronically with colleagues located anywhere in the world to perhaps get a second opinion on difficult cases; remote frozen sections where video images of a frozen section are transmitted and displayed on monitors and diagnosed remotely by pathologists; and checking in real time if cytology specimens are adequate.
4. Education including teaching medical residents and students using augmented reality; proficiency skills testing using virtual peripheral blood smears and other sample types; using QR codes in peer-reviewed journals and books to link to whole slide image scans that can spring to life before their eyes to make a quantum leap in the power of illustrations for the reader; and quality assurance as digital imaging makes it easier to share complex cases and review diagnoses.
5. Sharing cases with patients through links on the pathology report.

These uses for digital pathology are persuasive, especially when you zoom out and look at this bigger picture. Digital

technology has the capacity to hasten diagnosis, even when the pathologist and patient aren't in the same town, state or country, and consequently enable treatment to start earlier.

[1] A whole slide image is created using a single, high magnification digital image of an entire microscopic slide to create a virtual slide that can potentially be numerically analysed using computer algorithms.

Dr Eric Glassy presented the David Rothfield Memorial Oration '*Hitchhiker's Guide to Digital Pathology*' the RCPA's Pathology Update Conference in Sydney in February.

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Future digital trends could make pathology the ultimate App for medicine

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The fall of paper

The writing has been on the wall for a while, and it's getting bigger and bolder as the digital juggernaut keeps changing how we collect, store, use, and share knowledge.

"There is a move from traditional print to electronic media. Documents, reports, books, communication and the like will all be in the cloud and instantly available and interactive," explained Dr Glassy.

He outlined how this trend will affect pathologists:

- There will be a demand for more patient-friendly pathology reports driven by patient expectations.
- These pathology reports (no longer constrained by the limitations of paper) will include images, curated URLs, GPS-like features, and augmented reality.
- They will be integrated with other disciplines, such as radiology, to create more meaningful and understandable explanations. They will not only report the diagnosis but will also interpret a multitude of findings (molecular, genetic, morphology, etc.).

"These types of pathology reports can become a practice-differentiator," he explained.

The rise of smarties

Dr Glassy wasn't talking about the latest generation of tech savvy youth, but rather the Internet of Things (IOT) or smart devices.

"This means integrating smart phones and tablets into medicine. Having laboratory applications on a chip and other smart devices will also be universal," he explained.

Dr Glassy outlined how this trend will affect pathologists:

- Smart microscopes will connect to the IOT and enable pathologists to be more productive and accurate.
- Digital pathology will become more integrated into completing cases in terms of diagnosis and treatment options.
- Computers and hand-held devices will make pathologists better diagnosticians as they reshape their workflow.
- Dramatic workflow changes will occur including computer assisted analysis and pre-screening of slides with areas of interest highlighted.

"An example of the rise of smarties is a 'smart cutting board'. Pathologists use cutting boards to cut up surgical specimens before they are examined. New technology, such as the smarts being developed for ex-vivo microscopy, could be incorporated into this basic board to make it much more useful and 'diagnostic'. For example, it could weigh the specimen, scan it in stages during the cut up procedure, and store this information in a USB stick attached to the board," Dr Glassy explained

The quest for selfies

Dr Glassy said each disease has its own unique fingerprint or 'selfie', and new digital tools will advance the precision of diagnoses so that treatment can be individualised. This puts pathologists in the hot seat as translators and interpreters for clinicians.

"Pathologists once represented the 'Google' of medicine and they must recapture this role in terms of being translators for genomic medicine, interpreting the evidence for clinicians, and outlining the next steps in patient treatments," explained Dr Glassy.

He outlined how the trend for disease 'selfies' will affect pathologists:

- New image analysis algorithms will be developed such as immunoscore (a possible new method of classifying cancers) and immune profiling.
- Neoplastic tissue is multidimensional (tumour, stroma, inflammation, and immune response) and so new digital tools could facilitate treatment guidance.
- Pathologists will be the natural translators of complex molecular and genetic results that produce complex data sets (big data).

Once explained, the fall of paper, the rise of smarties and the quest for selfies are not as daunting. And when you consider where digital trends are steering the practice of medicine, there is a natural pinnacle.

"Pathology reports will become the centre of the medical record in terms of becoming a unifying document that provides not just a diagnosis, but a treatment plan and a GPS to healthy outcomes. Pathology will become the ultimate App for medicine."

Dr Glassy spoke about 'Riffs on Future Path' at the RCPA's Pathology Update Conference in Sydney in February.

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