the Translational Scientist

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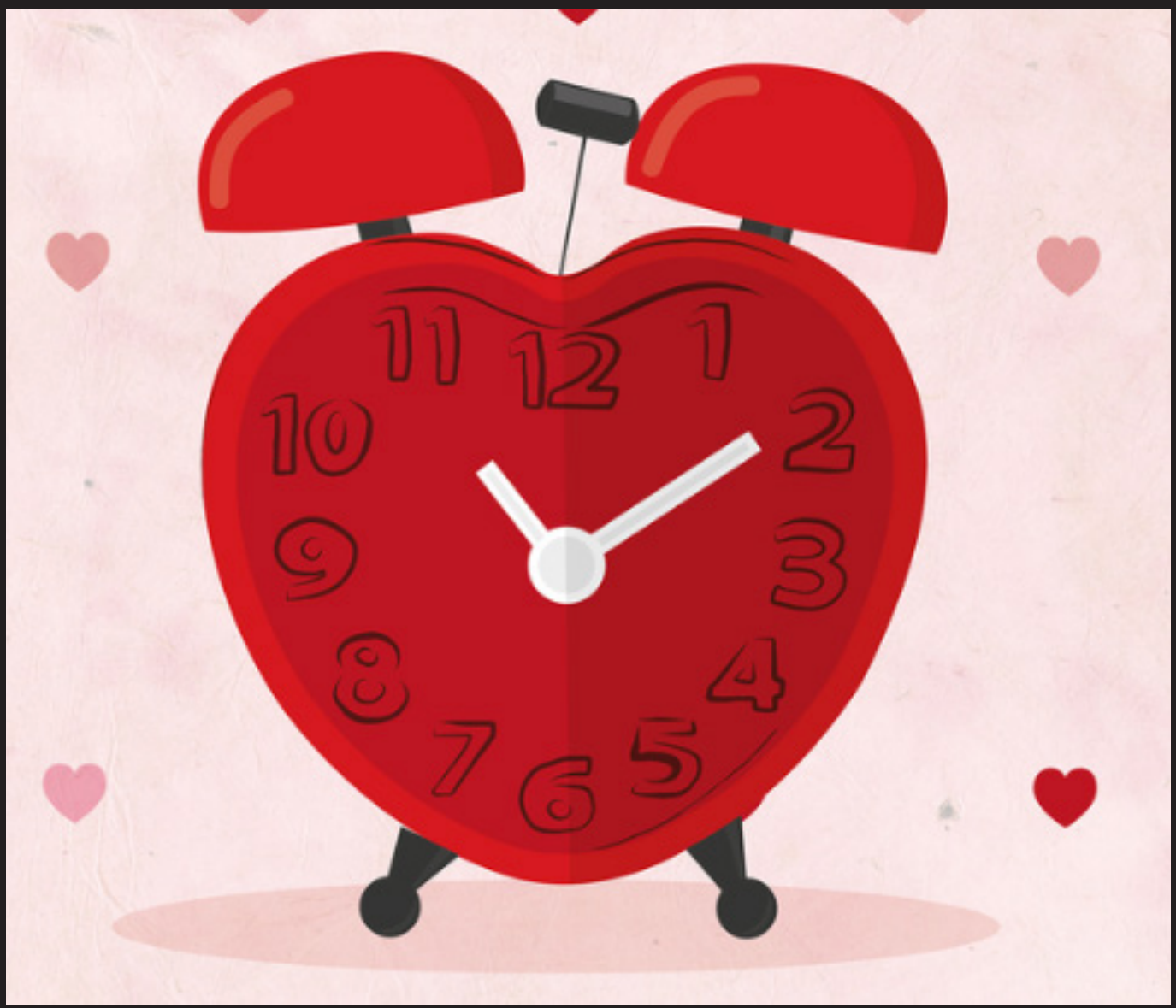


Upfront

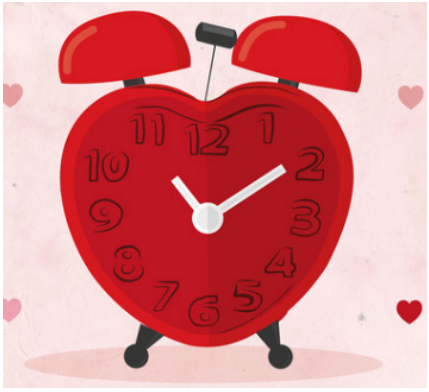
A Stitch in Time

Recent research finds that it may be best to have heart surgery after lunch

November 2017

Circadian rhythm – and its importance to human health – has received a lot of press lately. Not least because of last month's announcement that the 108th Nobel Prize in physiology or medicine has been awarded to a trio of scientists who discovered the molecular mechanisms controlling it (1). Although it is becoming increasingly clear that we should pay more attention to our biological clocks, the ways in which they influence human health remain somewhat mysterious. Now, researchers at the University of Lille, France, have found that heart surgery performed in the afternoon appears to result in better outcomes than surgery performed in the morning. Notably, the team discounted procedures between 12 and 6am in an attempt to exclude the potential effects of tired staff with reduced efficiency. Previous research has found that the risk of heart attack is higher in the morning, with the heart working better in the afternoon (reviewed in (2)).

The researchers looked at patients who underwent scheduled aortic valve replacement between 2009 and 2015. Of the 298 patients operated on in the morning, 54 had a major adverse cardiac event, compared with 28 of the 298 patients operated on in the afternoon – one less major adverse event for every 11 patients (3).



But why? Transcriptomic analyses of heart muscle biopsies from both the morning and afternoon patients showed that the expression of some 287 genes differed depending on the time of day, which appears to be linked to the heart tissue's tolerance for hypoxia–reoxygenation events. One gene that showed great variation depending on the time of day (with the highest levels in the morning) was Rev-Erbα. To investigate further, the team looked at the effect of Rev-Erbα knockout and inhibition in mouse hearts; myocardial hypoxia–reoxygenation tolerance was improved in both cases.

The team notes the need for further validation, but suggests several potential avenues to improve patient outcomes. Time of surgery could be considered – although this could prove impractical in some settings (for example, when organ donors are involved). Another option could be to develop novel compounds to effectively and safely inhibit Rev-Erbα to "hack" the biological clock.

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Trust Me, I'm a Doctor

A lack of faith in the healthcare system could be causing non-adherence in cancer patients – and, in turn, affecting cancer recurrence

November 2017

As many as a third of US patients with breast cancer could be avoiding treatments recommended by their doctors, because of a mistrust in healthcare institutions, according to a recent study (1).

A survey of 2,754 women from Florida and Pennsylvania followed over two years found that 30.2 percent reported either not beginning, or not continuing with, at least one recommended adjuvant therapy following breast cancer surgery. Lead author Lorraine Dean was not entirely shocked, noting in a press release (2): "While it is surprising in general that nearly one-third of patients are not following up with recommended adjuvant treatment, some earlier, more localized studies have reported even higher discordance rates, and it's possible that our own figures would have been higher if we had followed patients for more than two years."

Non-adherence to treatment was also linked to higher incomes, an earlier cancer stage, and living in Florida (a state in which insurance laws cover a second opinion following diagnosis). The findings also suggested that non-adherence wasn't associated with how much a patient trusted their individual doctor but, rather, a mistrust of the healthcare system as a whole.

Perhaps the most important finding was the effect that non-adherence had on health outcomes: patients who reported non-adherence to parts of their treatment were 40 percent more likely to see their cancer recur within the two year period covered by the study.

The study authors suggest that healthcare systems might look to the strategies of other large institutions to tackle the mistrust some patients feel. Said Dean, "If ordinary businesses can learn to increase trust in their brands, why not the same with health care institutions?"

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Ultrasound on the Brain

Creating a ceramic "window" in the skull could provide better access to the brain for diagnosis and treatment of neurological conditions

November 2017

Applying light and sound to the brain can have important diagnostic and therapeutic benefits. But there's one small problem: the skull. Ultrasound is a promising potential therapy for neurological conditions, such as Parkinson's and Alzheimer's – but the cranium reflects around half of the energy applied and absorbs most of the rest, rendering the approach ineffective.

A collaboration between researchers in the US and Mexico has hit upon a possible solution: a ceramic cranial implant, which is able to transmit ultrasound and light to the brain and has already proven its potential in bovine skull bone (1). We spoke to Guillermo Aguilar, Professor and Chair of the Department of Mechanical Engineering at the University of California Riverside, about developing the implant.

How did you get involved in this project?

I've always liked engineering, but I was also curious about biology and medicine. I chose to study mechanical engineering and, once I finished my PhD, I had the opportunity to work at the Beckman Laser Institute at UC Irvine, where I learned a lot about biomedical optics and lasers. This latest research was possible thanks to the formal and informal interactions I established with colleagues there who are experts in medicine, materials science and engineering, optics, and biology.

What inspired the approach?

It all started when my colleague and co-author Javier Garay showed me that he and his group were able to synthesize a material known as yttria-stabilized zirconia (YSZ) in a way that produced a macroscopic transparent disc (see Figure 1). He and I started by characterizing its optical properties, and I became very intrigued by it.

Having a transparent biocompatible material just millimeters in thickness that was as tough as bone gave us the idea of developing implants to

replace bone in anatomical locations where transmitting light would be advantageous. And that's how the concept of an optical "window to the brain" started.

We also partnered with another colleague in Mexico, Santiago Camacho-Lopez, who realized we could use ultrashort laser pulses to write waveguides (conduits to light) on YSZ implants and further facilitate light transmission.

Our latest work was all about extending the capability of this discovery, as we recognized that it is also possible to transmit ultrasound, given the much lower porosity the material has relative to a cranium of the same thickness.

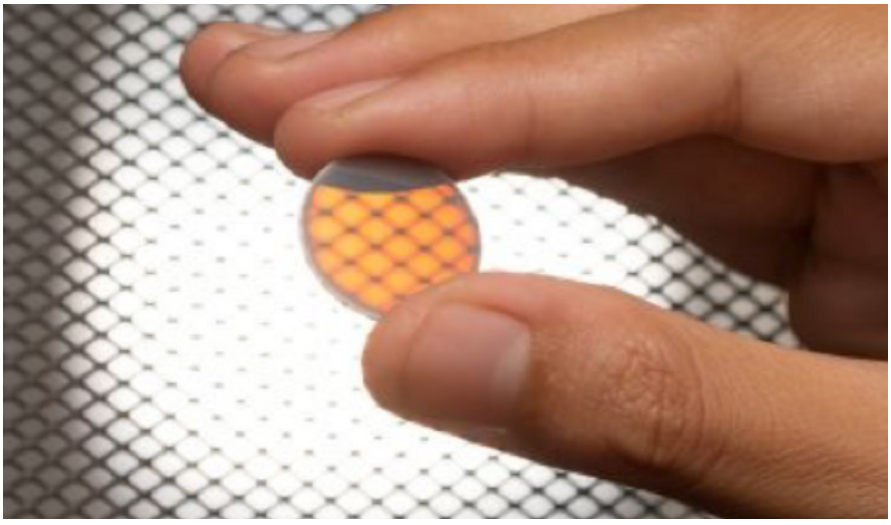

Figure 1. The ceramic skull implant made of yttria-stabilized zirconia.

It sounds like an invasive method...

It is invasive, but it's important to note that our hope is that this material could be used for patients who will already have to undergo a craniotomy, and a portion of their skull will have to be replaced anyway. Such implants could help patients avoid future invasive procedures by having a semi or totally permanent cranial implant that provides optical and ultrasound access to their neurologist, for either diagnostic or therapeutic purposes.

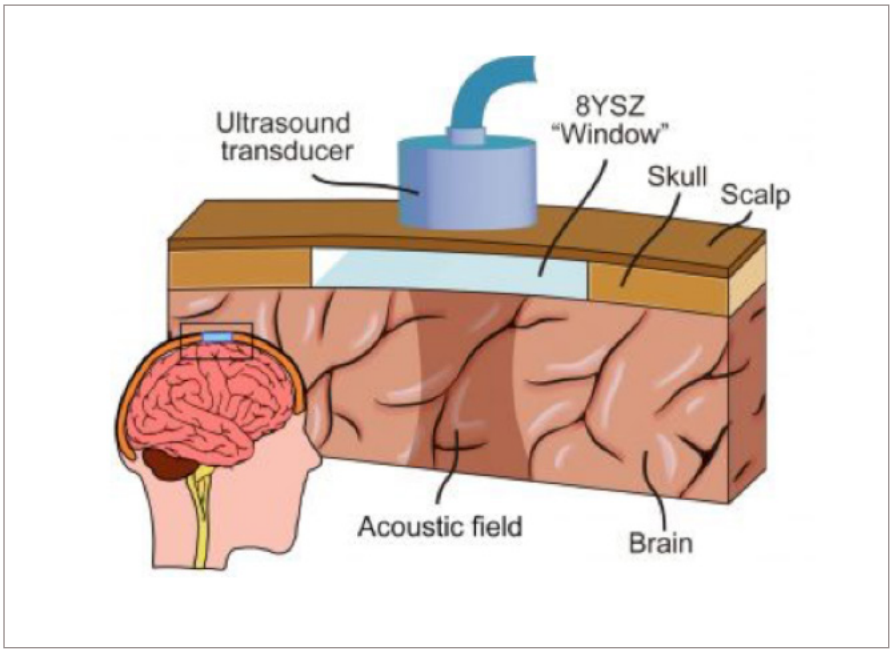

Figure 2. The method through which a ceramic cranial implant could allow doctors to deliver ultrasound treatments for brain

How important was collaboration to your success?

The work was very much a multi-disciplinary and multi-investigator effort! Mario Gutierrez and Elias Penilla were the ones who led the execution of the work and the analysis. Synthesizing, polishing and preparing the samples for the US tests was yet another challenge – we didn't have all the materials we needed in Javier Garay's and my laboratory, so some of the experiments were carried out in Mexico City. Without the contribution of all the authors, this work would have not been possible.

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Database Discrimination?

Precision medicine often relies on population databases – but this may render it less effective for non-European patients

November 2017

When is "precision medicine" not precision medicine? When it's used for patients of non-European descent, a new study from the University of Southern California reveals (1). Ideally, genetic mutations in cancer cells are highlighted in a comparison with normal tissue – but, in many cases, there's no normal tissue sample available. Genetic information from population databases can serve as a stand-in, but there's a catch: most of the genomes included in such databases come from individuals of European descent. What does that mean? Variants that are harmless in a given patient may stand out as potentially cancer-causing, simply because the population database lacks the information to identify them as benign.

"A physician could give a treatment that is toxic, ineffective or worse – unnecessarily," says David Craig, principal investigator and co-director of the Institute of Translational Genomics at USC's Keck School of Medicine. "This would be the case in the context of clinical decision-making based on tumor sequencing only." If reported mutations are interpreted as cancer-driving when they are, in fact, inherited and most likely benign, patients might undergo more intensive treatment than necessary, or might not receive the treatment best-suited to their particular disease profile.

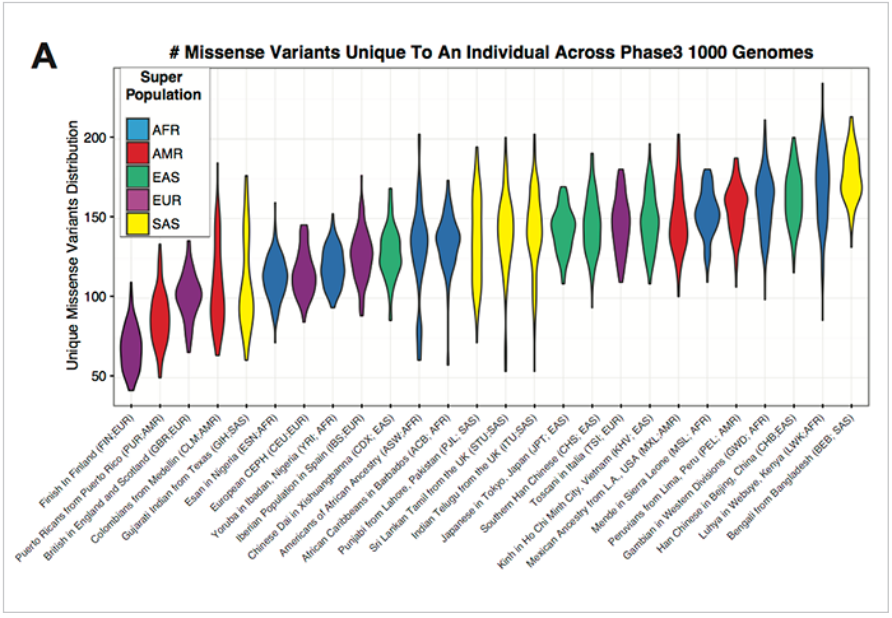

Figure 1. The number of unique missense variants in individual population subtypes. These variants are poorly represented in genomic databases and can lead to false positive results on genomic tests.

"The amount of incorrect inherited information within a precision medicine cancer genomics report is very important, as that speaks towards the precision of the test," says Craig. "Precision is a part of precision medicine. In research studies attempting to discover new driver mutations and link them to therapy, imprecision lowers the overall chance that a study will yield meaningful new insights."

The study shows that precision is ancestry-dependent. In some populations, particularly those of European ancestry, the precision is good. In others, it drops precipitously. But the report doesn't stop there; it goes on to demonstrate analytical approaches to reducing imprecision. How? By deconvoluting normal and tumor tissues from the same sample, taking advantage of the fact that most specimens sent to pathology are not pure tumor to allow comparisons between the two.

So why don't hospitals routinely collect healthy tissue from cancer patients? Craig says there are many reasons. "Some that are really important, but not frequently discussed, are due to the regulatory uncertainty of explicitly collecting normal specimens, and how it impacts the ability of the physician to act quickly to identify the best therapy."

In the United States, for example, some state laws require additional genetic counseling prior to conducting tests involving inherited information (2). Regulation around germline testing could add uncertainty to the process and, according to Craig, many view this uncertainty as counterproductive. "Think of it from the perspective of an oncologist working with their patient. The ordering physician may

be well aware of different cancer treatments, their effectiveness and how a patient may respond. However, there may be additional laws that require the patient to have genetic counseling before the test is ordered, as there may be incidental findings about family members. For many physicians, introducing regulatory uncertainty about what steps must come before even ordering the test is a major concern."

But understanding the nature of the problem also suggests a solution. "Our approach identifies ways to separate tumor and normal by recognizing most solid tumors are mixtures. We can use tools to computationally indicate which mutations are from the tumor and which are inherited. We have made those tools available in an open framework (github.com/tgen/LumosVar) that allows the approaches and concepts to be adapted, integrated and validated within future clinical tests."

LumosVar is not currently a clinical test. It is a research tool and algorithm that its creators hope will lead others to test and validate approaches to deconvolute mixtures. "We hope it enables sequencing of archival samples from diverse populations when requiring a normal means losing diversity," says Craig. "In our studies, we have seen examples where access to archival tumor specimens is available for African and Asian populations, and we want to make sure that we can maximize the utility of these samples." It's vital that our understanding of genetics incorporate as many different populations as possible – because what begins as research on an underserved population may eventually lead to better care for those patients.

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Understanding Pancreatic Cancer Prognosis

Mutations in four main genes influence survival rates of pancreatic adenocarcinoma patients

November 2017

Despite increased research efforts in recent years, survival rates for pancreatic cancer remain relatively low, with only 3.3 percent of adults surviving for five years with the disease (1), and researchers around the globe are working hard on new directions to aid in diagnosis, prognosis and treatment.

In a recent publication in JAMA Oncology, a group of US researchers studied 356 patients with resected pancreatic adenocarcinoma, and identified changes in four main driver genes that were associated with outcomes following surgery. Protein expression and DNA alterations for KRAS, CDKN2A, SMAD4, and TP53 were analyzed using immunohistochemistry and next generation sequencing. The research team found that patients with KRAS mutant tumors had worse disease-free and overall survival than patients with KRAS wild-type tumors. In particular, patients with KRAS G12D mutations had poorer outcomes, with a median survival of 19.7 months (2). The number of mutations present also influenced survival (see Table 1).

Number of mutations	Five year survival (%)
0 to 2	18.4
3	14.1
4	8.2

Table 1. Number of altered genes versus five year survival.

The authors hope that a better understanding of the molecular changes affecting patient outcomes could improve treatment approaches, and two of the collaborators – David Linehan and Brian Wolpin – are partnering on a further project investigating new therapies and biomarkers for use in metastatic pancreatic cancer (3).

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Benchmarking the Human Microbiome

What does analysis of the last five years of the microbiome literature tell us about the priorities and progress of the field?

By Roisin McGuigan

November 2017

Alexander Maue and Randi Lundberg discuss the increasing importance of effective translational studies on the human microbiome here [link to "exploring the microbiome – with mice"], and note that research in this area has greatly increased in recent years.

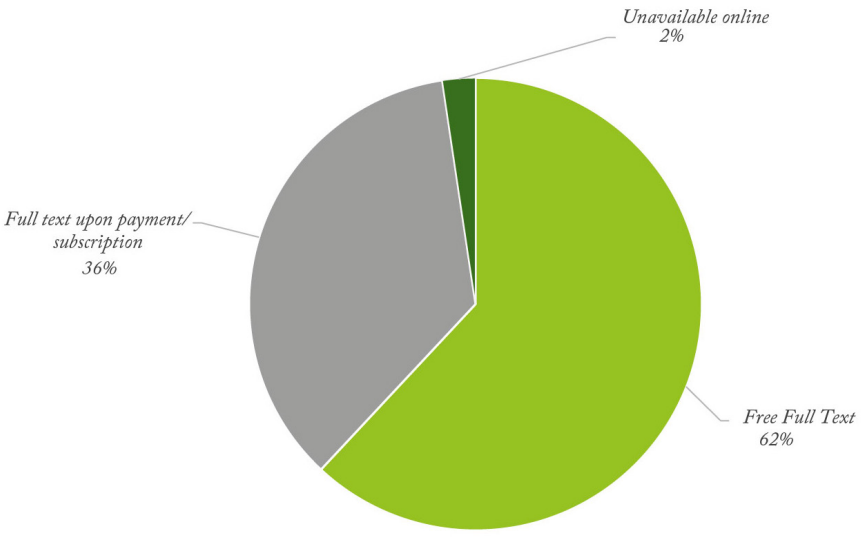
The human microbiome (the collection of all microorganisms found on and in the human body) has been increasingly implicated in both health and disease – but full characterization is challenging – as is elucidating its potential role in a wide range of conditions. To provide insight into the past and likely direction of the field, we applied a series of metrics to the last five years of published literature.

We asked:

- What are the major topics for the field?
- Which publications have the greatest impact?
- How is the knowledge available online?
- Who are the most prolific authors?

PubMed was searched for "human microbiome" (for a clinical focus), with results limited to the last five years. The data were analyzed in Microsoft Excel 2013.

Fee or Free?



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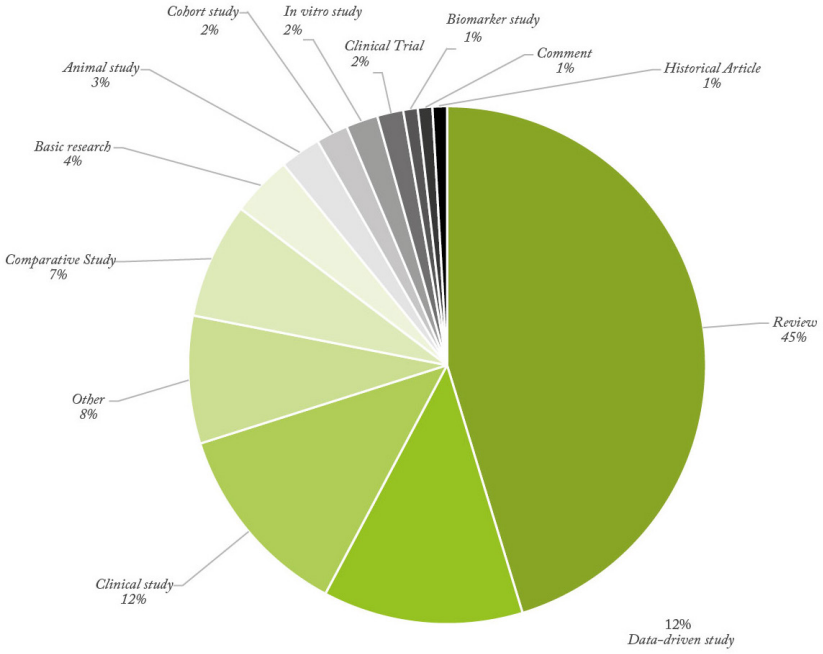
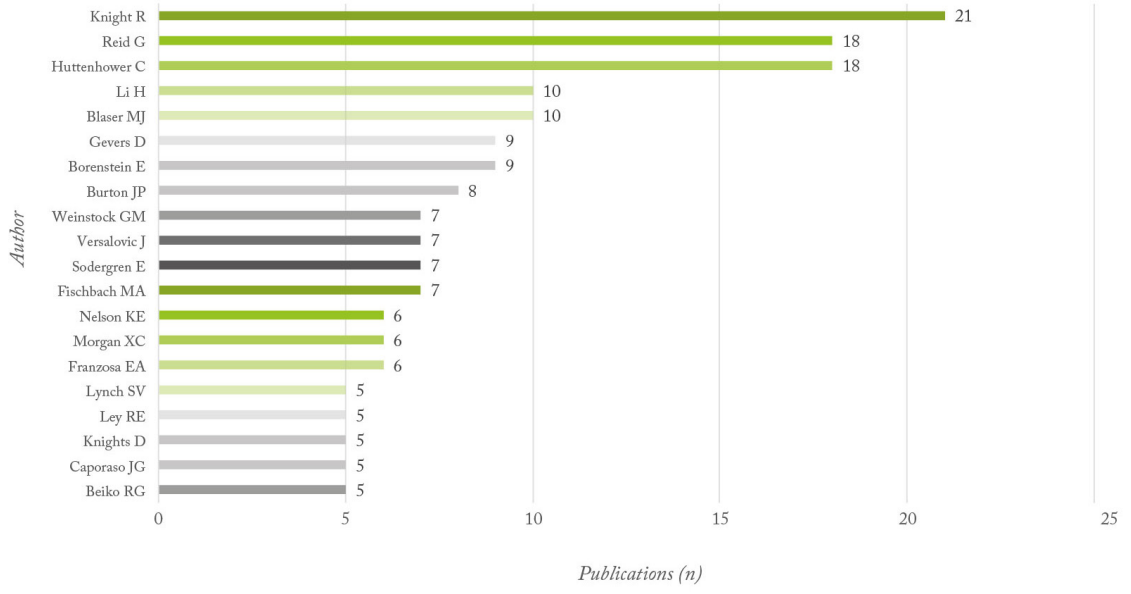
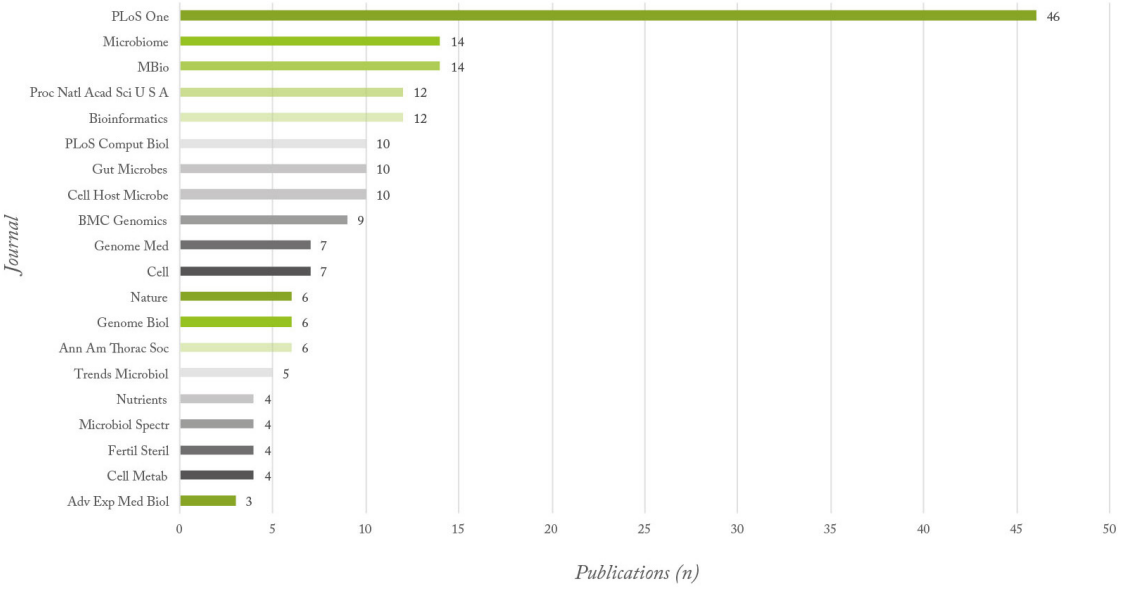


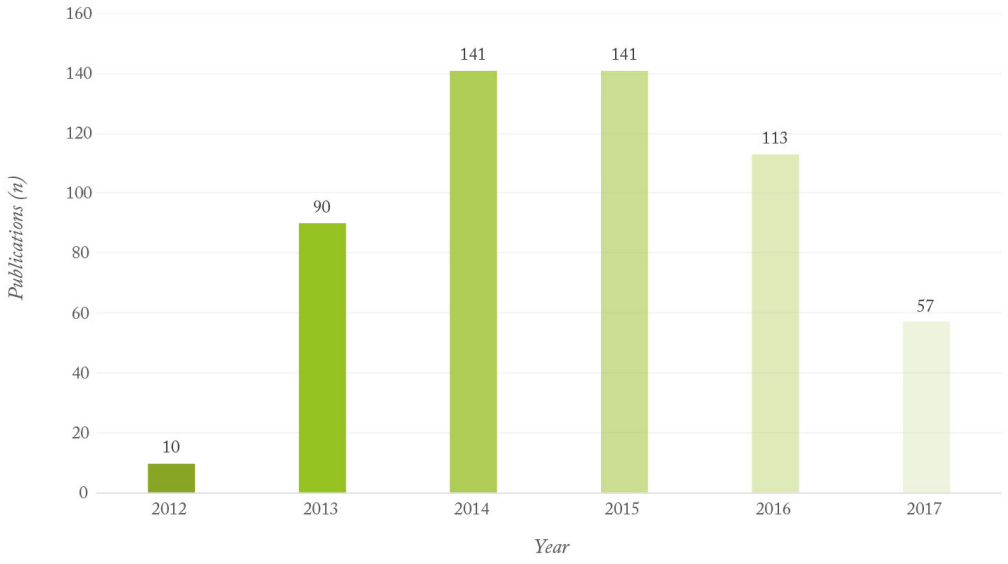
Top 20 Authors by Number of Publications



Top 20 Journals by Number of Publications



Publications by Year



Top Topics	
1. Microbiota	11. High-Throughput Nucleotide Sequencing
2. Bacteria	12. Host-Pathogen Interactions
3. Metagenome	13. Mouth
4. Metagenomics	14. Anti-Bacterial Agents
5. Gastrointestinal Tract	15. Computational Biology
6. RNA, Ribosomal, 16S	16. Intestines
7. Gastrointestinal Microbiome	17. Feces
8. Sequence Analysis, DNA	18. DNA, Bacterial
9. Phylogeny	19. Algorithms
10. Probiotics	20. Biodiversity

In My View

Don't Hold Your Breath

Clinical use of GC-ion mobility spectrometry has great potential, but major hurdles lie ahead

By Wolfgang Vautz, Scientist, Departments of Miniaturisation, Leibniz-Institute für Analytische Wissenschaften – ISAS – e.V., Germany and CEO of ION-GAS GmbH, Germany.

November 2017

Ion mobility spectrometry coupled to rapid gas-chromatographic pre-separation (GC-IMS) has enormous potential for non-invasive, rapid, sensitive and selective analysis of complex gas-phase mixtures. GC-IMS can provide a comprehensive analysis of a gas-phase mixture in a few seconds, after a non-invasive sampling of a small volume (typically 1–8 mL) – even with mobile instruments. Such non-invasive sampling could make the method very useful for the analysis of human breath (1) for (early) diagnosis of diseases, but also for analysis of medication and for the rapid identification of microorganisms.

Several studies have been conducted over the past two decades, demonstrating the potential of GC-IMS for quantification of the anesthetic propofol in breath during surgery (2), for the identification of characteristic patterns for kidney failure with potential for early diagnosis (3), or even for gathering additional information from animal models (4)]. Furthermore, characteristic patterns of bacteria and fungi cultures can now be identified after 24 hours of incubation, a step forward for the early application of specific antibiotics (5). So why is the method still not in routine operation in hospitals?

One obvious reason is the complex authorization process analytical instruments must undergo before they are approved for clinical use – a necessary but costly and time-consuming undertaking. More specifically to diagnosis, in most cases, explicit characteristic biomarkers are not yet known.

To develop a diagnostic application using non-invasive GC-IMS, we have to surmount three major hurdles:

First, and most challenging, we must conduct detailed investigations in a large cohort of patients and healthy controls to identify a characteristic pattern of biomarkers. Other stumbling blocks may include inaccurate gold standards for comparison, different states of the disease, comorbid diseases, and all this without having a guarantee of complete success in the development of a characteristic pattern. Regardless, this time-consuming step is most important with regard to method development for

medical diagnosis.

Second, once the pattern is defined, all biomarkers must be identified and their causal relation to the disease proven by means of metabolic pathways.

Third, the developed and proven diagnostic method must be validated in a blinded clinical study for specificity and sensitivity.

The first challenge – identifying the valid relevant pattern of biomarkers for a particular disease – is the real key to GC-IMS implementation in the clinic. With the right biomarkers, the conversion of a prototype into a proven medical instrument is, to some degree, a matter of course (although certainly requiring significant time and investment). Despite the challenges, the speed and ease of GC-IMS analysis puts it in an excellent position. And having seen it in action, I believe it will be only a matter of time before the first diagnostic GC-IMS will begin to conquer hospitals and point-of-care facilities.

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The Next (Air)Wave of Inhalables

The inhaler is an important drug delivery device – but for the technology to evolve, questions about efficacy must be answered

By David Lewis, Director of Aerosol Research, Chiesi Ltd, UK.

November 2017

Since they were first developed in the 1950s, advances in inhaler drug delivery technology have been substantial. But compared with tablets, the technology it still in its infancy. Inhaled drugs are delivered directly to the target tissue where they can act immediately, in contrast to systemic delivery methods. This localized delivery is a widely recognized benefit of inhalables, as a lower dose is generally needed to achieve therapeutic effect. Since their initial design, inhaler devices and formulations have undergone rapid innovations, most notably the introduction of hydrofluoroalkane as a propellant in metered dose inhalers, which improved the degree of drug deposition in the lung. Despite this, more improvements in inhaled delivery methods are required to further increase the drug dose reaching the lung by manipulating particle properties and therefore improving the treatment of prevalent respiratory diseases, such as chronic obstructive pulmonary disease.

The defining focus of research in the inhalable drug area has, until now, been aimed at learning how to disperse formulations efficiently

enough to deliver a clinically efficacious dose – and, in particular, how to create and disperse particles of a size that facilitates deposition in the lung. The importance of this work should not be overlooked, but there are important challenges yet to be tackled. To reach new levels of performance, and to better meet patient requirements, I would argue that we now need to start asking new questions. There are three key questions that the field must address:

i) How can we develop a better understanding of aerosolization performance by extending current research?

ii) How can we better understand particle behavior on the way to the lung (especially the influence of humidity on particle properties)?

iii) How can we improve drug uptake within the lung?

The aerodynamic particle size distribution (APSD) of the therapeutic aerosol produced by an inhaler plays a key role in the physical mechanics of particle deposition in the airways – which means it directly affects the efficacy of the treatment. Understanding the dynamics of dose dispersion is therefore a critical first step towards better drug delivery control. For pressurized metered dose inhalers (pMDIs), we require a detailed understanding of the atomization and evaporation processes that determine the size of particles delivered – a major challenge, but it potentially opens up a route to higher performance efficiency. The use of innovative imaging technology to investigate the aerosol plume, in combination with the intelligent application of computational fluid dynamics, is helping to pave the way towards increasing our understanding. New knowledge will be particularly valuable as the focus of research activity shifts to the potential of extra-fine particles (those less than two microns in size), which increasingly appear to offer both clinical and product performance benefits.

Next, it is important to establish a better understanding of the patient response to inhaled particles (and vice versa), ultimately allowing researchers and clinicians to understand why patients may respond differently to the same product, according to their age or disease state. For example, during drug development and manufacture, the aerodynamic particle size distribution of inhaled drug particles is usually measured in a low humidity environment, using the technique of cascade impaction. But there's a problem: the route the drug particles follow is close to a saturated water environment, meaning that test data may not accurately represent what is going to happen in vivo. Fine particles tend to be hygroscopic, which means that when they are subject to high humidity they will absorb water relatively rapidly because of the high surface-area-to-volume ratio, becoming larger than they were when they entered the body. In the past, inhaler testing may not have taken this into consideration. But now, researchers are paying more attention to the effects this can have on the deposition behavior of the drug, and the resulting dose received by the patient.

Oxygen levels in the lung are also known to affect the uptake and behavior of inhaled particles, as shown by research into the impact of pollutants (1). Within the lung, the steady state concentration of oxygen is significantly lower than the 21 percent used for many experiments. Once particles have deposited (frequently in an unpredictable manner), it is the respiratory tract lining fluid (RTLF) that has a defining influence on the uptake of inhaled molecules, and particle transportation at the air-lung interface. RTLF changes with age and with disease state, and therefore plays a role in the variable lung response in different patients.

Additionally, the composition of the RTLF changes depending on the region of the lung, so when particles transverse the lining, the dissolution, cellular uptake and therapeutic efficacy all depend partly upon where the drug particles reach. And that's one reason why dissolution testing has become an important theme. Once an inhaled drug has deposited, the absorption –and, therefore, the therapeutic effectiveness of the drug – depends on the active drug dissolving in the fluid available at the target site. As it stands, there are no dissolution test methods specified for inhaled products; however, FDA grants have been released to investigate this aspect of performance.

Improved understanding of in vivo particle behavior will allow us to more closely tailor inhaled products to meet the needs of specific patient groups in a more efficient way. There is potential to be explored by developing more efficient technologies that use formulations with reduced active pharmaceutical ingredient loading. Respiratory diseases represent a huge burden on healthcare services across the globe, with developing countries in particular struggling with the associated financial weight of such conditions. By improving inhaled drug delivery uptake within the body, we have the opportunity to improve the patient experience, and at the same time reduce healthcare costs.

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Toolbox

OCT for the People

Can a low-cost OCT device aid biomedical research and improve disease diagnosis in rural and low-income settings?

By Adam Wax

November 2017

I've been working in the field of biomedical optics for 20 years and, in that time, I've brought a number of different products through clinical trials and to market – mostly endoscopes. In general, I've been frustrated with how expensive it is to bring a new medical product to market. By the time you've completed research and clinical trials, you end up with a device that could cost upwards of a hundred thousand dollars, and costing up to a thousand dollars per use. And that means that it's very tough to get new technologies adopted. In short, we do a great deal of work, spend a lot of money, but end up with very few products that actually bring enough benefit to convince the market to buy them.

Coming from a physics background, I've always loved how optical approaches can provide very elegant and precise descriptions of scientific phenomena. Taking this technology and applying it to biology and medicine, a much messier field, is where the biggest challenges lie. Nevertheless, I was inspired to start a company with a different vision: to prove that we can create low-cost, high-quality biomedical imaging products, and still make a profit. Our first project? Optical coherence tomography (OCT).

An elegant – but expensive – approach

OCT is already an established technology with known benefits – it provides noninvasive, cross sectional imaging, and penetrates more deeply into tissue than confocal microscopy, without requiring a fluorescent reporter. Essentially, it's an optical analog of ultrasound. In ultrasound, you send a pulse of sound into your sample, and wait for it to 'bounce' back. The time it takes tells you how deep it's gone. With OCT you use light, which moves much more quickly – so you can't just time it with an electronic stopwatch! Instead we do interferometry: we break some of the light off into a reference arm, send it down a reference path, and when that light comes back it's matched with the light that has gone into the sample, giving you an interference pattern. By varying the length of the reference arm, you can map out a depth-resolved reflection profile from your sample. And you can get beautiful detail on all the cross sectional layers.

These benefits have led OCT to become the current gold standard in detecting diseases of the retina – it's a great approach for detecting diseases like diabetic retinopathy, age-related macular degeneration (AMD), and glaucoma. The main problem is the expense of OCT systems, which means that they are more typically found in big eye centers; if you're 100 miles away from the nearest city, you don't have easy access to the technology. And if you're in a low- or middle-income country, the problem is the same.

We set out to create a lower cost device to increase access to this imaging technology. The result is a device about the size of a shoebox that costs under $10,000, which essentially

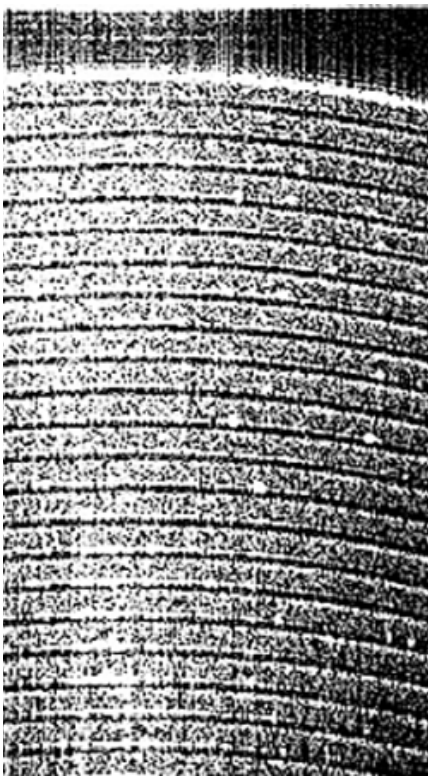
allows doctors to visit remote locations or perhaps a retirement home, where patients are less mobile, and scan 30 or 40 people in a single session.

Mice, materials and medicine

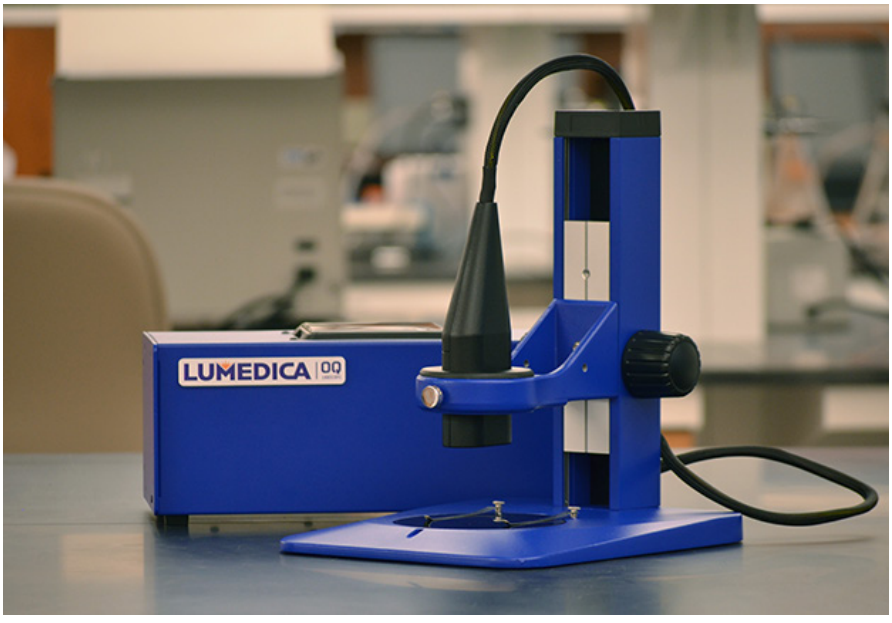
But before we can sell our device for human use in the US, we need FDA approval. Right now, we have a device on the market, OQ LabScope, for research and educational purposes. So far we've seen good uptake, especially by those who never thought about using OCT as it was simply too expensive. We've had biomedical researchers trying it on many different organ sites – for example, researchers interesting in imaging different parts of the mouse, from the eyes, to the skin or the teeth. We've had interest from pathologists who want to look at tissue sections on the lab bench, to figure out where to take their histological sections. We've also seen interest from people working on materials research. Say you're working on a new coating for a phone or television screen, or on optical fibers – our device offers a nondestructive testing option. There aren't a lot of imaging options for this type of work, so our relatively cheap and portable device, which can be easily shared among researchers, is getting a positive response.

Lowering the cost of the device dramatically was our main challenge – and the beautiful thing about the device, for us, is the design of the spectrometer which is the heart of the OQ LabScope. Usually, spectrometers are built from high tolerance parts that are locked down so they never move. But we took a different approach and decided to let our spectrometer "breathe" while still staying aligned; we built it with 3D printed parts that are pushed into place and glued by hand. When we ship it across country and it's taken out of the box it's already aligned – there's no need for a highly skilled expert to come in and calibrate it for you. It's "plug and play." Additionally, for many of

An image of a fingerprint taken using the OQ LabScope



An OCT image of scotch tape, showing over 40 layers of tape and adhesive.



The OQ LabScope OCT device

these devices you need to have a separate computer and screen. Our device doesn't need that – the computer is inside the system so you can plug it into a monitor, or you can use a tablet or cell phone to control it, keeping the footprint really small and the costs down.

However, there are trade-offs when developing a cheaper alternative. We meet nearly all of the specifications for standard OCT systems in terms of resolution and signal-to-noise ratio. However, our device is a bit slower – we're limited to about 9,000 A-scans per second which is about 20 images per second, while more sophisticated machines can take perhaps 20,000–30,000, or even as many as 50,000 A-scans per second, or 40-60 frames per second. If you're trying to image a really fast process, our device may not be the best option, but for many applications this slower image rate isn't a problem. The aim isn't to produce the most sophisticated OCT machine available, it's to aid research, increase access – and, eventually, to help catch disease early.

In fact, the push for incremental advances in current OCT technology is one of the reasons why it remains so expensive – if you're pushing to get another three or five percent performance, you can end up with a much more expensive instrument, with features that don't necessarily aid basic functions like diagnosis. Our aim is to strip all that back and democratize OCT.

A vision for the future

There was a time that ultrasound was only found in big hospitals, but now there are portable ultrasounds that they take out on ambulances when there's an emergency call. We hope that our version of OCT will have that kind of portability, and provide that level of access.

Our next goal is to get a retinal imaging product on the market. We're working toward FDA clearance and a CE mark. We're also looking at the international market, especially in areas where access to OCT is more limited, such as India and China. Ultimately, we believe that a low-cost instrument could help save the sight of millions of people. And it doesn't need to stop at OCT – cheaper, portable alternatives to expensive medical equipment could make a huge difference in all areas of healthcare, bringing the latest diagnostic tools to many more patients.

Adam Wax is a Professor of Biomedical Engineering at Duke University, North Carolina, USA, and President and Chief Scientist of Lumedica, Inc.

For more information about the LabScope, visit Lumedica.co or email info@lumedica.co.

Exploring the Microbiome – with Mice

Rodent models are a useful tool for gaining a better understanding of the human microbiome – but it's important to understand their limits

By Alexander Maue and Randi Lundberg

November 2017

The role of the microbiome in human health is one of the hottest areas in biomedical research today. A simple PubMed search for "Microbiota and Microbiome" demonstrates a 700 percent increase in the number of relevant publications from 2009 to 2016. Perhaps unsurprisingly, a large number of these studies used murine models. But how well do microbiome findings generated in mouse models translate to human health? It's crucial that researchers in this area have a clear understanding of the benefits and limitations of their model systems if they wish to extrapolate their findings to humans.

Benefits and caveats

The advantages of using mouse models are clear: homogenous genetics, accessibility to germ-free, mutant and/or transgenic models, a comparable physiology, and a relatively low cost of performing studies. In addition, the use of mouse models has been key in landmark studies determining the role of the gut microbiota in various diseases. But despite the clear benefits, there are caveats affecting translatability that include gross anatomy, compositional differences of the gut microbiota between humans and mice, and environmental factors that may confound studies.

In humans and mice, the majority of the gut microbiota is represented by two key phyla: Bacteroidetes and Firmicutes (1)(2). However, upon closer evaluation, 85 percent of bacterial genera found in the mouse gut microbiota are not present in humans (1). Krych et al. demonstrated that approximately 80 genera are shared between mice and humans (3), with some genera exclusive to each host (4). Despite these differences, profound shifts from control to disease states have been demonstrated and highlight the usefulness of animal models in elucidating the role of the gut microbiota in health.

Two key areas in which mouse models are being used in translational microbiome research are in obesity and inflammatory bowel disease (IBD) – with mixed results.

Obesity studies

Obesity is a serious and growing

health concern caused by an imbalance of energy intake and expenditure with contributions from environmental, genetic and societal factors. Starting from the early 2000s, the microbiome has specifically been described as one of the more important risk factors for developing obesity and associated disorders, such as metabolic syndrome and type II diabetes.

The first study linking the process of fat storage to the microbiome was performed in germ-free and microbiota-colonized mice (5). Since then, animal studies exploiting germ-free mice transplanted with microbial communities from obese or lean mice and humans have been instrumental in exploring the role of microbiome in obesity. Key findings from these studies include demonstration of a causal relationship between the microbiome and obesity, altered composition of the "obese microbiome", and the intriguing observation that the introduction of a "lean microbiome" can reduce obesity and obesity-associated symptoms. Fueled by the evidence in mice, these concepts have been clinically investigated and, in many cases, confirmed in humans (Table 1).

Mouse models have been a driving force in advancing the obesity-microbiome research field, but translating findings from preclinical studies to something meaningful and actionable in human health remains a challenge. Underpowered human studies have been mentioned as part of the reason, and too much emphasis on small effect sizes, questioning the biological relevance, has been flagged (7). As is so often the case, the myriad of uncontrolled factors in human studies complicates the understanding and interpretation of experimental data. The extensive variation of the microbiome between individuals makes it likely that the "obese microbiome" is an individual concept based on an extremely complex interplay involving at least dietary, genetic, and environmental factors, in addition to microbe-to-microbe synergy and crosstalk. This complexity may explain why a microbial biomarker, or signature, of obesity has not been identified. However, this doesn't rule out the microbiome as a key contributor.

Key findings	Demonstrated in mice	Demonstrated in humans	Comment
Altered *Bacteroidetes*:*Firmicutes* ratio in the "obese microbiome"	Yes (1)	Yes, but not consistently (2,6)	Various altered microbiome compositions have been reported in obese people, including altered *Bacteroidetes*:*Firmicutes* ratio, but no clear taxonomic signature of the "obese microbiome" has been found to date (7)
Decreased diversity of the "obese microbiome"	Yes (8)	Yes (9)	While not directly saying anything about composition or functionality, low diversity has also been linked to other diseases, such as atopic eczema, colorectal cancer, and inflammatory bowel disease (IBD).
The microbiome can be causal in development of obesity	Yes (8, 10)	No, only anecdotally	For ethical reasons, disease-inducing studies can only be performed in animals, but a case report of a woman who received a fecal transplant from an obese donor and subsequently gained weight have been published (11)
Fecal Microbiota Transplant (FMT) or cohousing with "lean microbiome" can alleviate obesity-associated metabolic phenotype	Yes (10)	Yes (12)	To date, only one clinical trial investigating the effect of FMT on obesity and obesity-associated conditions has been published, but a search on ClinicalTrials.gov reveals the expected potential: currently six clinical studies are ongoing around the globe

Table 1. Overview of key findings from mouse and human studies on the linkage of the

Better defining IBD

Ulcerative colitis (UC) and Crohn's disease are the two major types of IBD, and are characterized by chronic relapsing inflammation of the gastrointestinal tract. Underlying both of these conditions is an aberrant immune response to the gut microbiota (13).

The research field has developed multiple mouse models to evaluate specific aspects of IBD, but despite extensive modeling in animals, the precise mechanism through which disease arises has not yet been determined for the majority of patients. As it currently stands, no single mouse model completely recapitulates the pathology of IBD patients. However, many of these developed models remain useful tools when it comes to addressing specific questions relevant to IBD.

More than 790 types of genetic modification in mice have been shown to increase or decrease susceptibility to chemically-induced colitis/ileitis or epithelial barrier dysfunction (14). Additionally, genome-wide association studies (GWAS) have identified more than 160 susceptibility genes in humans, and 20 of these genes have been made into genetically engineered mouse models (GEMs) (14). GEMs are useful in

that they can mimic disease phenotypes associated with genetic susceptibility to IBD, but limitations exist in what can be inferred from study results, because these models cannot accurately represent the sum of all genetic differences observed in humans. Furthermore, targeted genes can be involved in numerous pathways, which can cloud the interpretation of results made regarding the associations between gene expression and microbiota.

The substantial differences in the composition of gut microbiota between humans and mice at the genera level make direct translation of experimental results challenging. However, many mouse models of IBD do support a role for the microbiota in experimental colitis (4)(15)(16). Typically, rather than providing translatable linkages between disease and specific microbes, mouse IBD models have demonstrated a role for the gut microbiota as a whole in promoting or preventing disease.

A key finding supporting a role for the resident microbiota in colitis was demonstrated by the observation that following chemical induction of experimental colitis, a significant increase in members of Bacteroidaceae and Clostridium bacteria were detected in the intestines of affected mice (17). Likewise, shifts in the diversity and composition of the gut microbiota of IBD patients are commonly detected (16).

Another finding that demonstrates the role of microbiota in IBD is the resistance of interleukin-10 (IL10)-deficient mice to spontaneous colitis, when they are reared under germ-free conditions (18). This research supports GWAS findings that identify certain IL10 receptor polymorphisms as being associated with the development of early onset IBD (4). In addition, germ-free mice exhibit more severe colitis than conventional mice in a chemically-induced disease model, showing that normal gut microbes may also provide a protective role against experimental colitis (19).

Losing the germs for better modeling

Germ-free mice associated with human microbiota represent a model that has the potential to improve translatability. It's a powerful tool for researchers because such models can recapitulate a large part of the human gut microbiota composition – 100 percent of phyla, 11 out of 12 classes and ~88 percent of genus-level taxa (4). As mentioned earlier, this model was key in demonstrating the role of the microbiome in obesity. The model was also used in IBD research with the transfer of gut microbiota from UC patients into germ-free BALB/c mice (20). And although none of the humanized mice went on to develop spontaneous colitis, the researchers found that the UC microbiota-associated animals exhibited an increased susceptibility to dextran sodium sulfate (DSS) induced colitis.

However, there are two key caveats to consider when using similar models: i) transplanted microbiota are present in a host that they have not co-evolved with, and ii) the immune system of associated animals has not developed normally from the time of birth with these transplanted microbiota. One partial solution is to vertically transmit microbiota through breeding transplanted mice and performing experiments on their offspring. The diversity and abundance of transplanted gut microbiota is conserved from parental (P) to F1 generation offspring (21). These humanized models have provided valuable insight into the factors that are involved in the progression of both IBD and obesity.

Considerations

Perhaps above all else, mouse models allow for the opportunity to experimentally manipulate and control variables in ways that cannot reasonably be accomplished in human trials. They remain relevant for performing reductionist studies that enable dissection of biological mechanisms and allow for sufficiently powered studies under controlled conditions. Despite the accepted utility of mouse models, and the known anatomical, physiological, and immunological differences between mice and humans, the reductionist approach of mouse studies compared with human studies can also prove to be a limitation: the relationship between the microbiome and the host can appear more complex in humans, and the relevance of single mechanistic pathways revealed through the use of mice may, in some cases, yield results that are not relevant to the human condition. Nevertheless, rodents have already proven their value in our quest to understand the microbiome – providing several solid links between the microbiome and disease that have gone on to be confirmed in humans.

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Molecules Against Microbes

As molecular diagnostic methods evolve, so does our approach to microbial testing – with important implications for the quandary of antimicrobial resistance

By Sherry Dunbar and Gunjot Rana

November 2017

We are witnessing a time of rapid change in the world of microbial testing. In recent years, molecular diagnostic tools have emerged from their previous niche use to become the gold standard for more and more conditions. Our need for the particular advantages molecular assays bring – which include fast results, and high sensitivity and specificity – is more pressing than ever, as we strive to overcome a range of diagnostic challenges. And most pressing of all is the growing crisis of antibiotic resistance.

"Molecular assays can shave many hours or even whole days off of the timeline compared to more traditional diagnostic processes."

Several developments are underway that will shape microbial testing for years to come. From determining targets to performing tests in the lab or at the patient's bedside, the entire process of microbial assays is undergoing a shift that should dramatically enhance care and outcomes for patients.

Antimicrobial stewardship programs are working to identify resistance markers in microbes to guide drug selection for the best chance of success. Improvements in molecular testing for microbes will help doctors ensure that the right treatment gets to the right patient at the right time, and inappropriate treatments are never prescribed – which benefits both individual patients, and public health. If this can be achieved, it would be a major step towards addressing antibiotic resistance. But how close are we? Here, we take a look at some of the most important trends affecting microbial

testing today.

Rapid testing

Molecular diagnostics offer a significant benefit to clinical labs and the physicians they serve: a much shorter turnaround time to generate results. Molecular assays can shave many hours or even whole days off of the timeline compared to more traditional diagnostic processes, such as culture-based tests. Typical process for culture is that the specimen is received and inoculated onto a variety of culture media based on the typical pathogens that would be expected for that specimen and infection type. Then the inoculated media are incubated and checked visually on daily intervals to see if there is any growth.

For a molecular test, the specimen is either directly placed into the test device and the results are available in minutes to hours, or the specimen may be processed to extract and purify any nucleic acids present first and then the extracted nucleic acid placed into the molecular test, with results available within a few hours.

Several recent studies show the clinical results of getting answers more quickly (1)(2)(3). In general, these analyses demonstrate that rapid tests allow patients to be treated more quickly with the right therapy, which in turn leads to shorter hospital stays and reduced readmission rates. They also provide evidence that this approach lowers overall healthcare costs for these patients and the institutions serving them.

Superior target selection

Some molecular tests are designed to detect a single microbe, but an increasing number can identify several species in a single assay. These panel-based tests allow clinical labs to look for some likely culprits in parallel, avoiding the time-consuming sequential testing of individual microbes as each diagnostic comes back with negative results. Physicians can now choose syndromic molecular tests to look broadly across several candidates multiplexed into a single test, which in many cases makes it more straightforward to diagnose the source of an infection.

For certain situations, however, pre-selected target panels may be too broad. For instance, during flu season, it would likely not make sense to start with more than flu and respiratory syncytial virus testing for an otherwise healthy patient presenting with respiratory symptoms. If an immunocompromised patient came into the hospital with the same symptoms, physicians might decide to use a much broader range of targets to cover all the bases.

A testing method known as masking allows clinical labs to implement either approach without changing assays. In this protocol, the lab runs the same multiplexed test for each sample, choosing which targets to report, and the masked targets report no results. If the first round of testing yields no useful answers, additional targets from the panel can be unmasked and viewed. In a new variation of this known as flexible testing, the lab only pays the manufacturer for the targets it chooses to be reported. Such approaches help labs keep costs in check while delivering as much or as little testing as requested by the ordering physician.

Sample to answer

As molecular testing becomes more mainstream, developers are improving automation to allow clinical lab teams to run tests with minimal hands-on time. These so-called "sample to answer" platforms essentially allow users to load the patient's sample, choose the test, and walk away. The instruments handle everything else, from adding reagents at the right time to managing complex thermal cycling profiles. Results can often be monitored at a central command station, rather than instrument by instrument.

Although convenience is a major factor here – these machines allow technicians to run more tests at once – another important element is the reduced risk of error. Every manual intervention carries a small opportunity for mistakes; eliminating such opportunities increases the accuracy of results. In the coming years, lab teams can expect that even more elements of microbial testing will become automated for a truly streamlined workflow.

Centralization and decentralization

The trends on where testing is performed are also shifting. Many types of tests that were traditionally performed in a central or reference lab, such as Clostridium difficile, MRSA, and flu, are moving toward the point of care, perhaps in a small regional lab, or even close to the bedside. At the same time, new high-complexity testing, such as sequencing-based testing of oncology markers, is shifting to modern centralized labs that have the capacity and sophistication to manage them. Where any individual test occurs can depend on the size of the healthcare system, geography, patient demographics, test type, and more. Medical professionals have more flexibility than ever to decide whether they need a very simple test that can be performed near the patient, or a more complicated diagnostic that is handled by a central lab facility. This allows lab teams to respond more nimbly to shifting needs for speed versus complexity.

At the point of impact

Following the decentralization trend, point-of-care testing has enabled a number of advantages for treating patients, such as responding more quickly to hospital-associated infections. Getting rapid results from onsite labs has also been essential for understanding antimicrobial resistance profiles, allowing hospital staff to choose more targeted treatments, and quickly quarantine patients when necessary.

The same information feeds into antimicrobial stewardship programs, making a real difference in how patients are treated for MRSA, C. diff, norovirus, and many other infectious diseases. Antibiotic resistance has become a major public health threat, with some experts estimating that 700,000 people die each year from drug-resistant infections (4).

In light of this trend, it is no longer enough to identify the microbial source of an infection –already a tall order in some cases. Now, labs must also quickly detect markers of resistance to support therapy selection for optimal outcomes and reduce the misuse of antibiotics (5)(6)(7)(8)(9).

Looking Ahead

Though we cannot anticipate every change that will affect microbial testing in the next few years, we can safely predict that most advances will be developed to support recognized needs in clinical labs today: streamlined workflows and information systems, cost-effective and accurate tests, rapid generation of results, and ultimately, better outcomes.

In the near future, many of the developments explored above will continue to gain traction. Increasing flexibility for clinical lab teams – whether in assay design, platform capacity, cost options, or other areas – will serve as a driving force for innovation. Particularly for microbial testing, where demand changes dramatically by geographic region, season, and more, labs need as much versatility as possible to meet the needs of their patient populations.

Advances in microbial testing have already had a noticeable positive influence on patient care and outcomes. As newer, more flexible technologies are developed, molecular methods hold tremendous potential to improve human health.

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Sitting Down With

Carving Out an Analytical Niche

Sitting Down With... Renã Robinson, Assistant Professor, Department of Chemistry and Principal Investigator at RASR Lab, University of Pittsburgh, Pennsylvania, USA.

November 2017

How did you get into analytical chemistry?

As part of my undergraduate chemistry research, I used GC-MS and LC-MS to detect fatty acids in glaucoma. It was my first exposure to using mass spectrometry for biological applications – and I was immediately excited by the possibilities. At Indiana University, I chose a dissertation project using analytical mass spectrometry methods to study proteins and aging in fruit flies. I used ion mobility-MS, which added another dimensionality to the data, increasing the separation space and allowing me to see more low-concentration proteins. It was a very interdisciplinary, collaborative research project, and everything was new to me – from the genetics of fruit flies to sifting through massive amounts of proteomics data to get something meaningful. It was exciting to be working in the field in the mid-2000s, when proteomics had just started to become a big deal.

How has proteomics changed since then?

The field has moved from establishing initial methods to measure proteins to advancing instrumentation in such a way that allows us to profile entire proteomes with incredible sensitivity, to detect differences in diseased and healthy individuals. We have gotten really good at quickly analyzing the resulting data and focusing on the functional implications for proteins. The question now is: how can we analyze dynamic networks, and use spatial and temporal information in the best way to advance research?

Where did your research take you after your PhD?

Collaborating with a colleague who was working on Parkinson's disease sparked my interest in the possibilities of applying MS in age-related diseases. I have personal connections to Alzheimer's disease (AD), and wanted to dig deeper into the mechanisms behind neurodegeneration. I started looking for postdoctoral opportunities where I could focus more on age-related pathology. One universal aspect of aging is a decline in the immune system, which led me to focus my work on the role of immunosenescence in age-related disease.

What are your current projects?

We're using Orbitrap technology – very high-resolution and sensitive mass spectrometers – to carry out multiplexing experiments (MS, then MS/MS, and then MS/MS/MS) investigating how proteins change during aging and immunosenescence, and looking for potential drug targets in neurodegenerative disease. It's exciting work – we're seeing things that have never been seen before. For example, we have been able to determine that the liver plays a significant role in Alzheimer's disease by identifying many proteins with different expression in AD mouse models compared to wild-

types. Additionally, we have begun to better understand the effects of oxidative stress in AD by measuring nitrated and S-nitrosylated proteins. While we are aware that AD is a brain disease, we have significant proteomics data to show that peripheral organs also have an important role. Our current projects are geared towards understanding the system-wide nature of AD and determining if there are systems which make certain populations more at risk for developing AD.

What motivates you?

It's a gift and a privilege to be doing this type of research; I feel like this is my purpose. The thought of all the people who are being left devastated by AD keeps me focused. It reminds me that we need to aim for more than just incremental improvements in our technology and analytical approach – there's a bigger picture that we have to keep in mind.

What's next for your lab?

Our lab is moving to Vanderbilt University this summer. There are lots of opportunities at Vanderbilt to do really top-notch mass spectrometry – and to engage with the Memory & Alzheimer's Center to help further research in this area. We'll be able to add to our repertoire of approaches and techniques, and beef up our mass spec platforms and technologies. As well as proteins, we're interested in measuring lipids and other metabolites. The team already has a lot of analytical expertise, but we're planning to expand our capabilities in informatics and functional biology, to allow us to follow up on our proteomics findings. We're particularly excited to have more access to human samples in the clinic. In ten years' time, I hope we will have been able to help advance AD research – and be one step closer to an effective treatment.

Congratulations on winning a 2017 Pittsburgh Conference Achievement Award...

It was a real highlight, especially to be presented the award by Sarah Trimpin (now at Wayne State University). Sarah has been a mentor to me since she was a postdoc and I was a PhD student at Indiana. She showed me how to push away at a problem and give it everything I've got! She works extremely hard and extremely smart; not only has she done so much with ionization techniques and mass spectrometry, but she also considers every angle that you could to approach a particular problem. She has carved out a niche for herself, and inspired me to ask myself, "What's going to be my thing?"

And what is your "thing"?

I hope I'll be able to look back at my career and say my niche was developing and applying quantitative proteomics in a way that has furthered our understanding of AD and aging – specifically, how things outside of the brain are related to what's happening in the brain. From the start, I knew I wanted to take on a problem in human health, and use my analytical skillset to help answer that problem.

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