

the Pathologist

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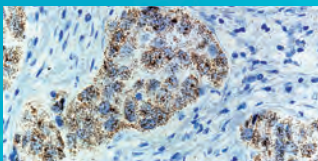
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Online this Month



The Pathologist on Twitter

What got you talking this month?
Here are some of our most popular tweets...

Cut back on biopsies, controversial study urges

The Pathologist @pathologistmag
Biopsies are the most expensive tool for diagnosing lung cancer and should be used less, says medicare cost analysis:
<http://bit.ly/1xHzgDu>
9:36 AM - 31 Oct 2014

Ground breaking protein pics

The Pathologist @pathologistmag
First pictures of BRCA2 protein show how it works to repair DNA in breast cancer <http://bit.ly/Ztl1qK>
8:01 PM - 27 Oct 2014

New guidelines advise against PSA

The Pathologist @pathologistmag
Don't use PSA test, says new prostate cancer screening guideline
<http://bit.ly/10wLGUw>
8:44 AM - 28 Oct 2014

CAP argues the benefits of pathologist-patient conferrals

The Pathologist @pathologistmag
CAP urges NY officials to allow pathologists to speak with patients.



Do you agree? <http://capatholo.gy/1rfAao9>
8:01 PM - 28 Oct 2014

We speak to Suzy Lishman about attracting new talent

The Pathologist @pathologistmag
This week's most popular article: Where is the Next Generation of Pathologists? <http://ow.ly/DgWRJ>
6:02 PM - 24 Oct 2014

Ancient genome gives clues about breeding with Neanderthals and human migration

The Pathologist @pathologistmag
Oldest-ever human genome sequenced from 45,000 year old femur
<http://bit.ly/12czJnq>
12:30 PM - 23 Oct 2014

Ebola deaths higher than expected

The Pathologist @pathologistmag
Analysis reports Ebola mortality rate is far higher than WHO estimates
<http://bit.ly/1tgPOOy>
10:01 PM - 5 Nov 2014

WHO mass vaccine production

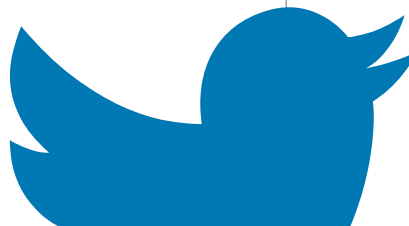
The Pathologist @pathologistmag
WHO plans to mass produce Ebola vaccine by next year <http://bit.ly/1yvamaZ>
11:00 PM - 30 Oct 2014

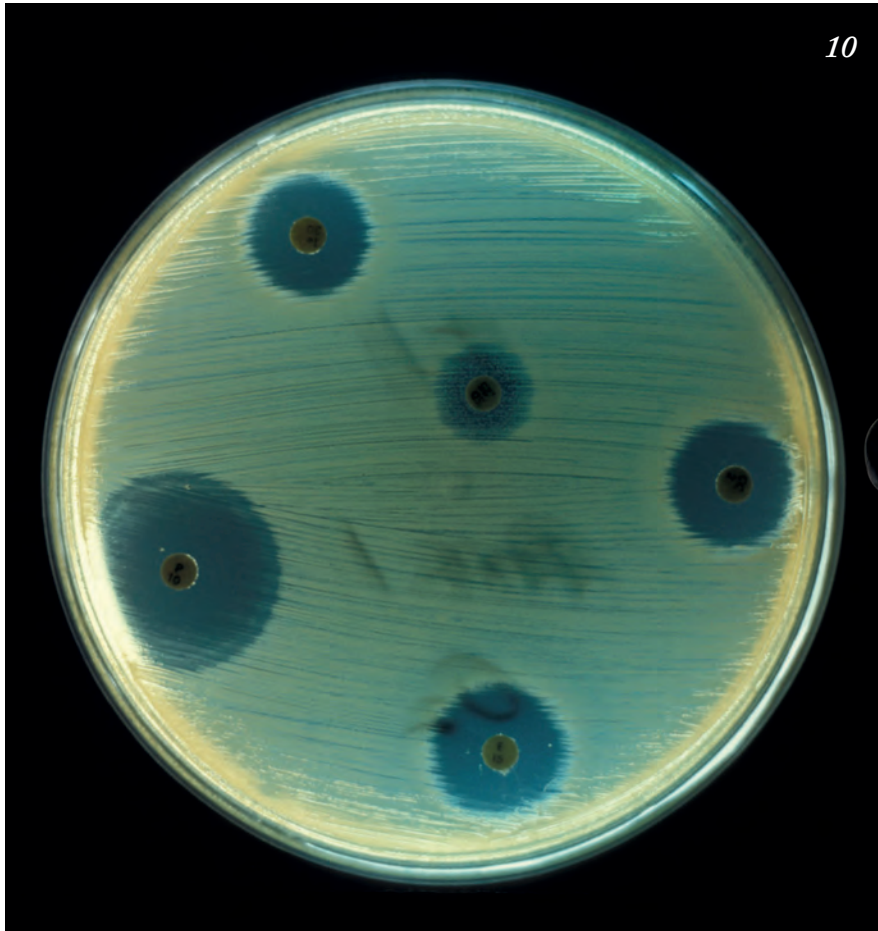
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Interview with an immunology guru

This month, we sat down with OncoSec's Chief Scientific Officer, Robert Pierce – a man who had a key involvement in the research and development program for Merck's breakthrough immunotherapy treatment for melanoma, the anti-PD-1 Keytruda. On page 51, we report on the highlights of that interview, but if you want to hear more about his interesting journey, go to <http://tp.txp.to/0214/sdw> to read the full interview.





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On The Cover



IFCC task force chairs face challenges with optimism

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Published by

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Booths Park, Chelford Road, Knutsford, Cheshire,
WA16 8GS, UK

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www.texerepublishing.com

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+44 (0) 1565 752883

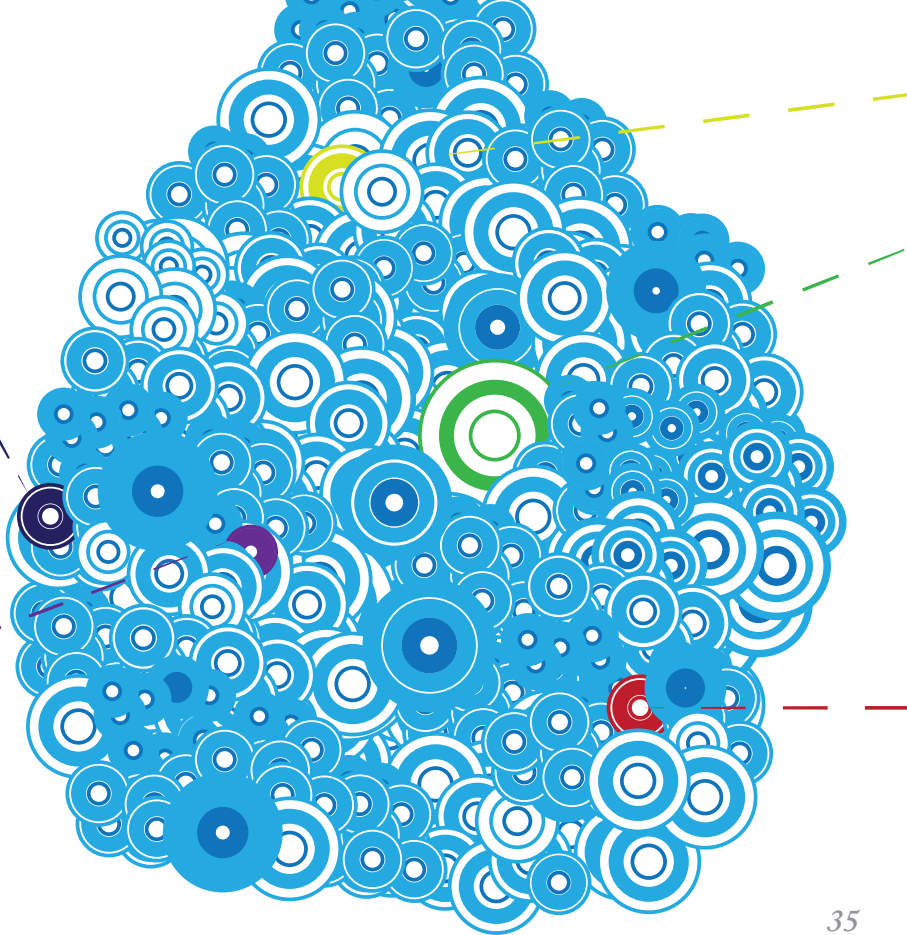
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Distribution:

The Pathologist is distributed worldwide through
10,000 printed copies to a targeted European
mailing list of industry professionals and 22,500
electronic copies worldwide.

ISSN 2055-8228

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The role of the pathologist is rapidly becoming more focused on ongoing patient care. Arnaud Roth believes that now, more than ever, clinicians and pathologists need to collaborate.

Sitting Down With

50 **Robert H. Pierce**, Chief Medical Officer, OncoSec, San Diego, CA, USA



AHCS
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The Academy will be hosting its inaugural Congress on 8th and 9th December, 2014
the theme of which is

'Passionate for Patients. Passionate about Science'

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One For All and All For One

Partnership – potential disaster lurks at the first signs of a wobble, but when it's strong, there are no limits to what it can achieve.

Editorial



You'll notice that the power of partnerships is a key theme in this month's issue. I guess the idea that unity adds strength is no great revelation; anyone can form a partnership – it's making it a success that's the hard work and that stands true for anything, from managing a multi-billion Euro corporation to marriage!

In UK politics this week, the main opposition party, Labour, is suffering from partnership nerves; just a few months away from an election that could see them voted into power, members of the party are admitting, off the record (of course), that they're not happy with their leader, Ed Miliband. Interestingly the resulting media frenzy has taken some of the attention from the current Prime Minister's party, which has seen members defect to the UK Independence Party in recent months. It'll be interesting to see how these partnership wobbles will affect the results on polling day in May...

Conversely, an example of strength in numbers was visible on November 5, when the organizers of International Pathology Day 2014 united more than 40 international societies this year, to pull off the field's first global educational and awareness-raising event. Such was the success of the activities (which saw hundreds of events taking place around the world) that plans are already being made for 2015. Who's betting it'll be even bigger next year? Congratulations to the organizers and participants of this ground breaking and valuable initiative.

This month's cover article provides another example, featuring inspirational people who have formed vital, international networks to improve and further laboratory medicine. Facing many challenges along the way, these people speak of how strength in unity has allowed them to overcome obstacles and to achieve great things. Read about how far they've come and what hurdles still lie ahead on page 18.

And speaking of international networks... I'm delighted to have had the opportunity to 'meet with' some of you via Twitter recently. It's so interesting to see the topics that are getting you interested and engaged. Controversies over the value of prostate and lung cancer routine diagnostics, and mind-boggling new methods of targeting antibiotic-resistant bacterial strains and cancers have all got you talking this month. Rest assured, we're paying attention, so expect to see some familiar themes in coming issues of *The Pathologist*.

Fedra Pavlou
Editor



Graham Beastall

Graham is the current President of the IFCC and advises Health Education England on the Modernizing Scientific Careers program. With 35 years of experience within the NHS, he has held numerous representative roles, such as Vice President of the Royal College of Pathologists and board member of Clinical Pathology Accreditation UK. With over 175 peer-reviewed articles published, Graham's main research interests include biochemical endocrinology and evidence-based laboratory medicine. As IFCC president he offers his perspective on the federation's task forces on page 26. "Experience has shown that a small number of charismatic 'champions' can be more effective in delivering positive outcomes than dry scientific publications."



Tibor Tot

Tibor is the breast cancer expert of the Swedish Board of Welfare and a regular course director of its pathology program. Also associate professor of pathology at the University of Uppsala, Sweden, he has published the book "Practical Breast Pathology", which has become official teaching material of the European School of Pathology. Radiological-pathological correlation of breast diseases are his main field of interest. "I don't believe molecular analysis can tell the whole story. Conventional analytical techniques are at risk of being overlooked, and I feel this would be a serious mistake," he says. Tibor discusses subgross morphological analysis and the need for a new prognostic index on page 32.



Arnaud Roth

Having studied and trained in Switzerland, the UK and the USA, Arnaud is now consultant and senior lecturer in oncosurgery at Geneva University Hospital, Switzerland. With over 100 articles and several book chapters published, his research interests include molecular biomarkers in colon cancer and the development of new systemic therapy in gastric cancer. Arnaud is head of unit physician at the digestive tumor unit, HUG, Geneva, and believes pathologist involvement in patient care is changing: "If pathologists aren't already actively involved in treatment decision-making, monitoring and therapeutic tailoring, they soon will be."

Read Arnaud's advice on the evolving role of the pathologist on page 46.



Tim James

After studying chemistry and training as a scientific officer, Tim completed his PhD at Queen Mary College, London. He is currently lab manager and head biomedical scientist for clinical biochemistry at Oxford University Hospitals NHS trust in the UK, and a visiting professor at Oxford Brookes University. He has published over 50 papers and several text book chapters, some related to laboratory automation. On page 35 he explains why purified water can have such a big impact on your workflow and the quality of your test results, and how to avoid problems. "Water is the single most important reagent used by those of us who work in laboratories, but it's often taken for granted. It's only when the supply is compromised that its value is appreciated."

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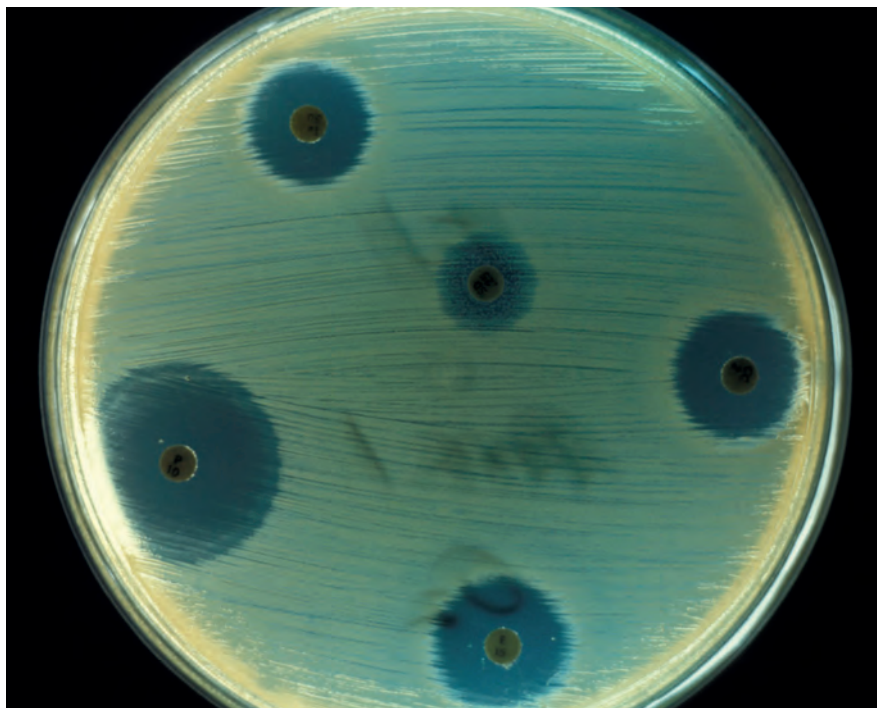
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Stamping Out Antibiotic Resistance

Researchers think they may have found a way to defeat superbugs

Imagine being able to diagnose a patient with a bacterial infection that is highly resistant to antibiotics, and knowing that it can be effectively treated as soon as the results leave your lab. This dream could soon be a reality if MIT and Harvard researchers have anything to do with it – they’re working to create entirely customizable antimicrobials, which can spot drug resistance genes and wipe them out. The method has already shown its potential, improving survival in an initial trial using an animal infection model.

The WHO has deemed antibiotic resistance a serious and worldwide threat to public health, predicting that without

intervention, we could be headed for a “post-antibiotic era” (2) – so a method that removes such microbes from the gene pool could be a game changer.

We spoke with Timothy Lu, associate professor of biological and electrical engineering and computer science at MIT, about developing this highly specific system and its potential to battle superbugs.

How did you get started?

Well, most antibiotics in use are broad spectrum, which leads to unwanted side effects such as *Clostridium difficile* overgrowth and the development of antibiotic resistance – an increasing problem. We decided to develop targeted agents that can kill bacteria based on their genetic content, with the main goal being to focus the therapy only on pathogenic bacteria.

We designed a system – based on a gene editing method known as CRISPR/Cas – that can essentially act as genomic scissors, cutting any arbitrary piece of DNA.

We used it to selectively target and kill bacteria that carry undesirable genes, such as antibiotic resistance and virulence genes.

Any surprises?

We showed that our targeted antimicrobials could discriminate between bacteria with a difference of only one DNA base – this was so exciting to us! They could also be multiplexed to target multiple undesirable genes simultaneously.

Further surprises came when we realized that the antimicrobials could be repurposed for use as a diagnostic for pathogenic genes – something that could prove useful for rapid point-of-care diagnostics. Finally, their ability to target pathogenic genes carried both on plasmids and in bacterial genomes, is also very valuable.

What's next?

We aim to extend our platform to other pathogens, test it in mammalian preclinical models, and continue to improve its efficacy and delivery modalities.

We believe that new technologies such as ours will play an increasingly important role in addressing antibiotic resistance. In particular, we want to create a new paradigm for personalized and targeted therapies where the causative bacteria in infections are rapidly diagnosed, allowing for the use of the most efficacious and targeted antimicrobial. At the moment, clinical practice allows for the indiscriminate use of broad spectrum antibiotics, and this needs to stop.

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2. WHO "Antimicrobial Resistance: Global Report on Surveillance 2014", April 2014, <http://www.who.int/drugresistance/documents/surveillance-report/en/>.



Research Voices Speak Out on Science Policy

An open letter to European leaders and policymakers garnered nearly 10,000 signatures in less than a week

Despite broad differences in research funding and support across Europe, one factor is unifying disparate countries and organizations: scientists believe that budget and hiring cuts are so severe that they're destroying national research and development infrastructures.

From grant reductions to hiring freezes, education cuts to laboratory downsizing, most countries across Europe have witnessed a drop in resources devoted to scientific research. Places like Spain and Italy are claiming the biggest hardships – it is thought that the former has seen a 40 percent decrease in grant funding, while the latter has cut higher education spending by 20 percent and recruitment to permanent research positions by as much as 90 percent (1). But even in countries less rattled by the economic downturn, science appears to be taking a hit. In France, for example, scientific and academic positions have

declined by over 20 percent, whereas in Germany, some institutions are seeing as much as 80 percent of research being conducted by scientists on fixed-term contracts rather than in permanent positions (2).

"The drastic budget and hiring cuts [...] are triggering a brain drain," says Amaya Moro-Martin, an astrophysicist and science policy spokesperson, in *Nature*. "Where they can, scientists are shifting from the less-affluent south to the north of Europe. Where they cannot, many are abandoning the continent altogether."

Along with eight other researchers from six European countries, Moro-Martin wrote an open letter to science policymakers and government leaders decrying what they refer to as "destructive policies." So far, nearly 10,000 researchers and concerned citizens from over 60 countries have signed the letter. With a movement extending far beyond a single petition, though, involving rallies, protests, meetings and even a cycling tour of France – it's evident that now, more than ever – European scientists are feeling the need to make their voices heard. *MS*

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2. E. Pain, "European scientists ask governments to boost basic research", *ScienceInsider*, (2014).

Rabies: the Hijacker in Your Brain

Pioneering rabies research may provide new insights into common neurological disorders

A new technique that traces connections between nerve cells has revealed a brand-new way the rabies virus hijacks those connections for its own benefit. Jumping aboard neuronal transport machinery, the virus travels along the neurons in both directions and is able to move much faster than even the proteins for which the transporters are actually intended. This is an exciting discovery not just for rabies research, but because it may present promising new

avenues for research into many common neurological conditions, such as Alzheimer's and Parkinson's diseases.

The rabies virus is the definitive member of the Lyssavirus family, named after the Greek goddess of madness, rage and frenzy. Appropriately, the disease itself is known to present with acute brain inflammation, which causes psychosis and violent aggression, before progressing to the rest of the body where it causes paralysis and failure of organs one by one. If not treated in time, rabies is always fatal, leading to over 55,000 deaths per year globally, according to WHO estimates – but for a disease with such a significant impact, little is known about the way in which the rabies virus actually enters and infects the nervous system. And it has been hypothesized that determining a transport route for the disease could help uncover previously uncharted research territory for more common neurodegenerative disorders.

For the first time, researchers in Germany and Israel have observed a novel mechanism the of entry into the central nervous system (1). Using a pioneering technique for tracing connections between individual neurons, Eran Perlson and Shani Gluska of Tel Aviv University's Sackler Faculty of Medicine and Sagol School of Neuroscience were able to dynamically track the rabies virus using live cell microscopy as it hijacked its way into the brain through the sensory neurons.

Using the nerve growth factor receptor p75NTR, the rabies virus transports itself through specific types of neurons from its entry site into the brain. p75NTR is a regulator of neuronal survival, development and function. Also implicated in synaptic

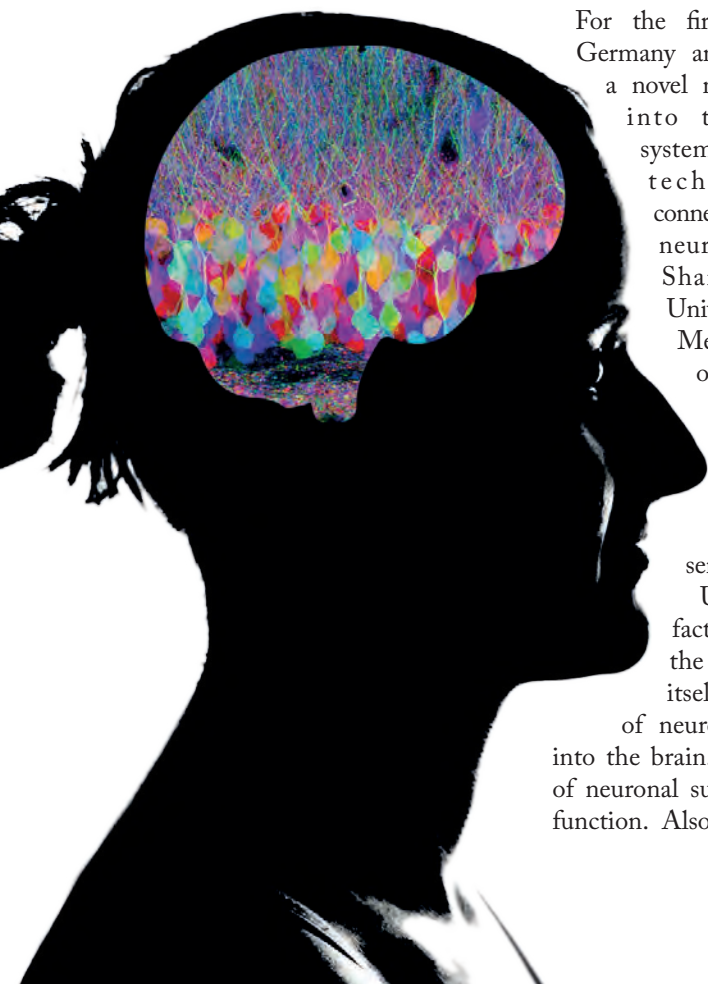
transmission and axonal elongation, p75NTR binds and transports nerve growth factor and other proteins to perform essential maintenance functions in the central nervous system. So not only is the virus capable of hijacking this axonal transport system for its own needs, but it does so at remarkable velocities of up to 400 mm per day – much faster than the neurotrophins that naturally use the receptor.

Scientists were able to see the virus hijack the p75NTR receptor in real-time by growing peripheral neurons in a controlled system and infecting them with fluorescently-labeled viral particles. They watched the virus enter the cells, replicate in the somata, and then travel in both retrograde and anterograde directions – unique because until now, rabies virus transport has been widely considered to be unidirectional. Now we know that the virus is capable of traveling in either direction along the axon and that, in fact, the newly-discovered anterograde travel takes place via active transport and is more than twice as fast as retrograde travel.

Naturally, this new discovery should pave the way for better treatments for the disease. Its usefulness doesn't end with rabies, though; the neuron train is disrupted in many neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, and a better grasp of the neuronal transport machinery may allow researchers to restore and even therapeutically manipulate these processes themselves. *MS*

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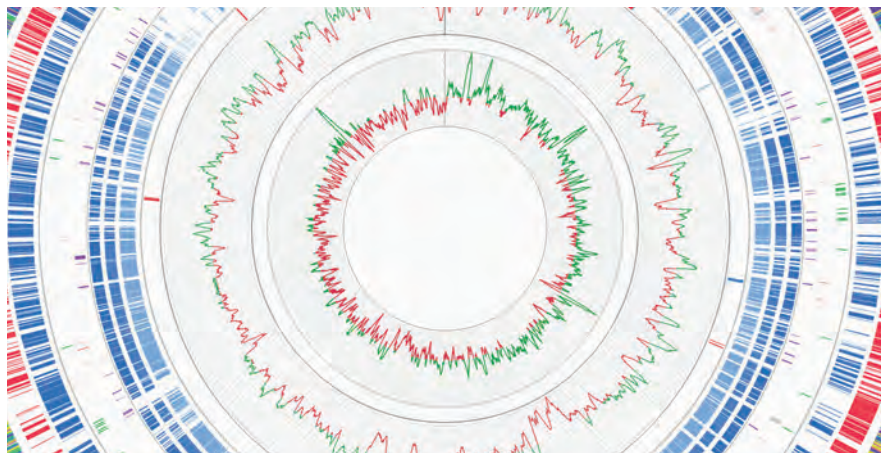
Exome Expectations

Clinical exome sequencing provides high diagnostic accuracy and uncovers over 400 new mutations

Our exomes contain roughly 1 percent of our DNA, but 85 percent of disease-causing mutations (1), and now a study has highlighted just how powerful a diagnostic whole exome sequencing (WES) could be.

Published in *JAMA*, the research details the results of 2,000 patients referred to the Baylor College of Medicine in Texas, US, with suspected genetic disease – mostly pediatric patients with neurological disorders or developmental delay. Twenty-five percent of those patients sequenced received a molecular diagnosis, including detection of rare genetic events and previously unseen mutations. This is a much higher diagnostic rate than that of karyotyping (5–10 percent) and chromosomal microarray (15–20 percent) (2). The researchers believe that 65 of their diagnosed cases would not have been diagnosed correctly by other conventional methods.

Peripheral blood and tissue samples, collected from either probands or their parents, were analyzed using next generation sequencing and compared to a reference sequence: 708 variants in causative genes were found in 504 patients, 57.8 percent of which were novel mutations. Twenty-three patients were also found to have more than one causative mutation, resulting in more complex, blended phenotypes. The diagnosis rate differed depending on phenotype: despite being the smallest group, patients with specific neurological problems, such as seizures, were most



likely to receive a diagnosis.

An additional 95 incidental medically actionable mutations (mutations which did not cause the phenotype being investigated, but also clinically important) were found in 92 patients, which included the discovery of genes related to familial breast cancer, Fanconi anemia and familial hypercholesterolemia. To obtain a diagnosis, the team considered the specific variable identified, the gene involved and the clinical case history.

According to the research team, many of the unexplained cases in the study are also likely to have mutations in disease genes that have yet to be discovered, and it's possible that the information needed to diagnose them could already be waiting in their exome.

WES analyzes only the coding regions of DNA, as opposed to whole genome sequencing (WGS). It also provides broader coverage than other approaches, such as SNP arrays and techniques that only focus on a small number of genes or loci, based on the presentation of the patient. But it isn't perfect. Sequencing only exons means that WES cannot provide information on splice site or intronic mutations, which occur in non-coding regions. The technical limitations of current WES methods also mean that complete coverage cannot be achieved and some exonic mutations could be missed.

Despite the limitations, the study authors believe that WES represents a cheaper and more available alternative to WGS, while still providing superior coverage compared with some other genetic analysis methods – its diagnostic rate was upheld by both their original study of 250 patients and the much larger cohort (3). In particular, WES could be very useful in certain patients where a genetic disease is suspected but not easily identifiable, because it can allow for analysis of multiple genes in tandem. “For years we’ve known that whole-exome sequencing can identify new disease-causing mutations,” says Yaping Yang, co-author of both studies and a geneticist at the Baylor College of Medicine. “But this puts it on the map as a tool for clinical medicine.” *RM*

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The Six Faces of *Streptococcus pneumoniae*

The multifaceted microbe has been hiding an epigenetic secret

Since the first paper describing the phenotypes of pneumococcus was published in 1933, bacteriologists have known that it is able to change forms (and with it, disease severity); but the way in which it does so have remained a mystery. Until now. An international team of researchers has discovered that the bacteria can take a staggering six different forms depending on the methylation status of its DNA, meaning that scientists who thought they were working on one bacteria may now be surprised to learn that, in effect, they've been studying six different ones.

Published in *Nature Communications*, the study describes how the team created mutant strains of the bacteria, each expressing one of six possible variants of the gene *hsdS*, which codes for a restriction modification system able to mediate gene expression via methylation (1). "Pneumococcus is an ideal organism, which is highly amenable to genetic manipulation, and models of pathogenesis are well described, so this study was fairly straightforward for us. Even so, finding a clear cut correlation of epigenetic control to carriage and invasive disease was a very positive surprise," says lead author Marco Oggioni.

The team found that each of these six subpopulations has a different DNA

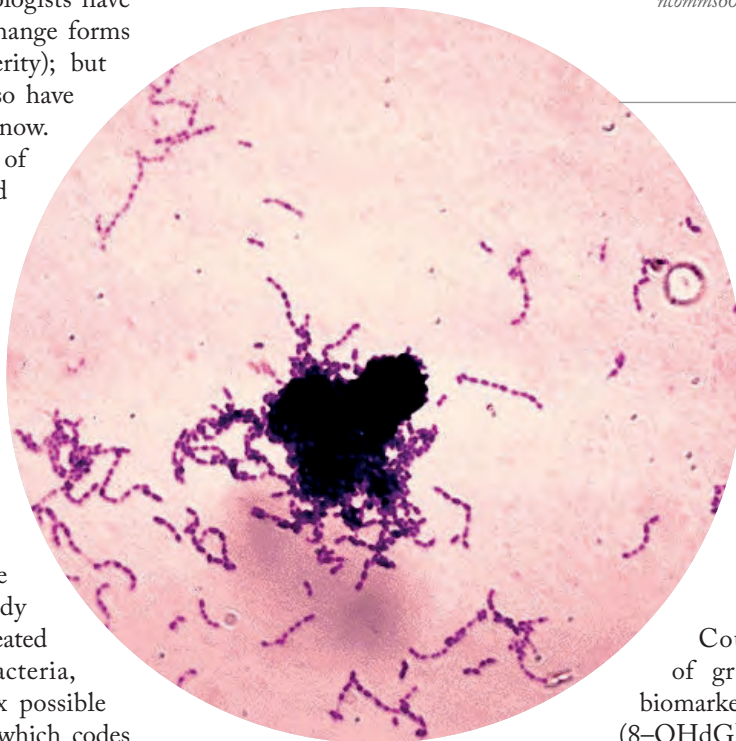
methylation pattern, differences in gene expression and, based on experimental infection of mice, its own pathogenicity.

Oggioni believes this work represents a paradigm shift in the understanding of bacterial gene regulation; one which will completely change the way in which *S. pneumoniae* is studied; "Researchers will have to control the methylation state of the bacteria they are working with, because it determines

mechanisms remain unclear. They also plan to investigate what effects the system has on human disease and infection, as their discovery may have far reaching implications for the treatment and prevention of pneumonia. *RM*

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Detecting Cancer with Carbon

Initial results suggest that a graphene biochip is faster and more sensitive than ELISA

Could a nano-biochip made of graphene detect the cancer biomarker 8-hydroxydeoxyguanosine (8-OHdG), faster and more sensitively than conventional enzyme-linked immunosorbent assays (ELISA)? Researchers from the University of Swansea, UK, claim the answer is yes.

8-OHdG is a DNA adduct produced by oxidative stress that has been linked to bladder, lung, and prostate cancer. It can be detected using ELISA but the assay isn't perfect as it can't always identify the low levels of the biomarker that may be present in the early stages of disease or in a urine sample. In comparison, the Swansea team say their graphene

such strong differences. Work on this pathogen, and many other bacteria which appear to have this same type of epigenetic control, will have to change significantly. It goes without saying that pharmaceutical companies evaluating in vitro vaccine efficacy will also have to check the methylation profile," he says.

The team now hopes to further investigate how changes in methylation affect gene expression; the exact

biochip can detect the biomarker at concentrations five times lower than ELISA, as well as being easier and faster; apparently testing can be carried out in minutes. “We were surprised at how sensitive our graphene sensor is,” says co-author Owen Guy, professor of engineering at Swansea University, “but with improved design, we may be able to achieve even higher sensitivities.”

Since it was first made in the lab in 2004, the unique properties of graphene have made it a popular substance within the research community. The authors describe graphene as a “disruptive technology” in next-generation electronics and healthcare diagnostics since its electronic properties and high surface-to-volume ratio allow for high sensitivity. For the biosensor, the researchers created functionalized graphene channels by coating them in monoclonal antibodies (using spectroscopy to check they had bound correctly), that then enabled the channels to selectively bind 8-OHdG. Changes in the electrical conductivity of the biochip were then measured to test for the presence of the biomarker (1).

Owen adds that once the device has been validated through further testing, it could also be used to test for other cancers or diseases, simply by changing the antibody that’s attached. He says, “We’re now working on developing scale-up processes for fabricating graphene sensors in much higher volumes. We are also very interested in adapting the graphene sensor platform for simultaneous detection of a number of biomarkers on the same chip. This is very challenging, but could result in much more informative diagnostics.”

RM

Reference

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Microscopists Given Greatest Honor

Scientists who developed live cell molecular imaging awarded the Nobel Prize

Three microscopists have taken this year’s Nobel Prize in Chemistry for discovering ways to image some of the most basic components of life. It’s an honor that brings welcome publicity to the field of microscopy, generating enthusiasm across the scientific community. It’s also a major step forward in the use of optical microscopes, breaking the Abbe diffraction limit – the absolute boundary of optical resolution – for the first time.

For over a century, microscopists knew that it was impossible to visualize anything smaller than half a wavelength of light, about the size of a large virus or small bacterium. This restriction meant that microorganisms and subcellular structures could never be seen clearly through an optical microscope. But now, Eric Betzig, Stefan Hell and William Moerner have broken through that barrier.

Hell, of the Max Planck Institute in Germany, developed a method that uses a laser beam to stimulate molecules to glow, then applies a second beam to cancel out all but a tiny volume of those emissions. American researchers Betzig, of the Howard Hughes Medical Institute, and Moerner, of Stanford University, each separately devised a slightly different technique that stimulates certain molecules to fluoresce; by combining individual images of different types of molecules, researchers can assemble a complete picture of the living cell.

It’s a mark of the significance of these new methods that the Nobel Prize was awarded only a few years after the techniques were discovered. In fact, progress is still underway – Susan Cox, a researcher from King’s College London, says, “We’re still at the start. It’s a little messy, and the technological development is happening as the scientific results are coming in” (1). But despite the novelty of nanometer-scale microscopy, its broad applications and detailed results represent an important development in studying life at the cellular level and beyond. MS

Reference

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Five Minutes of Fame?

How will the fight to cure ALS benefit from its newfound fame?

People taking the ice bucket challenge to raise funds for amyotrophic lateral sclerosis (ALS) were everywhere this summer. The challenge – which involves dousing yourself in freezing water, and/or making a donation – was all the rage with the public, celebrities and politicians. It became a viral phenomenon, and raised millions of dollars.

The wacky challenge gave a much-needed boost to research donations, but it also raised awareness of a condition that is in desperate need of effective therapies. ALS is the most common

form of motor neuron disease and has no cure. The one therapy available (riluzole) provides only marginal benefits; there's still a long way to go. As a recent article in *The Lancet* points out (1), the current level of funding may not last, unless ways are found to keep the momentum of the recent ice bucket campaign going. The laboratories and charities who have received these donations must also decide how best to use funds to combat the disease.

Despite nearly 30 years of work, two people per 100,000 die of ALS every year in Europe (2) and it is well known for its bleak prognosis and severe shortening of lifespan – the median survival is two to four years from onset, and one to three years from diagnosis.

It's this gloomy outlook that has spurred University of Turin's Adriano Chiò to dedicate years of research into the condition and to set up the

Turin ALS Centre, where researchers (among many other achievements) have identified a genetic mutation in up to 10 percent of patients (in *C9orf72*), a possible link with dementia in some instances, and insights into structural and functional changes in ALS. Interestingly, one of their latest research crusades could see a blood test that tracks disease progression soon become reality. When testing samples from newly-diagnosed as well as progressed ALS patients, Chiò's team found a link between low serum creatinine levels and muscle wastage, and low serum albumin with raised inflammatory markers levels. Importantly, the combination of low serum creatinine and albumin was associated with significantly impaired clinical function at diagnosis (3).

"These two simple measurements, which are already part of many clinical examinations, can give us a much more accurate prognosis on how long the patient has to live than we have at the moment," explains Chiò. Considering how widely available and routine tests for serum albumin and creatinine are, it's not hard to see why this approach to prognostic testing would be welcomed by the medical community.

Researchers no doubt hope that this rare but deadly condition will remain in the public consciousness, resulting in much higher levels of funding. But work will continue and progress will be made even if fame proves to be fleeting. *RM*

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Europe's Most Wanted

Taking a big data approach to infectious disease

What are the most studied and impactful pathogens in Europe? A UK research team decided to find out, and they've now published the top 100 human and top 100 animal pathogen lists in PLoS ONE (1).

It goes without saying that knowledge and prioritization of pathogen impact is important, and common methods to gather this information take values such as incidence of disease, mortality and morbidity, prevalence, and more, into account. But for many diseases, accurate data for those parameters don't exist. Researchers from Liverpool University's Institute of Infection and Global Health (along with collaborators from Montpellier University, France) have devised an

alternative approach: the Hirsch Index (H-index) proxy.

They looked at the number of citations and original papers published concerning a pathogen, and concluded that the levels of interest and volume of research within the scientific community correlated with its impact burden. Sound far too simplistic? It is, but when comparing their list to those of the Global Burden of Disease Study (2) and the diseases prioritized by the European Commission (EC) (3), the researchers found a 42 percent correlation. Although this makes it far from perfect, the authors believe their method has applications; it's fast, objective and evidence-based, and could be used both alongside other systems such as the EC's, and alone to estimate disease impact when there is a lack of data.

We've included the top 10 human pathogens in Table 1. Do you agree with the list? Let us know by commenting online.

The full top 100 list can be viewed online at: <http://tp.txp.to/0214/pathogens>

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Rank	Pathogen	Taxonomic Division	Hirsch Index Score	Interesting Observations From Top 100 Pathogens Study
#1	Escherichia coli	Bacteria	524	<ul style="list-style-type: none"> - There are very few fungi or helminths in the list and none within the top 10 (only one makes it into the top 20); the authors do not speculate why. - There is an even split between bacteria and viruses (five of each) within the top 10. - 43 pathogens occurred in both the top 100 human and top 100 animal rankings. - Impact does not equal disease toll – WHO numbers estimate that more people die of HIV and tuberculosis than from any other single infectious agent. These pathogens hold spots 2, 3 and 10. - Limitations of the H-index exist – false positives could result for pathogens frequently used as model organisms (such as <i>E. coli</i>); trends can occur for certain pathogens (i.e. studying them can become “fashionable”); literature unavailable in English wasn't used; time lag between study and publication means emerging pathogens may be underrepresented (Ebola may be a good example: interest in this virus has grown exponentially in recent times, which means it's H-index score may also increase).
#2	Human immunodeficiency virus 1	Virus	410	
#3	Human immunodeficiency virus 2	Virus	399	
#4	Hepatitis C	Virus	289	
#5	Staphylococcus aureus	Bacteria	271	
#6	Human herpes virus 4	Virus	257	
#7	Helicobacter pylori	Bacteria	246	
#8	Hepatitis B	Virus	246	
#9	Pseudomonas aeruginosa	Bacteria	243	
#10	Mycobacterium tuberculosis	Bacteria	238	

Table 1. Information on the top 10 European pathogens, ranked using the H-index.



Team Laboratory

The ‘better together’ approach has proven itself time and again – and the world of laboratory medicine is no different. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) is committed to progression through partnership. Here, seven special task forces describe their focus, discuss what further challenges must be addressed to achieve ambitious goals, and highlight how those issues are likely to affect you – the pathology community.

By Fedra Pavlou

“Alone we can do so little; together we can do so much”. It’s such a simple statement and yet such a powerful concept from Helen Keller, whose philanthropic achievements truly demonstrated the strength of unity. In pathology, you face many challenges on a daily basis – from meeting accreditation obligations to keeping up to date on the optimum procedures; delivering the best possible result doesn’t always come easily. Working in collaboration with others who share the same goal is not just beneficial, it’s a necessity.

Whatever the specialty, international societies are formed with this same ethos in mind: progression through partnership. But I believe there are three key factors that differentiate societies and their level of success: 1) the ability to attract proactive individuals; 2) the strength of the partnerships formed; and 3) the ability to promote themselves and their work.

One particular society – the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) – stands out from the crowd. Why? Perhaps because IFCC’s spokespeople take every opportunity to command symposium airtime – to let people know what they’re doing and to rally international support. IFCC has set up ‘task forces’ – international groups of multi-disciplinary teams formed in response to issues raised by its members as being of “international significance”. Though that may sound vague, IFCC’s task forces are gathering quite a following and, as a result, they’ve been able to make progress that could have some impact on your work, if not now, then perhaps in the future. Tackling issues such as the lack of standardization in chronic kidney disease and thyroid function testing, through to assessing the impact of lab medicine on clinical outcomes to better promote what you do to the wider community – there’s no doubt that the aims of some of these groups will strike a chord.



What About POCT?

By Rosy Tirimacco

Whether you support it or feel threatened by it, point of care testing (POCT) has an important role to play in patient care – and its role continues to gain importance.

In my experience, pathologists' views on POCT can vary significantly, from extremely proactive to potentially disruptive. Having said that, more pathologists are coming on board with POCT and understand that it is better to work with and support users rather than to ignore them. In fact, our POCT task force not only consists of clinical scientists and industry representatives, but it is represented by clinical pathologists too.

There is a vast array of POCT equipment available. And because the end user may not be a scientist, the decision on what piece of equipment best suits their needs is often a difficult one. So there is a real need for guidance on selecting equipment suitable for clinical intent. Users need to be encouraged to think about local resources and conditions to ensure the equipment they use will work efficiently in their environment.

Our current key focus is developing education and providing assistance to underdeveloped countries starting out on their POCT journey or wanting to improve the current POCT service.

To anyone who regards POCT as a threat to more traditional laboratory testing, I would remind them that pathology tests are performed for the benefit of the patient. In many rural and remote areas around the world there are no labs available, so basic tests, such as electrolytes, hemoglobin, INR and blood gases, or

tests for an acute presentation, are difficult to perform, if they are performed at all! There are also concerns for those who require regular pathology testing and need to leave their family support network behind to get it. In each of these scenarios, POCT is invaluable.

As with all pathology tests, pathologists have an important role in the education and support of POCT. Ideally, doctors who require assistance with interpretation of a POCT will have the opportunity to contact their local laboratory service or a pathologist for assistance. Pathologists will also be involved in determining analytical requirements of tests. It is up to the scientific community, including pathologists, to drive improvements in the quality of POCT by working with industry and setting quality goals for future development.

We are currently involved in developing educational materials on different aspects of POCT, including a quality framework, appropriate clinical use, connectivity, and cost-effectiveness. Integration of POCT into routine clinical care of the patient is also important in cases where the laboratory can either not provide timely results, or is not available. In particular, quality testing for POCT – that is to say, making sure POCT operators understand the importance of running internal and external quality control and how often – is a particularly significant issue and one that we are addressing with our educational efforts.

One of our main challenges is reaching out to other professions performing POCT. Increased use of POCT in pharmacies has prompted a lot of discussion with IFCC members concerned internationally that pharmacies are not subjected to the same quality demands as laboratories. Our challenge will be to work with pharmacists and other groups running POCT to ensure that any pathology tests performed outside of the laboratory are run within a quality framework.

What we would now like to do is to grow a communication network that is inclusive of all groups – expert individuals in IFCC, other expert groups, regulatory agencies, and users of POCT. This specialist network will assist individuals who want to implement POCT or improve their current service by providing appropriate education that ensures quality service. This effort constitutes a major goal for our task force.

Whatever pathologists or scientists may think of POCT, isn't it better to be involved and influence the process positively rather than to sit back and see performance of pathology tests deteriorate? POCT is here to stay, so we all need to work together to ensure it is performed in a quality framework so that patient care is not compromised.

Rosy Tirimacco is network operations and research manager at Integrated Cardiovascular Clinical Network (iCCnet), Australia, and chair of the IFCC task force on POCT.



Supporting Tomorrow’s Leaders

By Pradeep Kumar Dabla

It’s so important that young scientists have the opportunity to make contributions to, and get involved with, programs that support the growth of their specialty field. I say this not only because they have valuable skills, knowledge and ideas, but also so they can be best prepared for the ongoing challenges that they will face during their careers.

Indeed, obstacles start to present themselves from day one of entering the lab – lack of global support networks, lack of funding, lack of availability of lab exchange programs, to name a few. But more generally, young scientists often struggle to get involved in advocacy and decision-making too, when they really do have valuable contributions to make. We recognized the need for a support group to help young scientists address these challenges and so, in 2010, the task force for young scientists came into being.

It’s not easy to create a support group that caters for the needs of individuals working in different countries (and are therefore subject to national requirements that vary from one country to the next), but it’s something that we manage to achieve through the strong network that we have been building over the years. We’ve partnered with many national societies to deliver educational workshops, training, mentorship programs and, importantly, we take advantage of the easy availability of social media to make

sure that our networks stay connected, 24/7. Not long ago, most people would have turned their noses up at the thought of using Facebook or Twitter for professional networking and support. Now we use both, and LinkedIn, actively. Each channel supports a key aim of this taskforce: connectivity.

Our network now includes young lab medicine specialists from 15 different countries, each of whom are supported and encouraged by the senior society members to learn, participate, share and take control and responsibility of their careers. We want to empower them so that they are not afraid to initiate their own educational and training programs.

Currently, we’re planning to conduct a global study to establish the existing key challenges that this group faces (on a general and a national level), so that we can make sure that our programs and support networks are moving in the right direction. We’ve made some fantastic progress so far, but we still strive to build the most optimum support and learning network for our new generation of scientists. It’s a challenge, but it’s so important to us that the field of lab medicine is as attractive and supportive for the next generation as possible.

Pradeep Kumar Dabla is assistant professor and head of the department of biochemistry, Chacha Nehru Bal Chikitsalya, Pediatric Superspeciality Hospital, associated to Maulana Azad Medical College Delhi, India and chair of the IFCC task force of young scientists.

The Undisputable Value of Pharmacogenetic Testing

By Ron H. N. van Schaik

Pharmacogenetic testing is escalating in both the number of requests and its importance – these are undisputable facts. But out of this rising interest spring five important questions:

- How useful is it, exactly?
- What is the current perception amongst clinicians and laboratory specialists?
- What are the clinical recommendations?
- How can it be integrated into routine diagnostic testing?
- How can we assure quality standards?

The task force on pharmacogenetics was established to address all of these questions, with the aim of supporting the full, efficient and effective integration of pharmacogenetic testing into labs.

We must overcome the existing barriers to pharmacogenetic testing, which include: a lack of access; missing clinical guidelines (even when pharmacogenetic information is present in the drug label); a lack of knowledge on what is possible and available; a lack of clarity on reimbursement strategies – and, sometimes, disagreement on the level of evidence needed to accept testing as valuable.

If someone questions the value of genetic testing to patients in terms of adapting drug type or dosage, I offer several convincing examples. A first positive example is the fact that 99 percent of people who are hypersensitive to the HIV/AIDS treatment abacavir, test positively for HLA-B*5701, a known genetic risk factor (1).

A second example, which has been widely debated, is CYP2D6 testing for tamoxifen therapy. Patients with little or no working CYP2D6 represent around 5–10 percent of the population – are not able to activate tamoxifen, and so are theoretically at risk for undertreatment on standard doses. About 10–15 papers have shown that the CYP2D6 variant genotype is related to a poorer outcome with tamoxifen, but 8–12 papers have shown otherwise (2). So, how much evidence does one require? Is common sense enough? I think not. Should it be confirmed with pharmacokinetics? Yes – that's much better. Confirmation with pharmacodynamics would be another step further, but is a distribution of 10–15 papers showing an effect enough to routinely include this type of testing? Or is the fact that not all studies find the association sufficient to deprive a large group of patients from this test? Actually, these aspects were all solved by a meta-analysis showing that there is indeed significant evidence that patients with deficient CYP2D6 have a poorer outcome on tamoxifen (3). Yet, despite the evidence, the clinical community still hesitates to propagate this type of testing.

Another example is CYP2C19 testing for clopidogrel – again a drug that needs activation by a genetically polymorphic

enzyme (4, 5). CYP2C19 carriers of one or two inactive alleles (approximately 20 percent of the Caucasian population) are less effective in activating clopidogrel, and have been shown to have an increased risk of myocardial infarction, stroke or death. The US FDA has now a boxed warning in the drug label on CYP2C19 for this, but still CYP2C19 testing for clopidogrel use has not been implemented in clinical guidelines. Our task force is trying to facilitate the discussion between clinical chemistry and, in this instance, cardiology, to ensure the uptake of this testing in routine clinical care.

So far, a strong association between genetics and drug sensitivity has been proven for at least 60 different drugs (6) and, in fact, pharmacogenetic information is now included on the drug label for more than 120 drugs.

To date, we've successfully established connections with many other organizations operating in this field to support the implementation of guidelines, to update our members and to answer questions. But, as a task force, we still have lot of work to do.

Our ultimate goal is to secure the proper implementation of pharmacogenetics into patient care within the next two years throughout the world. It's a huge undertaking, but we believe that we can achieve it, if we:

- create an international clinical laboratory network,
- ensure high quality testing,
- create a forum for interaction and information exchange,
- interact with clinical organizations.

The anticipated result? The production of globally-accepted clinical guidelines for pharmacogenetic testing.

Ron H. N. van Schaik is a professor of pharmacogenetics at Erasmus University Medical Center, Rotterdam, The Netherlands, and chair of the IFCC task force pharmacogenetics.

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“Our ultimate goal is to secure the proper implementation of pharmacogenetics into patient care within the next two years throughout the world.”

A black and white portrait of Howard Morris, a middle-aged man with short, light-colored hair, wearing a dark suit jacket, a light-colored shirt, and a patterned tie. He is smiling slightly and looking towards the camera. The background behind him consists of a grid of thin, light-colored lines.

“Our recommendations of pathology best practice for CKD have been adopted internationally.”

Striving for Global Excellence in Chronic Kidney Disease Testing

By Howard Morris

We set out on a mission when we formed the task force on chronic kidney disease (CKD) – a joint project between the IFCC and World Association of Pathology and Laboratory Medicine – to recommend and support the implementation of pathology best practice in CKD testing, globally.

I'm proud to say that we have achieved a lot so far, but it hasn't been easy.

At the start of this undertaking, we collected information on the current state of national and international activities in the area of pathology testing in CKD. Through consultation with international specialist organizations, such as Kidney Disease Improving Global Outcomes (KDIGO), we assessed current best practice and recommended guidelines and policies.

I admit that one of our biggest tasks is one of communication. Volunteers amongst the medical specialists, primary care physicians and clinical laboratory specialists involved do all the work necessary on top of their normal health service delivery

workloads. So, efficient and effective communication is crucial to engage all stakeholders in the process. It's not easy and there are no well-documented strategies in place. The knowledge that we share and gain is largely region- or country-specific, so it's a challenge working with cross-boundary differences. The idea behind our best practice recommendations – when adopted as policy by renal specialists and clinical labs – is to facilitate the effective communication between renal medical specialists and primary care physicians by way of the clinical laboratory report.

What have we achieved so far? Our recommendations of pathology best practice for CKD have been adopted internationally. The traceability of creatinine assays to recognized international reference materials using reference measurement procedures have been adopted by the major in vitro diagnostic equipment and reagent providers. But with approximately 100 companies now providing reagents and instruments for creatinine measurements, considerable work is still needed. Professional organizations, such as KDIGO and IFCC, as well as clinical lab workers must inform these companies of the importance of establishing traceability to

recognized international reference standards for their clinical CKD assays.

We've also achieved the worldwide recommendation of estimated glomerular filtration rate reporting based on creatinine measurements, using traceable assays and the best available equation. Adoption is widespread in regions across North America, Europe, Australasia and Asia-Pacific.

We're now working hard to extend these concepts to remaining global regions. Major obstacles will continue to be the effective communication between all stakeholders, and the adoption of appropriately traceable assays within clinical laboratories. We've come a long way so far, and we will continue working until we've achieved our overall aims.

Howard Morris is a professor of medical sciences at the University of South Australia, vice president of the IFCC and chair of the IFCC-International Osteoporosis Foundation Working Group on standardization of bone marker assays.

How Clinically Useful Are Bone Turnover Markers?

By Howard Morris

Metabolic bone disease is highly prevalent, and although bone turnover marker (BTM) assays have a key role to play in its diagnosis and monitoring, the lack of internationally recognized guidelines for the interpretation of patient results has limited their clinical usefulness.

Patients with osteoporosis, in particular postmenopausal osteoporosis, make up the largest group of BTM assay recipients, where it is used to assess fracture risk and/or to guide therapy and monitor response.

We set up a task force, in collaboration with the International Osteoporosis Foundation, to identify a consensus reference standard BTM. Although we believe in its clinical usefulness, a thorough review of current reports has indicated that there are insufficient data to guide the use of any particular BTM for clinical use, despite the availability of a body of evidence to suggest that they may be useful. For example, of 22 studies that reported on the relationship between a BTM and future risk of fracture, 18 linked elevated BTM level with fracture risk (1). However, the problem is that a number of BTM assays have been used in these studies, so no apparent benefit has been found for any one particular BTM as a bone formation or a bone resorption marker.

Based on our own research of these reports, we agreed that serum beta-CrossLaps (β -CTx) appeared to be a suitable bone resorption marker, and procollagen type 1 amino-terminal

propeptide (PINP) was a suitable bone formation marker. A second working group from the North American National Bone Health Alliance also conducted a review and reached the same conclusions.

We're now in a position to investigate this further, but we do have some concerns: we are currently investigating whether or not current commercial clinical assays for serum β -CTx and serum PINP provide comparable results. Once we are satisfied that all assays are producing comparable results, we can confidently conduct metaanalyses of clinical trial data where these assays have been used and combine data from all assays used by clinical laboratories.

Our plan is to calculate the discrepancies in measurements for these BTMs across different manufacturers, reagent lot numbers and laboratories. Our goal is to establish the least significant change for each BTM that will allow clinicians to confidently analyze data irrespective of the clinical lab or assay used.

Right now, I admit that it's not guaranteed that our recommendations will be incorporated into clinical guidelines. A major immediate task is to reduce variation between BTM levels so that only variation in bone turnover is being assessed. If we achieve this first and foremost, the clinical use of BTMs for fracture prognosis can be optimized. However, there is still a lot about the basic physiology of BTMs that is not understood; for example, we know that levels of some BTMs are markedly affected by eating. Initially, this was attributed to calcium consumption, based on the rationale that calcium affected calcitropic hormones and, therefore, indirectly affected bone turnover (2). But more recently, it's been suggested that gut hormones, such as GLP-1, markedly affect serum β -CTx levels (3), while another BTM, osteocalcin, might actually be a hormone that regulates whole energy metabolism of the body (4). If whole energy metabolism is related to BTMs, there will be a great deal of variation between individuals independent of their bone status.

Irrespective of ongoing research, we will not be able to proceed further unless we successfully conduct the studies and harmonization of the assays as planned.

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Time to Standardize Thyroid Function Testing

By Linda Thienpont and Katleen van Uytendaele

Thyroid disease is a highly prevalent and severe health problem that requires timely diagnosis and disease management. Whereas the diagnosis of overt hypo- or hyperthyroidism is rather easy, identification of subclinical dysfunction is not trivial and requires an integrated clinical laboratory approach (1, 2).

Despite the importance of laboratory thyroid function testing (TFT), several confounding factors may hamper optimal use of the results; for example, if certain aspects, such as time of phlebotomy, analytical and biological variation, index of individuality, the patient's setpoint and reference change values, are not properly accounted for, test results can be misinterpreted. But perhaps the factor with the highest clinical importance stems from the fact that today's current assays for common TFT

(thyrotropin [TSH], free thyroxine [FT4]/triiodothyronine [FT3]) generate results that differ by up to 30–40 percent (3–5). Admittedly, we can compensate for these differences using assay-specific reference intervals (RIs) and/or clinical decision limits, but is this really state-of-the-art? After all, it does not allow the use of evidence-based clinical practice guidelines for application of consistent standards of medical care, nor the use of electronic patient records.

Before endocrinologists can agree on what constitutes “normal” thyroid hormone levels, we need to first accomplish comparability of laboratory testing results. Only through standardization or harmonization can we ensure that all TFT assays are fit to address modern clinical and public health needs (3–5).

To that end, back in 2005 the IFCC established a task force to develop ISO 17511 conforming reference measurement systems that could be used to standardize/harmonize TSH and FT4/FT3 tests. Although we had to start the process from scratch, we are proud that we made some great achievements so far. We have established the key elements of the reference measurement systems for both TSH and FT4 (6, 7), and have developed a practical concept for implementation – the “step-up” approach (8). Step-up consists of performing a method comparison with as many assays as possible and the use of a panel of clinically relevant samples assigned with values by the FT4/FT3 reference measurement procedures (RMPs) or surrogate RMP (for TSH). These method comparison data are then used for recalibration of the assays, so that, after alignment, they generate comparable results.

We are particularly proud that we have formed close collaborations with all of the major in vitro diagnostic (IVD) manufacturers, who are extraordinarily committed. Together, we have established a relationship with the US FDA, which was very important, because recalibration of an assay can entail major regulatory activities. Making such relationships way ahead of the actual implementation of the process will hopefully limit delays to making the newly standardized/harmonized assays available for clinical use.



The IFCC Vision

IFCC President Graham Beastall offers his overarching perspective on the importance of its task forces.

What are IFCC task forces and why were they formed?

A task force is made up of a panel of international experts spanning many

different disciplines (for example, laboratory managers, geneticists, pathologists, regulators, analytical scientists), to address a broad, contemporary issue that is relevant to the laboratory medicine and clinical chemistry community.

The IFCC structures its activities around three specific areas: science, education, and management. Around 10

“We are particularly proud that we have formed close collaborations with all of the major in vitro diagnostic (IVD) manufacturers, who are extraordinarily committed.”

So, where do we go from here? We're currently working to provide a clinically relevant serum panel for the final technical process of standardization/harmonization of the FT4 and TSH assays (this will happen in spring 2015), and to provide infrastructure for sustaining the status that we will have established. Although we would like to establish a network of competent reference laboratories, the laboratory at the University of Ghent is currently the only lab in the world that's listed in the JCTLM database to offer the FT4 (FT3 coming soon) reference measurement services.

We also want to define a platform that proves the applicability of a common RI after standardization/harmonization. To do this, we will determine the FT4 and TSH concentrations in a cohort of 120 individuals with the FT4 RMP and the TSH surrogate RMP, in parallel with the standardized IVD assays. After achieving this RI for common use, it will be up to the IVD manufacturers to establish reliable reference ranges from much bigger cohorts.

Once we get to that point, we will work with all key stakeholders (clinicians, patients, laboratories) to support the implementation of standardized/harmonized TFT in routine clinical practice. Indeed, in view of the significant change in values for TFT that will be introduced, healthcare providers/receivers need to be well prepared to avoid confusion. We will develop an outreach program to inform and educate them.

Our plan is to act as a central coordinator to ensure that the switch happens globally and at the same time. The implementation process will also be preceded by a global benefit-risk analysis, which should result in an action plan to

oversee and proactively avoid any causes of patient harm after standardization/harmonization.

It's a big challenge, but one that we believe we can achieve with confidence.

Linda Thienpont, professor of instrumental analytical chemistry, statistics and quality control, head of mass spectrometric reference laboratory, at the University of Ghent, Belgium, and chair of the IFCC committee for standardization of thyroid function test (C-STFT).

Katleen van Uytendaele is technical supervisor of the reference laboratory at the University of Ghent, Belgium, and scientific secretary of the C-STFT.

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years ago, we realized that many of our activities straddled all three, which led to the formation of our very first task force – ethics in laboratory medicine. Eleven task forces now exist, each with the aim of identifying issues, providing guidance and best practice support, and promoting international collaboration. We're continuously under pressure to ensure the

clinical relevance of what our laboratories do, and collaboration with international clinical organizations has become a high priority for us. The task forces offer the best way to do this and through them, we aim to facilitate harmonization of high quality laboratory practices, which results in improved clinical outcomes and patient safety.

What have been some of the biggest successes?

There are three that instantly come to mind. The task force for chronic kidney disease (CKD) is doing some great work for developing countries – they're providing guidance on how to estimate glomerular filtration rate, to report it in standard ways, and to encourage collaboration with



national renal organizations. This is making a positive difference to huge numbers of patients with CKD.

Millions of diabetes patients worldwide are benefiting from the work of the task force for implementation of HbA1c standardization, which is working with manufacturers to ensure all HbA1c methods are aligned to the global standard. They're

also collaborating with the International Diabetes Federation, IFCC member societies and national diabetes societies to agree reporting criteria and action limits.

I'm also very pleased with the achievements of the task force for young scientists, which has identified hundreds of senior trainees in laboratory medicine from scores of countries around the world. By

networking these young scientists through social media they're identifying common issues (such as training standards) and communicating successes and achievements. Tomorrow's leaders will have something in common – and a network of friends.

What broad challenges has the IFCC faced?
As with any international project

Proving Our Worth

By Mike Hallworth

We know the positive impact that laboratory medicine has on healthcare, but is the general public aware? In fact, are those who actually work in the healthcare community even aware? The short answer in most cases is: no.

Laboratory medicine is not very visible – I believe that those of us working in the field have not been as active as we need to be in taking responsibility for improving the total testing process, and getting out of the lab and talking to patients, clinicians and administrators. I believe that this needs to change.

It's so important that the value of what we do is recognized – not only so that we can promote better use of tests and patient care, but also for our own job satisfaction – and the only way that we can do that is to present the evidence. The task force on the impact of laboratory medicine on clinical management and outcomes was set up with that precise objective in mind. And there are two key methods of achieving this. First: we evaluate the available evidence supporting the impact of lab medicine on healthcare. Second: we develop new retrospective and prospective studies to support the promotion of the importance of laboratory medicine to the healthcare community and to the general public.

What drove scientists from across Europe, the US and Asia to come together in this task force? Quite simply, it's the lack of hard data. Laboratory workers have traditionally been good at assessing the reliability of tests, but when it comes to assessing the outcomes of their work, studies have been neglected. And it might surprise you that the often-quoted statement, "70 percent of clinical decisions are based on laboratory tests" is, unfortunately, not supported by any studies published in the literature.

It is clear that any blanket figure will be misleading and dangerous. We have reviewed a lot of evidence on the impact of laboratory medicine interventions on clinical outcomes and cost-effectiveness – the resulting paper has been submitted for journal publication. However, we face two main obstacles to

"And it might surprise you that the often-quoted statement, '70 percent of clinical decisions are based on laboratory tests' is, unfortunately, not supported..."

getting the evidence that we need to link testing with outcome. Firstly, to improve outcomes, a lab test must be appropriately ordered, properly conducted, returned with results on a timely basis, correctly interpreted and finally, of course, it must affect a decision for further diagnosis and treatment. Laboratory medicine workers have done a huge amount to improve the quality of results, but improving patient outcomes requires us to look at the whole of the testing process. Secondly, traditional evaluations of laboratory tests have focused on the performance of the tests in terms of diagnostic accuracy and predictive value for disease. We need more studies that are designed from the start to include patient outcome measures.

Our evidence review, in conjunction with the presentations that we deliver at congresses, will stress the need for laboratory professionals to be more involved in the total testing process (from initial request to interpretation and action) and for better evaluations of laboratory tests. Laboratory doctors and scientists need to help produce guidelines for investigation, advise clinical staff on the best test for individual clinical presentations and on further studies needed to confirm a diagnosis, ensuring that key results are not misinterpreted or missed, and that services are used appropriately.

Getting that right means better use of tests, better patient care, lower healthcare costs, improved job satisfaction for laboratory workers and enhanced ability to recruit and retain good scientists. That's a goal worth working for.

Mike Hallworth is chair of the IFCC task force on the impact of laboratory medicine on clinical management and outcomes, UK.

the challenge is to get a high level of engagement and then to find a way forward that attracts unanimous support. The level of engagement is rising as the quality of laboratory medicine improves in developing countries, but unanimity of support is not always possible. For example, practice in Europe and the USA may differ, or some recommendations are

beyond the resources of some countries.

What further success can we expect?

We have to be realistic about our expectations – international projects generally progress slowly. However, with modern communication methods it is possible to reach large numbers of people in an interactive manner. Experience has

shown that a small number of charismatic 'champions' can be more effective in delivering positive outcomes than dry scientific publications (no matter how authoritative). As a society, we benefit hugely from talented volunteers who give freely of their time and expertise in the interests of international harmonization – we have to be optimistic!

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Speaker

Russell Watts, BSc (Hons), MRSC

Russell attended Nottingham Trent University where he obtained his Bachelor of Science degree in Applied Chemistry. He has over 13 years' experience within analytical chemistry field starting his career at Nottingham University as a research technician at the School of Chemistry in 1998. He then changed roles in 2000 to work at Safeparm Laboratories (now Harlan) as a laboratory analyst. In 2005, he joined Waters Corporation in the Clinical Business Operations group where he worked various scientific, sales and business development roles. All of these roles involved increasing the adoption of mass spectrometry technology into clinical laboratories and allowing these laboratories to realise the benefits of this analytical technique in a healthcare setting. Most recently, Russell joined AB SCIEX in 2013 as the Manager of their clinical business unit in the EMEA region with the goal of making mass spectrometry accessible to routine clinical laboratories.





In Practice

*Technologies and techniques
Quality and Compliance
Workflow*

microflow

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Traditional Methods with
Modern Outcomes

Molecular testing provides us with new data to inform disease prognosis. But these data cannot stand alone – in fact they're strengthened by traditional morphological assessments.

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Water - When Things Go Wrong
Water is the most ubiquitous reagent in the laboratory, but it's taken for granted far too often. Without a watchful eye on water supplies, problems can cause severe disruption in lab functions.

Traditional Methods with Modern Outcomes

A new prognostic index, combining morphological and molecular parameters, is needed to improve breast cancer guidance

By Tibor Tot

Molecular biology is an exciting and fast moving area, which has provided pathologists with a wealth of new information about health and disease. Despite this, I don't believe molecular analysis can tell the whole story. Conventional analytical techniques are at risk of being overlooked, and I feel this would be a serious mistake.

In my work in breast carcinoma (BC), histopathological methods to assess disease and provide prognosis are, and will continue to be, completely essential.

Traditional, not out of touch

While more conventional approaches to analyzing disease may not be seen as cutting-edge, they still hold a lot of value.

At a Glance

- *The advent of molecular testing can leave other prognostic methods overlooked*
- *Morphological information is an essential component of breast cancer assessment*
- *Subgross and molecular parameters are related and should be studied together to gain as much information as possible; a new prognostic index is therefore needed*
- *The principles outlined could be applied to other cancers and the pathology of other conditions*

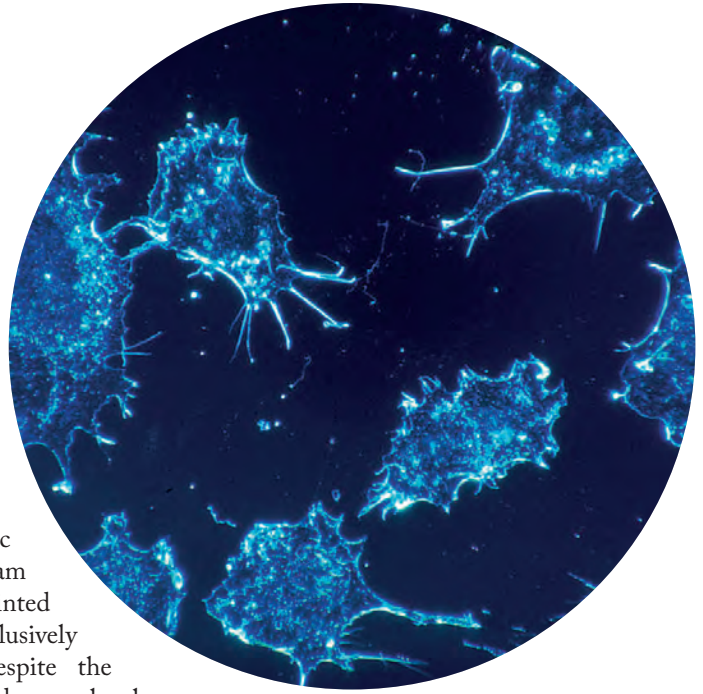
They are proven and consistent – tried, tested and improved upon over many years of use. Classifying BC is not a simple process, and I am very disappointed when we focus only on microscopic tumor images. I am even more disappointed when we focus exclusively on biomarkers. Despite the emphasis now placed on molecular phenotyping, it cannot replace classic morphological examination, which provides answers molecular tests can't – how large is the tumor? How extensive is the disease? Is it multifocal or diffuse?

Instead of focusing only on some sources of information, providing a prognosis must be a multimodal process, and in collaboration with our clinical and radiologist colleagues. With such a complex disease, the more information we can get, the better.

To highlight the importance of combining prognostic techniques, I have focused on BC as this is the area that I have studied most widely, but I believe these principles could be applied to a range of other cancer types and indeed the pathology of other conditions.

It goes without saying that BC has a complex pathology and outcomes can vary greatly. Despite this, there are many methods for assessing tumors, and these can be split into two main groups: subgross and molecular (Table 1). Both take in many different factors and are far from straightforward, but both have clear links to patient survival (1, 2, 3).

Morphology meets molecular
I believe there is currently a problem in the way in which we study subgross morphological parameters (SMPs) and



molecular phenotypes – separately. We now have defined molecular phenotypes in BC, and we know the ways in which SMPs can aid in characterizing the disease; but we are not giving enough attention to the relationship between these two areas.

My colleagues and I at Falun County Hospital, Sweden, use both in our everyday practice. We use large-section histology to judge disease parameters, such as extent and focality, and we gain further insight from radiology results – we discuss every case at multidisciplinary meetings in which the radiologists demonstrate their findings, and the pathologists project their slides parallel with the radiological images, in order to correlate all our information. At the same time, we use a panel of biomarkers to define molecular phenotype (different classifications exist, but within our lab we use the St. Gallen 2013 system, as modified by the Swedish Breast Cancer Group).

So how exactly do these morphological and molecular parameters relate to each other? In a review of over 1,000 cases at my hospital I noted many examples (4):

Size

- The number of luminal A cases decreased as tumor size increased, and the opposite was true for triple negative cases (Table 2).
- The likelihood that an invasive BC less than 10 mm in size was HER2 positive, triple negative or ER negative was very low.
- HER2 expression appeared to begin during the early stages of some BC cases (though overall number of HER2 cases was low in this study; 3 percent of the total, or 32 cases).

Shape

- The radiological shape of the tumor (i.e. spherical or stellate) increased the correct prediction of molecular phenotype (Figure 1).
- The majority of HER2 and triple negative tumors appeared to be spherical (Figure 1).
- Both luminal A and B types were more likely to be stellate.
- 95% of stellate tumors expressed ER.

Focality

- In 60 percent of cases, the invasive component of the tumor was unifocal, and multifocal in roughly one-third.
- In HER2-type cancers, over half of the cases were multifocal.
- Diffuse cases were very rare, and in 92 percent of cases were ER positive. This was of particular note as diffuse, invasive cases have an unfavorable prognosis, in contrast with their luminal phenotype, which confers a more favorable prognosis.

Microcalcifications

- HER2 positive tumors were most likely to be calcified, and high HER2 expression is associated with high grade tumors.

<i>Subgross</i>	<i>Molecular</i>
<i>Parameters</i>	
<ul style="list-style-type: none"> • Tumor size • Disease extent • Focality • Heterogeneity • Grade • Lymph node status 	<ul style="list-style-type: none"> • Estrogen receptors (ER) • Progesterone receptors (PgR) • Proliferative activity • HER2
<i>Methods of assessment</i>	
<ul style="list-style-type: none"> • Large, thick (3D) or thin section histology • Microscopic examination • Mammogram • Ultrasound • MRI 	<ul style="list-style-type: none"> • Immunohistochemistry • Gene expression profiling
<i>Results</i>	
<ul style="list-style-type: none"> • Early (size < 15 mm) or more advanced cancer • Extensive tumor/limited extent • Unifocal, multifocal or diffuse distribution • Intertumoral or intratumoral heterogeneity • Low/high/intermediate grade • Lymph nodes involved/not involved 	<ul style="list-style-type: none"> • Luminal A: ER and PgR positive, HER2 negative, Ki-67 low • Luminal B: ER positive, AND either HER2 positive OR Ki-67 high, or PgR negative/low • HER2 type: ER negative, HER2 positive • Triple negative: ER, PgR and HER2 negative

Table 1. Breast carcinoma prognosis: parameters, methods and results.

<i>Tumor size</i>	<i>Luminal A</i>	<i>Luminal B</i>	<i>HER2</i>	<i>Triple negative</i>
1–9 mm	52.2%	37.9%	5.6%	4.5%
10–14 mm	47.3%	47.0%	0.8%	4.9%
≥40 mm	28.0%	54.9%	3.7%	13.4%

Table 2. Molecular phenotype in relation to tumor size.

Key recommendations

Based on my experience, when describing malignant breast lesions, regardless of the imaging method used, I would highly recommend that the following morphological parameters are always assessed as standard:

- ✓ The distribution of the lesions (unifocal, multifocal or diffuse) – separately for invasive and in situ lesions.
- ✓ The extent of the disease (including all invasive and in situ tumor structures).

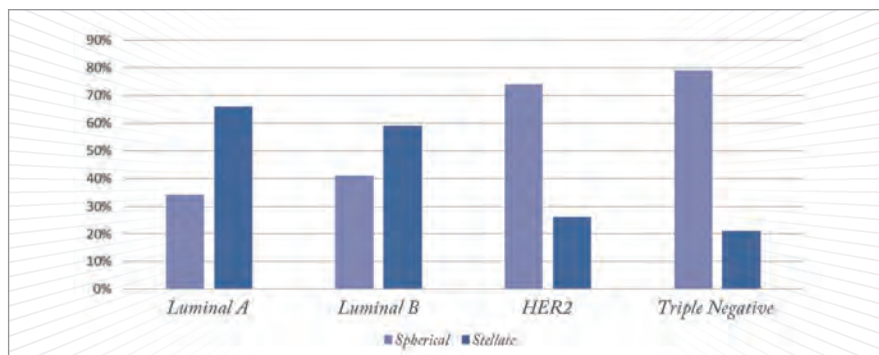


Figure 1. Molecular phenotype in relation to radiological shape of tumor.

- ✓ The size of the tumor – this corresponds to the largest dimension of the largest individual invasive tumor.
- ✓ Evidence of intratumoral or intertumoral heterogeneity.

I believe that our research has clearly shown correlations between molecular phenotype and subgross morphology. The most important take home messages, in my opinion, are: HER2 type tumors are more likely to be multifocal and have a high-grade in situ component; luminal A types are commonly small and stellate; and diffusible invasive BC, while rare, has an unfavorable prognosis, which contrasts with its luminal phenotype. I am sure that as this area becomes more widely studied, we will discover more such associations.

As well as providing us with a more comprehensive understanding of the carcinomas we are studying, this approach may also improve patient outcomes. For example, work done by my colleagues at the Carillion Center, USA, is now beginning to show that the use of MRI and large section histology may influence survival rates in multifocal cases – although unfortunately, their results are not yet published.

Histological pitfalls and missing guidelines I believe that of all the methods we have available for assessing SMPs, histology is by far the most accurate, but as with all of

the techniques I have described, there is room for error: inadequate sampling, for example, including only part of the tumor in your sections; inadequate interpretation, such as mistakenly including invasive extensions when sizing a tumor.

There is also the risk of failing to properly correlate radiological and pathological information available to you. For example, it is common for pathologists to have no information on radiological findings, or only a text report, meaning they may not know how many foci were identified within the breast and therefore how many should be found.

The guidelines and quality control measures available in this area are another issue; I believe they are simply not sufficient, and require revision. The WHO classification of tumors of the breast (5), a basic reference for pathology departments all over the world, has 240 pages but does not mention disease extent as a parameter. Multifocality is mentioned just once, in connection to rates of lymph node metastasis. Also, the Tumor Node Metastasis (TNM) classification of breast tumors was produced a long time ago, and although repeatedly revised, is still oriented towards naked-eye examination and specimen sampling, and does not appreciate the importance of detailed radiological-pathological correlation.

On a positive note, there is an International Agency for Research on Cancer (IARC)/ WHO initiative for

producing an additional document, focusing on the above mentioned subgross parameters (the Eurocan Platform), but the work is progressing very slowly. The lack of international guidelines which properly interpret these parameters concerns me, as the pathology community is mostly guideline-governed, and currently this information is not fully standardized and available to everyone.

Better together

To summarize, it's only if we assess all of the parameters discussed here, and we correlate all of the information we receive, that we can provide our colleagues and our patients with the best possible guidance. While both molecular and morphological analytical techniques undoubtedly have much to offer, we can improve them by combination. It is for this reason that I believe a new prognostic index is required. Molecular classification is, of course, a powerful tool – but it's even more powerful when combined with conventional parameters. Surely this should be our goal.

Tibor Tot is associate professor of pathology at the University of Uppsala, Sweden.

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Water: When Things Go Wrong

When it comes to quality control in your lab, don't overlook the obvious – contaminated water can lead to a host of problems

By Tim James

Water is the single most important reagent used by those of us who work in laboratories, but it's often taken for granted. It is only when the supply is interrupted or compromised that its value is appreciated.

The technical aspects of water quality are well defined (1, 2) and whilst most lab scientists won't have an in depth knowledge of these details, the impact of system failure are immediately evident and can stop a service completely. So it goes without saying that the quality, purity and reliability of the water supply is a critical part of running any laboratory.

The world's most common reagent in clinical chemistry laboratories, the majority of water is used in high-throughput

At a Glance

- Laboratory procedures often require large volumes of water
- A supply of purified water is essential, but there are many risks for contamination, which could stop a lab service completely
- Sources of contamination include the water supply, the purification unit and the equipment
- It's important that laboratories have good lines of communication with purification system suppliers, estates/maintenance teams, and understand what to look out for when things go wrong to minimize disruption



chemistry analyzers; a medium- to large-sized laboratory, for example, may have a peak hourly demand of 50 to 100 liters. Lower volumes are needed for more specialized analytical techniques, such as tandem mass spectrometry or atomic absorption spectroscopy (AAS). Needless to say, any failure in quality – in most cases, contamination – could be a burden on time and resources, and could cause delays in the delivery of clinically important results.

Water contamination in a routine clinical biochemistry service can be introduced at any one of the following three stages: upstream of your purification unit; within the unit itself; post-purification (see Infographic). Being aware of what can go wrong with your supply – and how to address it – can help to keep your results accurate and your workflow smooth.

Pre-purification pitfalls

In my experience, the supply to the unit

(either through a direct mains feed or via a cold storage tank) is the most common source of water contamination. Interruptions at this stage, fortunately, are automatically evident through either an alarm mechanism within the purification unit, or through pressure indicators.

Any scheduled (pipe maintenance) or unscheduled (leaks or bursts) interruptions upstream of the unit can also interfere with the supply. Knowing when planned work will be taking place and recommending that it happens during times when laboratory workload is low, will certainly keep disruptions (and therefore possible quality compromise) to a minimum. So it's important to maintain a good working relationship with the estates/maintenance department within your hospital or institute. It's also important to maintain those relationships and to keep lines of communication open to minimize the impact of impromptu interruptions; if laboratories are alerted of them early,

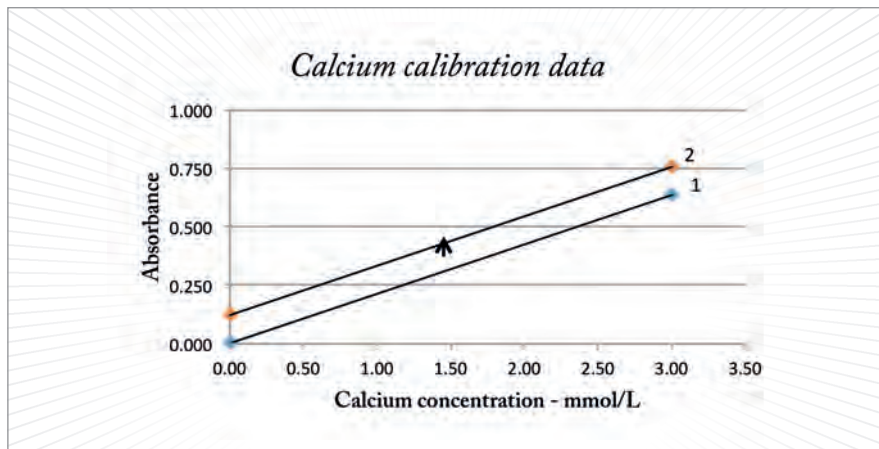


Figure 1. The graph shows an upwards shift in calcium calibration curves over time, due to the incomplete removal of calcium impurities in the water supply. Calibration 1 represents the normal absorbance pattern compared with calibration 2, where the background of increased calcium results in increased absorbance in both the blank and the calibrant.

contingency plans – such as prioritizing urgent samples only – can be put in place.

When supply comes through a cold storage tank, ironically the cleaning of the tank can present a contamination source; specifically cleaning agents, some of which are chlorine-based, can enter the unit and damage components. It's important to be aware of when cleaning is scheduled, so that the supply can be diverted while it takes place.

More substantial pipe damage and repair can result in damage to the unit consumables. In our laboratory, for instance, we have seen significant silt deposits in our supply following a major mains repair. Our water remained pure and the unit was able to remove the deposits, but the filters become quickly overloaded and needed changing several times.

It's also important to recognize the impact of geographical and seasonal variation on the quality of your supply. Limestone areas produce what's known as "hard water", that's to say water containing the divalent ions calcium and magnesium. Where this is problematic, discussions with suppliers can help to optimize your unit design, for example, by incorporating softeners (such as sodium salts) into the

process. The impact of seasonal variation is usually more apparent in the summer months when supplies are generally lower and impurity content consequently higher. As a precaution, I'd advise that laboratories keep a larger stock of replacement parts during this time of year, as they may need to be replaced more often than they would the rest of the year.

Purification unit problems

Units will vary between manufacturers and by laboratory requirements. As a general rule, the complexity of a unit increases in line with the water quality grade that it produces. As with all pieces of laboratory equipment, occasionally these systems fail so where an uninterrupted supply is required, you may need two or more units.

In many situations, the unit will monitor the quality of the water it produces by tracking resistance, but this is only one indicator. It is important to assess overall quality using a variety of analytical parameters, for example, the absorbance characteristics of blanks in spectrophotometry and baseline changes in chromatographic techniques.

Within the standard repertoire of investigations carried out on a clinical

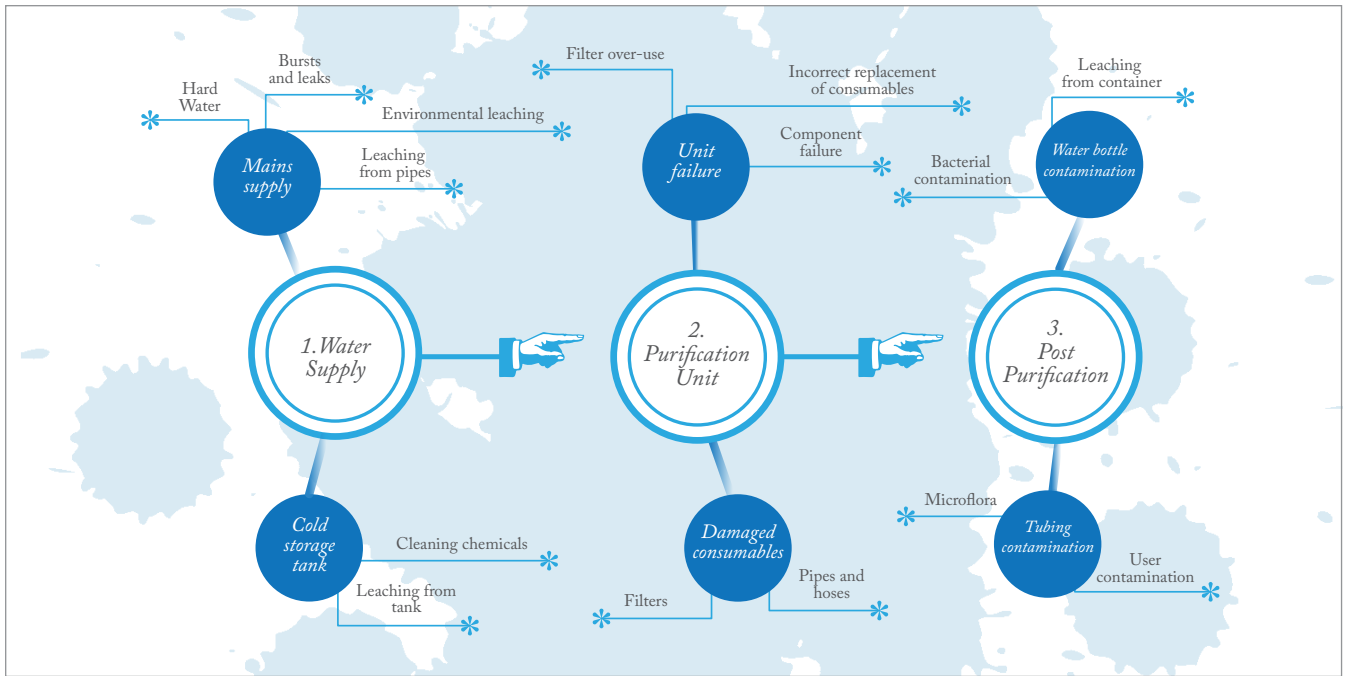
chemistry analyzer, certain tests are more susceptible to deteriorating water quality. Calcium and magnesium analysis are two examples that are often compromised and this may be evident from the calibration data. Some analyzers will hold previous data within their software, which can allow serial calibrations to be graphically compared for changes over time. Figure 1 shows a shift in calcium calibration curves, where the removal of calcium impurities has not been completed. Both baseline and calibrant absorbance should remain relatively constant, but in the example given, both show a shift upwards, which should alert operators to water quality problems.

Equally, changes to blank readings might indicate that a unit is unable to remove organic impurities – typically in chemistry methods, this may be most apparent where the reaction is monitored in the UV region of the spectrum (on a standard clinical chemistry analyzer, this will be at 340 nm methods that utilize the transition of NAD to NADH). Specific method parameters may show flags where baseline absorbance deviates by more than a defined threshold.

In AAS, water contamination issues may also cause blank readings to deviate from what is expected, and this should be monitored. For chromatographic methods, the baseline chromatograms may show characteristic changes as impurities increase. Monitoring these parameters as a method of quality control should be standard practice.

Post purification glitches

Occasionally, problems arise after the purified water is produced. Most commonly, small water bottles that are used to hold supplies of water locally to an analytical area can become contaminated with bacteria. This is most easily avoided by using single use containers, or by only using the container for short periods of time to prevent bacterial accumulation.



Stages in the supply of purified water to the laboratory and common sources of contamination; introducing contaminants during any stage of the process can have an effect on the resulting water purity, which in turn can affect the operation of lab equipment and therefore test results. Identifying what can go wrong, and how, is crucial to preventing and resolving contamination issues.

However, a more complex version of this problem can occur in the tubing that carries water to the analyzers. Careful, periodic cleaning, carried out as per the guidance of the instrument manufacturers, can help to prevent this problem. Again, this kind of contamination may appear in results; many contaminants seem to cause spectral changes in the UV region – I have observed this problem in both ALT and AST enzyme tests where the NADH:NAD transition is monitored.

The impact of poor quality water

In a routine clinical chemistry laboratory failure to produce good quality water will typically lead to a requirement to repeat tests as quality control procedures are usually able to detect the problem. However, this leads to greater utilization of resources – both staff time and reagents. In some cases it may lead to delay in the availability of results, and in the worse case scenario, the patient may need to have a repeat sample taken. The simplest example of this might occur where there is bacterial contamination present in a secondary aliquot of purified water which leads to a high absorbance during instrument

calibration. Even if spotted early this will require a repeat of the calibration and delays to processing. A more complex pattern of contamination occurs when there are intermittent water quality issues. In my experience plasma calcium analysis has often been the most apparent test affected by poor water quality, possibly because our laboratory is in a hard water area.

In a research laboratory the effects of poor quality water are different in nature but equally negative on analysis. For example, the binding of antibodies during well coating of an ELISA can be affected and can lead to sub-optimal assay conditions affecting assay sensitivity.

Avoiding problems

My key recommendations for ensuring a high quality, uninterrupted supply of water to your laboratory are as follows: 1) work with the suppliers of your purification system to ensure it is installed and configured in the best way for the conditions in your laboratory; 2) work closely with the estates/maintenance team and ensure good communication; 3) understand which type of supply

system you have, what the most common problems are, and how to go about fixing them; 4) in the event of a problem which cannot be fixed by staff on-site, make sure the supplier of your unit is contractually obligated to respond to your issues within a short period of time.

Access to purified water may seem like a simple requirement, but if it fails, it is one that could have far-reaching consequences. It's important for anyone working in a lab to think about how the water is supplied, and to ask yourself this: do I have the right measures in place to monitor the quality of water? And how do I plan to respond to any supply-related issues if, and when, they occur?

Tim James is head biomedical scientist of clinical biochemistry at Oxford University Hospitals NHS Trust

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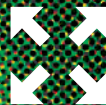
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CLIC to Enhance

Imaging biomolecules can be a challenge using current techniques. Could there be a simpler, cheaper way of doing it?

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The Google Genome

The new Baseline Study from Google[x] Life Sciences is assembling a database of healthy human genomes. Will the project's benefits to disease prevention and detection outweigh concerns over ethics and privacy?

CLIC to Enhance

Molecular imaging for the normal lab – a simple, cost-effective alternative

By Sabrina Leslie

We've been able to visualize single biomolecules for years, but the techniques we use are not without their limitations: keeping molecules in focus, background fluorescence interference, inadequate resolution, and DNA loading and viewing challenges, can make the entire process pretty difficult and the end result an inaccurate one. And that's without taking into account the risk of losing sight of valuable interactions between protein and DNA – these often disappear from view when using traditional methods (1).

Although confocal and total internal reflection fluorescence (TIRF) microscopy techniques, for example, have supported our molecular imaging efforts well so far, I feel we need to take it a step further. It's particularly pertinent as the importance of molecular imaging continues to increase at an astounding pace.

In light of this rising interest, we are hearing about a lot of exciting new technological developments, but many are considered out of reach to the normal

At a Glance

- *Imaging biomolecules can sometimes be a challenge using current techniques*
- *CLIC imaging technology could provide a solution to some of the current issues in microscopy*
- *CLIC can be easily integrated with your existing inverted fluorescence microscope*
- *The technology could provide advantages for various pathology disciplines, including prenatal testing and cancer genomics*

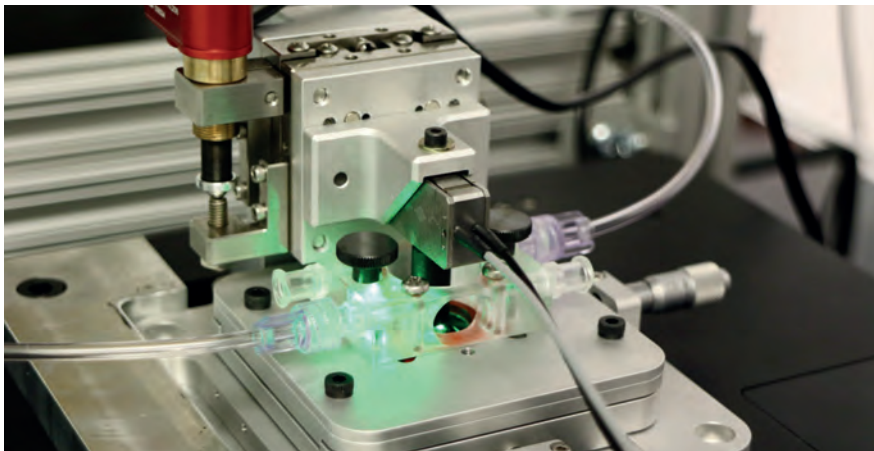


Figure 1. CLIC module.

lab, for one main reason – cost. The other reasons? Workflow changes, training needs, lab space challenges. Recognizing the limitations of current microscopes, my colleagues and I set about finding a solution that was both easy to implement and cost-effective. And we think we have. Convex-lens induced confinement, or CLIC.

CLIC imaging relies on a simple principle: molecules are forced into a well-defined nanoscale space, which can be used to confine the molecules to the focal plane of your existing inverted fluorescence microscope. The thinness of this space means that background fluorescence is reduced (so image quality is higher), molecule conformation is easier to change and manipulate (an advantage which has implications for genome mapping), and importantly, CLIC imaging chambers can be assembled by you, which means you can customize the process to your own needs.

Based on our own studies of using the CLIC imaging system, which we incorporated onto an inverted fluorescence microscope, we have found several key advantages relative to other single-molecule techniques (which are also typically employed on inverted microscopes), including: enhanced observation of single molecules, reduced background fluorescence, and over a thousand-fold

increase in observation time (2).

CLIC imaging can be done in four steps (see Box).

How can it help molecular pathologists? In a recent article by my colleagues and I (2), we discuss a number of applications for CLIC, one being in genome mapping of long DNA strands.

Open-face nanochannels on the bottom surface of the chamber make it possible to observe molecules as they load into the chamber. They are able to fully extend along the channels without breaking, which is important as it allows the mapping of long-range structural rearrangements of the genome. In contrast, conventional methods, such as nanofluidic technologies, often use large applied fields or pressure to load the DNA, which may cause the strands to break into smaller pieces and clog the channels.

I also see the potential for CLIC to be used as a detection method for a panel of cancer biomarkers, for example, because of the sensitive imaging chamber which can detect molecules over a range of volumes.

We are now engaging in collaborations to combine CLIC with other nanotechnologies to create platforms for optimal sensing of biomolecules – something I think many molecular pathologists will be excited about.

How can it help clinical pathologists?

In addition, clinical laboratories which already have an inverted fluorescence microscope could incorporate CLIC, and our belief is that this could be used in clinical diagnostics should our follow-up project yield the results we expect it to.

As part of a recent collaboration (2), we aim to develop a single-cell imaging device which first lyses a cell, next purifies the DNA and then loads it into a CLIC imaging chamber. We expect to have a basic prototype within one year. This will enable faster and cheaper diagnostics of single cells, in particular when compared with current methods used for prenatal (where few cells are available to work with) and cancer diagnoses.

If we consider cancer; the genome for each cell can be very different, so the ability to map cancer genomes one cell at a time may be important in understanding disease onset. Most current techniques work with the average of a population of cells, which might cause essential information to be missed. It is possible for a small fraction of cells among a population to be virulent and persistent, and I believe single-cell diagnostics are needed to understand this behavior.

Geometry glitches

I think CLIC imaging could provide a leap forward in microscopic imaging, but as with any new innovation, there were challenges during its development. Difficulties included loading samples and caring for surfaces. We also had to create an approach to control and measure imaging geometry. However, these technical problems were interesting to solve along the way, and I believe we have succeeded in creating a user-friendly device that overcomes the issues we have faced. Currently, we are augmenting the microfluidic capabilities of our CLIC device to allow us to insert multiple reagents in a controlled fashion, and temporally resolve their interactions.

We are pushing the buffer exchange capabilities, and the flow chamber design and material is being optimized for imaging quality and control over the imaging geometry.

Where to next?

The modular CLIC device (Figure 1) my team has built is now ready for distribution and use in laboratory settings, and we are looking into commercialization. More long-term (over many years), we hope to create a miniature, hand-held CLIC device which is diagnostic specific.

I believe that current microscopy techniques and equipment do not always provide high enough quality imaging, and I think CLIC could provide better-quality results. Importantly, using CLIC imaging would not require a laboratory overhaul or the installation of large or complex new pieces of equipment.

I hope to establish CLIC as a helpful tool for tackling a wide range of challenges in pathology, biology, medicine and biophysics, and to me, the best way to do this is to get CLIC out there and into the hands of the scientists who could use it in exciting and ingenious ways. So far, the overall response to our technology has been positive, and is growing, which I find very exciting. We also encourage any scientists who are finding their own applications for CLIC imaging to get in touch with us.

Sabrina Leslie is an assistant professor in the Department of Physics at McGill University Montreal, Canada.

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The CLIC imaging step-by-step process

1. *Flow chamber is assembled* using two glass coverslips separated by a custom adhesive spacer, with a thickness of between 10 and 100 μm . This is mounted within the CLIC device, where it is held tight and sealed.
2. *The sample is loaded* using a pipette and then air is used to push the liquid from the reservoir into the flow chamber. Usually, the imaging buffer is inserted before the sample; this creates a good environment for biomolecules and minimizes nonspecific adsorption.
3. *Imaging chamber geometry is formed* by reshaping the planar flow cell into a thin volume suitable for imaging. A convex push-down lens is lowered onto the top of the flow chamber, gradually bringing it into contact with the bottom surface. This creates a graduated chamber. The bottom surface can also contain embedded nanostructures designed to manipulate the shape of molecules once they are squeezed into the chamber.
4. *Imaging is performed* by acquiring high-resolution fluorescence images, usually at a series of locations within the chamber, thereby allowing the user to optimize image settings.

The Google Genome

The tech giant's newest "moonshot" aims to create a complete genomic picture of the healthy human being

By Michael Schubert

With their newest project, the Baseline Study, Google is positioning itself as a key player in the world of healthcare Big Data. The study is a part of Google[x]'s life sciences division and aims to build a complete database of the human genome. If the Baseline Study is successful, it may yield not only the world's largest and most detailed genome database, but also something no one else has yet attempted – a gene-by-gene picture of a healthy human being.

The study intends to take a proactive stance against disease by creating a genomic definition of human health. This could prove particularly valuable for pathologists, because reliable databases of disease-related genetic variations

are needed to effectively design, carry out and interpret laboratory tests – and, more than ever, we need to be able to extrapolate from the results of those tests to inform patient treatment decisions going forward.

You might be wondering why this is big news, given that genomic databases already exist. Well, Google has several reasons to feel smug about this latest undertaking. First, current databases are built on limited populations – many genetic variants and biomarkers are detected only in patients with established disease – so their effectiveness in disease prediction and early-stage detection so far has had mixed results. Second, existing databases are assembled largely to support research, rather than clinical applications, so they're not standardized and can be difficult to use in translational settings. Third, it's very important that these large, complicated databases are well-indexed, searchable and standardized – and no one is in a better position than Google to deliver organized, accessible data. Google is claiming that its database will establish a set of baseline genetic markers for good health, as well as helping to identify and catalog new biomarkers that can be used to improve laboratory testing and treatment design.

How do they plan to do it?

The team of around 100 biomedical scientists is being headed by Andrew Conrad, former head of the National Genetics Institute and developer of a high-volume, low-cost HIV test for blood-plasma donations (1), and Vik Bajaj, an expert and innovator in using nuclear magnetic resonance (NMR) for early disease detection (2). They'll be teaming up with Stanford and Duke Universities and members of the research elite – people who are actively involved in study design and data analysis and whose schools' Institutional Review Boards (IRBs) are responsible for approving the

experimental process.

Genetic and molecular information is already being collected anonymously from 175 people in a pilot project started this summer (3). Testing includes the collection of bodily fluids to create a tissue sample repository as well as to sequence participants' DNA; information is also gathered on family genetic histories and on physiological traits like heart rate and metabolism. Clinical researchers will first collate and anonymize the data, then compare it with study participants' age, lifestyle, habits and other physical factors (4). Expected to scale up to about 400 participants by the end of the year, the study is being assisted by new technology, like Illumina's HiSeqX Ten, to facilitate low-cost genomic sequencing (5). It's also likely that Baseline will incorporate genomic data collected by 23andMe, Inc., a personal genomics company providing direct-to-consumer testing, as well as by Calico, a Google startup aimed at extending longevity by, among other things, analyzing the genomes of healthy centenarians (6).

The good, the bad

But despite its thoroughness, the Baseline Study still has limitations – for instance, its ability to examine the complex interactions of physical, environmental and behavioral traits is limited, and the study isn't geared toward short-term gain; progress will be incremental at first, and the ultimate payoff is many years away.

That isn't to say that we shouldn't be excited about it though. Even in its early stages, the study will make more human genome data available for research, expanding on the assemblies in existing databases. It will also focus explicitly on understanding the genomic characteristics of healthy humans – an area that isn't currently well-studied. As the database grows, it will allow scientists to compare and contrast the genomes of healthy and disease states, which should

At a Glance

- A new pilot study from Google[x] Life Sciences is collecting information to build a database of healthy human genomes
- The Baseline Study will record in-depth genomic and clinical laboratory data to identify new biomarkers for disease predilection or early onset
- The project raises concerns about ethics, privacy and commercial use of the data that Google is working hard to forestall
- Though controversial, if successful, this study could help us make the big leap from an era of treatment into one of prevention

hopefully lead to the discovery of new biomarkers. Because at the moment, biomarkers are identified using patient populations with established disease, known markers are typically indicative of ongoing or late-stage conditions. The Google[x] project hopes to locate new biomarkers that signal either a predilection for, or an early stage of disease, which would help pathologists and clinicians predict the onset of diseases far earlier than is currently possible.

Ultimately, the goal of the Baseline Study is to move medical science from a focus on treatment to a focus on prevention.

Should we be cynical?

A study with the scope and ambition of Baseline doesn't come without reservations, though. Questions have been raised about the ethics of this research – how can the participants be guaranteed anonymity given the data to be collected for the study? Will the information ever be used for commercial purposes? Who will have access to the genome database?

Google is doing its best to forestall doubts about the study design by working with medical clinics and academic institutions. Health Insurance Portability and Accountability Act (HIPAA) regulations and the conditions of IRB approval impose ethical restrictions on use of the information – including a stipulation that it may never be mined for commercial purposes or connected to Google's consumer products, despite company cofounder Larry Page's expression of regret at the loss of these "really great possibilities" (5,6). It's unclear exactly what uses these restrictions will and will not permit, but the hope is that the data will be used to further research and development for patient – rather than commercial benefit. Though the information will not be hosted publicly, it may be shared with academic researchers if their studies are IRB-approved. If

Baseline's data is merged with Calico's, though, it could then also be shared with scientists in industry, for instance to accelerate the development of gene-targeted therapies in pharmaceutical research. Google claims that its goal for the genome study is to improve scientists' and doctors' understanding of human health and disease, but only time will tell what actual uses are found for the new information.

“The hope is that the data will be used to further research and development for the patient – rather than commercial benefit.”

The involvement of data from outside sources complicates matters, too; the ability to cross-reference participants' genomes with databases maintained by Calico, 23andMe and others could lead to a loss of anonymity for those whose genetic information is stored in more than one place (7). Additionally, both affiliated companies have close ties to Google: Calico is an independent subsidiary of the company, whereas 23andMe's CEO, Anne Wojcicki, is married to Google[x] head Sergey Brin. Perhaps because of this list of concerns, Google has been somewhat closemouthed about the Baseline Study to date, meaning that much of the available information comes from only a few sources.

Nevertheless, despite these potential reservations, the study is proceeding as expected – the pilot project has begun, and if it's successful, Google expects to

add thousands of genetic profiles over time. Research will be conducted on a long-term basis, which may mean that participants are followed for as much as 10 years or more. As genomes are cataloged and information added to the database, Google hopes that the study will yield the most comprehensive picture of health and disease to date.

One thing is certain – with the Baseline Study, for the first time, pathologists involved in both research and treatment will be able to examine the complete, healthy human genome, which could help you to spot the early signs of disease or even to predict and prevent issues before they take hold. And, most importantly, as a pathologist, this could allow you to play an ever-larger role in disease monitoring and treatment. If Google delivers on its lofty ambitions, pathology and medicine could soon be moving from an era of “catch-up” treatment into an era of prevention and health optimization. Though much of what Google does is usually shrouded in a veil of secrecy, I think they'll be shouting about it if they pull this off. Watch this space.

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46-48

Collaborate or Cave in
Arnaud Roth talks about the increasing role of pathologists in treatment monitoring and decision-making, the advancement of new techniques like liquid biopsy, and the need for constantly-evolving collaboration between pathologists and clinicians in patient care.

Collaborate or Cave in?

Pathologists' involvement in patient care is changing – are you keeping up?

By Arnaud Roth

The profession of pathologist is an ever-evolving one, and has come far from the early pioneers who studied the nature and origin of disease. Today, the pathologist's list of responsibilities is far longer, and it continues to grow. Disease screening and diagnosis are now an integral part of that list, but with knowledge of diseases (their genetics, various subclasses and mutations) increasing by the day, if pathologists aren't already actively involved in treatment decision-making, monitoring and therapeutic tailoring, they soon will be. This is no simple task, but things are changing drastically, and I believe pathologists need to extend their traditional lab work to partner with other disciplines and fully enter this era of treatment evolution.

At a Glance

- *With huge advances in the molecular understanding of disease and treatment, the role of the pathologist is changing rapidly*
- *Research has provided compelling reasons for pathologists' involvement in ongoing treatment decision-making and monitoring*
- *Through assessing levels of circulating tumor DNA, liquid biopsy is showing real promise in tracking treatment success and disease progression*
- *Pathologists need to take note of this and similar technological evolutions to become full partners in treatment monitoring*

Don't get me wrong, I know that involvement in treatment determination is not a new challenge, but with the advent of detailed molecular screening and advanced disease characterization, the nature of pathologists' participation is changing. Tools like genetic and genomic profiling can now assist in selecting the most promising therapies for patients and eliminating inappropriate options. Though this is already happening, as an oncologist, I urge pathologists to collaborate even more with other disciplines. Now, more than ever, we need you. Certainly as an oncologist, I believe your knowledge and skills are critical in securing the most optimum outcome for patients. The situations listed below should help you to appreciate this at its best.

Targeting, testing, treating

Let's look at some examples of how our changing knowledge has impacted the traditional role of the pathologist. A good place to start would be the well-known EGFR signaling pathway in colorectal cancer. In many cancers of the colon, EGFR phosphorylation activates Ras, which stimulates Raf and the MAP kinase pathway to enhance cell proliferation and tumor invasion. Treating patients with an EGFR antibody blocks the pathway and induces a tumor response; but, in cases where the *KRAS* or *NRAS* genes are mutated – so that the protein can act without EGFR stimulation – an upstream blockage of the pathway will not yield any tumor response (1). So *KRAS-NRAS* is a useful negative predictive marker; patients who will respond poorly to treatment can be excluded from antibody therapy up front, and this will increase the percentage of positive responses in treated patients. It will also prevent the cost and toxicity of unnecessary therapy for others.

Pathologists also have an integral role in maximizing the effectiveness

of targeted drugs and accelerating the development of new therapies by improving understanding of disease. Molecular classifications of disease allow us to distinguish between effective and ineffective treatments and make recommendations based on tumor gene profiles. In non-small-cell lung cancer (NSCLC), for instance, tumors that were previously separated into only three categories based on morphology and phenotype, can now be classified much more powerfully using genetic mutations. One recent study of crizotinib as a second-line treatment for NSCLC yielded a 57 percent response rate (2). This is almost unheard of for such a treatment and it's thanks to the pre-screening of patients for the *EML4-ALK* translocation, which is a specific target of that drug and allows it to take effect. Numbers like this not only demonstrate to us the benefit of collaborating with pathologists to improve treatment performance, but also support drug development.

Parallel pros

There is also a new push toward parallel trial screening, a system in which patients undergo a single pre-screening and consent process for possible admission to multiple clinical trials, rather than repeated testing for each individual protocol (see "A Pioneering Approach to Trial Screening" Sidebar). By participating in more efficient screening strategies, we can build a better bridge between basic and clinical sciences, enabling laboratory studies to be more easily and efficiently translated into patient-based research. Avoiding repeated testing saves both time and money, as the cost for a single pre-screening is shared by several industrial partners, and may improve enrolment and optimize results by exposing a more diverse range of patients to many potential trial options.

A major research benefit of the parallel screening system is that all samples undergo the same handling, storage and quality assurance procedures, so that the collected data are more homogeneous and can be used for comparative evaluations, secondary “cross-trial” investigations and meta-analysis. Here, too, I believe the input of pathologists is key to developing the best and most efficient methods for patient sample screening, verification and preservation.

Mind the monitoring gap

The importance of collaboration between pathologists and clinicians does not end with screening and treatment determination, though. I see a vital new role for pathologists in ongoing patient monitoring and treatment modulation. Diseases are never at rest; they change throughout the treatment process, so patient therapies must change as well – and now, for the first time, there is a place for pathology in this process.

Cancerous tumors, for example, develop heterogeneity during treatment. This may occur as a natural consequence of metastasis, or it can be a result of treatment. Differential sensitivity to therapeutic agents can eliminate some tumor cells and allow others with different genetic characteristics to flourish; in some cases, even the treatment itself can induce mutagenesis. Clearly, such a significant issue must be addressed, it would, however, be impossible to biopsy every single metastasis in every patient. But without this ability, how can we investigate the changing nature of an individual patient’s disease?

The answer lies in new, efficient and less invasive technologies, and I believe that liquid biopsies could be the key. Already in development as a prognostic survival tool and early-identification technique, liquid biopsy technology could potentially be used to monitor patient treatment by screening for new

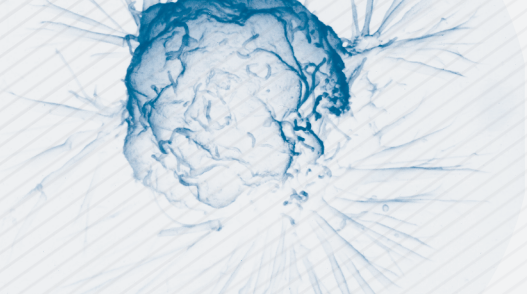


mutations that arise during therapy. This screening is conducted on the DNA shed by tumors into the bloodstream, known as circulating cell-free DNA (cfDNA) (3,4). According to research, this cfDNA can be detected in the blood of over 50 percent of patients with localized tumors and over 80 percent of those presenting with metastatic disease (5). In the same study of 24 colorectal cancer patients, who did not initially present with any *KRAS* mutation and who were treated successfully with anti-EGFR therapy before progressing, 23 developed mutations that were revealed by liquid biopsy. These mutations coincided with patients’ development of resistance to the treatment (4). Another very recent study reports on the detection of *KRAS* and *BRAF* mutations in cfDNA in 95 patients, comparing assessment by liquid biopsy with traditional assessment on classic pathologic material (6). With 100 percent specificity and sensitivity for the *BRAF* V600E mutation and a concordance value of 96 percent with the results obtained from tumor material, the study authors came to a compelling conclusion: “cfDNA analysis could advantageously replace tumor-section analysis and expand the scope

“cfDNA analysis could advantageously replace tumor-section analysis and expand the scope of personalized medicine for patients with cancer.”

of personalized medicine for patients with cancer.”

Liquid biopsies could also potentially evaluate tumor burden and detect residual tumor cells after surgery, in addition to resistance monitoring and the identification of specific mutations. For the latter, liquid biopsy is actually the only appropriate method currently available to us, considering vast tumor heterogeneity and the impossibility of taking biopsies of every single lesion in metastatic disease!



A Pioneering Approach to Trial Screening

What? SPECTAcolor, or Screening Platform for Efficient Clinical Trial Access for patients with pathologically confirmed metastatic colorectal cancer (CRC), is an initiative led by the European Organization for Research and Treatment of Cancer (EORTC).

Why? SPECTAcolor is a pioneering clinical research model that hopes to revolutionize the approach to cancer research and treatment. Instead of screening each patient for each available trial separately, patients are prescreened once and then invited to participate in trials with drugs selected according to their prescreened profile. The idea is to give these patients the best chance of accessing the most suitable clinical trials with new, molecularly defined approaches.

When? SPECTAcolor prescreening began in October 2013 and is currently increasing its accrual speed, while trials with new targeted drugs (antibodies, tyrosine kinase inhibitors, etc.) are in preparation.

Who? Supported by a network of 29 clinical centers in 10 countries, the ultimate goal of this initiative is to enable better access to new treatment options. Between 600 and 1,000 patients with advanced CRC are expected to enroll each year. SPECTAcolor is supported by the EORTC Charitable Trust and the corporate social responsibility program of Alliance Boots. It is also actively supported by the European Society of Pathology (ESP) and the Sanger Institute.

Key achievements? As of 14 October 2014, 440 adult patients had already given their informed consent to be tested for mutations in CRC biomarkers. Next-generation sequencing is being used to identify genetic alterations that may intrinsically drive cancer cells and could therefore be targeted by new therapies.

Who should be taking responsibility?

With new technologies come new opportunities for pathologists, but it's important to proactively take the opportunities that are available. The liquid biopsy, for instance, is not a true biopsy but a blood draw, which means that responsibility for the technique is as yet unclaimed – will it lie with pathologists, with molecular biologists, or elsewhere? Each institution will need to make a call on this, but I would strongly encourage pathologists to get involved and continue building on the amazing work you already do. Collaborations with clinical researchers are on the rise and

should continue to increase as long as the power of prognostic and predictive markers remains an important part of the selection and administration of patient therapies. Now more than ever, pathologists are working at the interface of basic and clinical science, and their job is not that of the static diagnostician of years past, but a dynamic and integral participant in patient care. In a changing situation like this, then, pathologists can play an active part in redefining the role. I, for one, am looking forward to growing my partnerships with my pathologist colleagues – I truly believe this is the best option for both of our professions and, ultimately, should lead to the best outcome for our patients.

Arnaud Roth is head of unit physician at the digestive tumor unit, HUG, Geneva, Switzerland.

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"I would strongly encourage pathologists to get involved and continue building on the amazing work you already do."

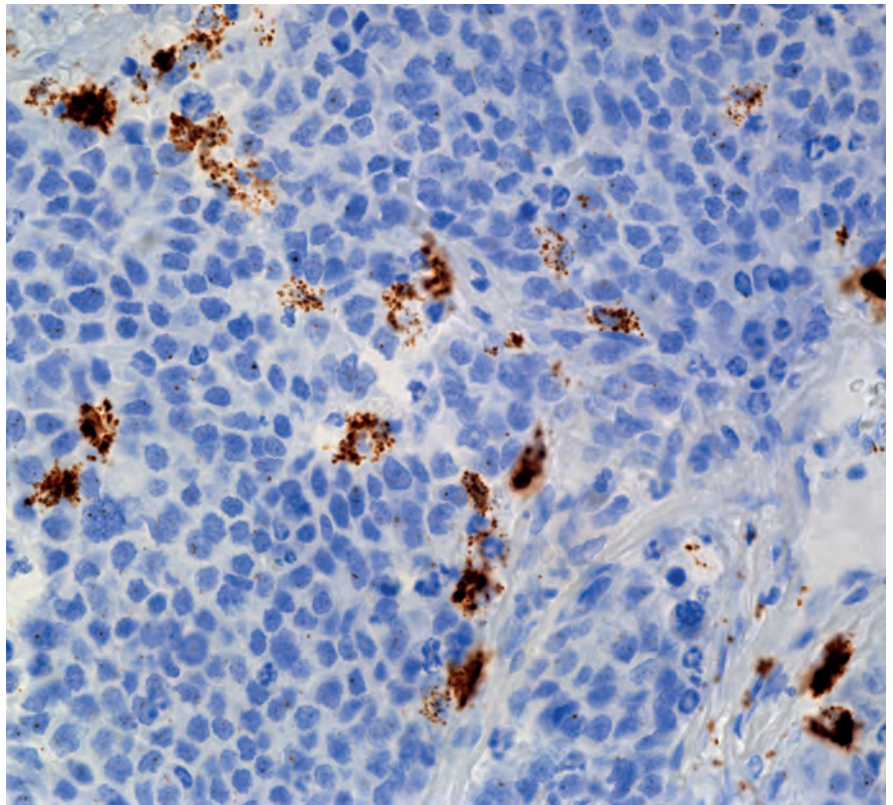
The RNA Revolution

A guide to RNA as a biomarker and its detection

Gene expression profiling yields many insights into the disease state, particularly in discovering those molecular indicators known as biomarkers. Indeed, the widespread application of transcriptomic techniques in cancer research over recent years has proven that, like protein, RNA is a rich source of clinically valuable biomarkers for diagnosis, prognosis and predicting therapeutic response. Although such approaches may identify many potential biomarkers, translating these discoveries into the clinic for routine measurement has traditionally been hindered by established analytical technologies. While it is commonplace to detect and visualize DNA and proteins in their native context within single cells, until now the best routine measurement tools for RNA have been those that detect and quantify RNA in solution, losing all morphological context. Times are changing, however, and the ‘RNA Revolution’ is here.

The intriguing molecule of RNA is no longer viewed as merely the ‘messenger’, especially with new classes of non-coding RNAs being discovered on a regular basis that have a hand in genetic regulatory control and a wide range of cellular activities. The discovery of this “new world” of RNA has sparked an unprecedented drive towards better tools to characterize the complexity of RNA – in terms of quantity, function and spatial distribution. In particular, pinpointing the localization of specific RNAs within cells and tissue architecture is an important factor in realizing its true potential as a biomarker.

Exploring how RNA presents an



Revealing the RNA expression signature of individual cells within the tissue architecture. The above image shows human breast cancer FFPE tissue probed for MMP9 mRNA expression using ACD's RNAscope® technology

ideal biomarker, especially in light of novel RNA analysis methodologies, the new whitepaper from Advanced Cell Diagnostics (ACD) will discuss:

- **The Biomarker:** What makes a valuable biomarker, and how a direct path from RNA biomarker discovery to the clinic is vital, avoiding the use of DNA or protein surrogates.
- **The Method:** A biomarker is only as good as its routine analysis methodology, but what constitutes the optimal biomarker method? Advantages and pitfalls of existing methods for routine biomarker analysis will also be discussed.
- **The Future:** How the utilization of RNA as a biomarker

is achieved through the latest RNA analysis methods, such as ACD's RNAscope®.

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Changing the Nature of the Game

Sitting Down With...

Robert Pierce, Chief Scientific Officer,
OncoSec, San Diego, CA, USA

What motivated your career in pathology? I knew all along that I wanted to do mechanistic research. I was in medical school thinking, “What’s my quickest route back into the lab?” My mentors were doing lab-based work and patient care, so I asked, “How can I do that?” They said, “Don’t. Go into pathology.”

Although choosing pathology meant I gave up seeing patients, I never gave up interacting – I see the doctors and their patients as “my patients,” which is just as rewarding.

I arrived at the University of Rochester fairly pluripotent as a pathologist; I could have developed in a number of different ways. I wanted to join a group I could learn a lot from, so I became an immunologist. Immunologists and pathologists speak different languages, and by having a foot in each world, I was able to translate things. It set me on the path of understanding what I call immune subversion – that is, how tumors block the immune system.

Why the move to pharma?

Personal reasons took me to the Bay Area and, out of the blue, a fantastic job emerged at DNAX, which is legendary in immunology. Schering-Plough, amazingly, funded this research institute and never put much pressure on drug development – so for almost 20 years, it produced great science. When they decided to make DNAX a drug discovery enterprise, they brought in John Curnutte, a strong proponent of translational medicine. He felt they needed pathology to understand tissue architecture and cellular organization. I took the job in a heartbeat and never regretted moving into pharma.

What was the story of PD-1?

The PD-1 program came to DNAX when we acquired Organon, who had planned to move forward in human development without “companion” mouse studies. This was a bold approach. Although it was clear from the literature that anti-

PD-1 was a strong candidate molecule for immuno-oncology, Schering-Plough were more conservative and tasked us with building the mouse surrogate program. When Merck and Schering-Plough merged, the PD-1 program was deprioritized until Bristol-Myers Squibb published their candidate’s Phase I data. Then it was like Lazarus – raised from the dead! It’s amazing that Merck still got first approval in the US. I think they benefited from going after ipilimumab-refractory melanoma patients as their main indication; that triggered the breakthrough therapy designation.

It’s exciting that we have such a good idea of who responds to anti-PD-1 and who doesn’t. That’s critical to why PD-1 development is going so fast – in large part, we understand the mechanism of action. My first ah-ha! moment came when I saw tumors IHC-stained with PD-1 and PD-L1. Patients who respond to anti-PD-1 have cytotoxic T cells in their tumors; you only need immunology 101 to say, “Wow! The T cell coming in is generating a cytokine which upregulates PD-L1 to shut off the T cells.” It’s a homeostatic mechanism we evolved – every immune reaction contains its own brakes, and tumors hijack them.

It took a long time to convince the scientific community that immunotherapy would work – over 100 years of chasing Dr Coley’s vision of harnessing immune responses to treat tumors. If you think about where we are with anti-PD-1 today, where might we be if this transformation had happened earlier?

What new treatment strategies hold most potential?

The future is in combination immunotherapies – I predict they’ll become the backbone in many indications. We just need to figure out how to use current targeted agents and chemotherapies judiciously.

Immunotherapies are not innocuous.

PD-1’s safety profile is pretty good, but when we combine therapies, we’ll have to be sensitive to synergistic immunotoxicity. That’s a benefit of a multimodal therapeutic paradigm that includes intratumoral therapy – we can harness treatment efficacy without systemic exposure and toxicity.

I think the most important question we need to answer in immuno-oncology now is: how do you make PD-1 non-responders into responders? That’s our current strategy at OncoSec, and our primary candidate is intratumoral delivery of IL-12.

Some of the luminaries in the literature today are beginning to talk about intratumoral therapy. I think we’ll see these therapies come of age in the next decade; Amgen’s T-VEC, a virus that encodes GM-CSF, has met with some success, but there are many different ways you can approach it and I think others will follow suit.

I also think we’ll come back to DNA damage and repair. Tumors depend on their ability to mutate but this can be their Achilles heel; they become dependent on DNA checkpoints, unlike normal cells, so we have a therapeutic leverage point. I think we’ll see a resurgence of this as a field to explore.

How do you see the role of pathologists evolving?

It’s going to be increasingly important for pathologists to perform and interpret companion diagnostic tests in clinical labs. On the research side, we need pathologists to further our understanding of interactions within tumors, discovering potential mechanisms and research angles. That’s where I’ve spent my entire career. The technology is coming, but you still need the brain behind the scope.

I think we really are at this transformative moment in oncology. We’re no longer just trying to out-poison the tumor; we’re changing the nature of the game. I think everyone should be as excited as I am – it’s a brilliant time to be in this field!



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