Dr. Margie Morgan and
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Cedars-Sinai Medical Center,
Los Angeles, CA, USA

Expert Insights

Expanding the applications of the IR Biotyper® in the hospital

Researchers at the Cedars-Sinai Medical Center, Los Angeles, CA, USA, have broken new ground in clinical microbiology by using their Bruker IR Biotyper® not just to support routine microbiological analysis, but also to provide new insights into emerging pathogens.

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Working with Bruker
Dr. Margie Morgan is the Medical Director of Clinical Microbiology for Pathology and Laboratory Medicine at Cedars-Sinai Medical Center.
Dr. Deisy Contreras is the Clinical Associate of the Clinical Microbiology Laboratory, in the Department of Pathology and Laboratory Medicine at Cedars-Sinai Medical Center.

"At Cedars-Sinai, we're using the Bruker IR Biotyper to assist in epidemiological surveillance cases for a range of pathogens, and also to develop predictive trend analysis for emerging microorganisms such as Candida auris. Our clinical colleagues are both appreciative and amazed at what we've been able to do with the IR Biotyper."

Candida auris: A pathogen of concern

As COVID-19 showed all too clearly, viruses have an unrivaled ability to spread rapidly. Throughout the recent pandemic though, another pathogen has also been giving clinicians cause for concern – *Candida auris*.

Candida auris is a type of yeast that, although only first reported in 2009, has spread quickly and caused outbreaks in more than 30 countries. Particularly at risk are healthcare facilities, where it can spread through contact with colonized patients and contaminated surfaces or equipment. *Candida auris* typically gives rise to infections of the bloodstream, wounds or ears, and can become life-threatening if the infection spreads to the heart or brain. Moreover, it is often resistant to all three classes of anti-fungal drugs, including azoles, polyenes and echinocandins.

Routine analysis and methodological research at Cedars-Sinai

Cedars-Sinai Medical Center has a strong focus on the challenges posed by *Candida auris*. Clinicians at Cedars-Sinai carry out comprehensive tests in order to understand and treat such pathogens – which is where the work of departmental Medical Director, Dr. Margie Morgan, and Clinical Associate, Dr. Deisy Contreras, comes in.

Dr. Morgan is in charge of clinical testing within the microbiology laboratory and provides oversight for the 55 staff members who carry out diagnostic tests, as well as provide teaching services for residents and fellows. She is therefore aware of the need for reliable identification – and also of the challenges that might arise. She explains that:

"Candida auris has very similar characteristics to other Candida species, making it easy to misidentify even with the latest fluorogenic and biochemical tests, which can be both cumbersome and expensive to carry out."

With a view to improving existing identification methods, Dr. Contreras' role is to research diagnostic techniques and assess their application within the laboratory workflow:
"I'm looking at the various diagnostic needs and seeing if we can use different approaches – whether that's next-generation sequencing, IR spectroscopy, or molecular methods – whatever is needed to improve the reliability and speed of analysis,"
she explains.

Dr. Morgan highlights the benefit of being involved with both routine diagnostics and methodological research:
"I think the skills and experience of Deisy and I, complement each other. Having worked at the center for 38 years and been raised on all the traditional biochemical methods, I'd describe myself very much as an old school microbiologist. Deisy's combination of an in-depth knowledge of the molecular basis of microbiology with her new perspective gives an exciting insight into the future of molecular research and diagnostics."

Fast molecular methods for microorganism identification

Dr. Morgan and Dr. Contreras have first-hand appreciation of what chemometric methods such as mass spectrometry and infrared (IR) spectroscopy can bring to microorganism identification.

"We have been at the forefront of mass spectrometry and IR spectroscopy for clinical and hygiene applications in California and have pioneered their more widespread use."*

says Dr. Morgan.

"We have worked with Bruker for nearly ten years, starting when we were the first laboratory in the state to acquire a Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) mass spectrometry system for identifying microorganisms to species or genus level," she says. *"At that time, we were using a different system for the more in-depth strain typing work, but we had the opportunity to be the first center in the USA to evaluate the IR Biotyper – and we jumped at the chance."*

We were initially using the IR Biotyper mostly to identify outbreaks of Gram-negative rod bacteria like Pseudomonas aeruginosa *and Gram-positive cocci such as* Staphylococcus aureus *– and it proved to be very useful,"* she explains.

What is IR-based strain typing?

IR-based strain typing – as implemented in Bruker's IR Biotyper used at Cedars-Sinai – uses spectroscopy to analyze the molecular vibrations caused by absorption of infrared (IR) light. Different chemical structures vibrate at different wavenumber regions – for example, the carboxyl group in fatty acids and lipids vibrates at 2800–3000 cm^{-1}, the amide group in proteins vibrates at 1500–1800 cm^{-1}, and the carboxy bond in polysaccharides vibrates at 900–1200 cm^{-1}. IR-based strain typing combines the information from these ranges into a molecular 'fingerprint' that provides information about the motifs, especially carbohydrates, present in many molecules such as glycoproteins, allowing microorganisms to be classified (Figure 1).

Efficient microorganism strain typing is vital in healthcare settings, for infection control, epidemiological studies, and to better understand the causes of infection. Traditional strain typing technologies like pulsed-field gel electrophoresis, multi-locus sequence typing, latex agglutination and whole-genome sequencing are time-consuming and resource-intensive, and not always readily available in every microbiological lab.

In contrast, IR-based strain typing is easy to carry out and takes just three hours from harvesting to result, for 30 samples (a single sample can be analyzed in approx. 30 min).

* The Bruker IR Biotyper® is not intended for the examination of specimen from human body for diagnostic purposes including the definition or monitoring of therapeutic measures.

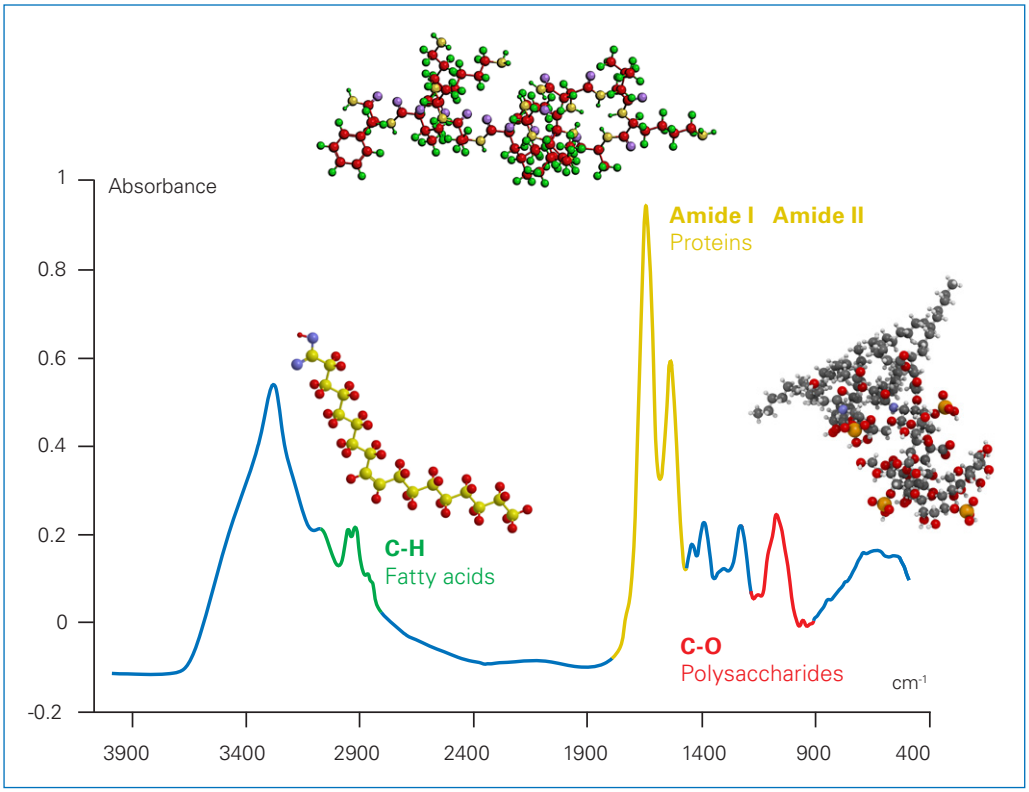

Figure 1:
A typical IR spectrum for a microbiological sample, showing how the different regions provide information about the chemical bonds present in different types of molecules – so building up a 'fingerprint' that allows rapid identification of the strain.

Developing a rapid surveillance test for *Candida auris*

By 2019, the IR Biotyper was well-established for routine testing of outbreaks at Cedars-Sinai – but the emergence of COVID-19 initiated a new phase in its application. Dr. Contreras picks up the story:

"In late 2020, we were in the middle of the COVID-19 pandemic, and although the Center for Disease Control and Prevention (CDC) had not long declared multidrug-resistant Candida auris *to be a significant threat to hospitals and long-term care facilities, the funding had, understandably, been diverted to COVID-19."*

"It wasn't an easy time but, nevertheless, we were motivated to find a way to carry out surveillance for Candida auris. *We first had implemented a rapid RT-PCR platform for the identification of* C. auris, *which worked, but we wanted to implement another layer of surveillance, so I wondered – is there an application of the IR Biotyper?"*

Dr. Contreras explains that it was a bit of a leap in the dark:
"At the time, I hadn't worked much with chemometric systems, but that was why I wanted to test out this approach."

The results have been very promising:
"Not only are we able to identify the respective samples, but we now have a database of results from everyone who's been admitted to Cedars-Sinai who tests positive for Candida auris. *"*

"Bruker has been very helpful, pushing us to be better and to try new ideas."

The help that Cedars-Sinai received from Bruker has been invaluable, says Dr. Contreras:
"We've had a very positive experience with Bruker – especially regarding support with data interpretation and software in the early stages."

Dr. Morgan agrees:

"I think they've been really supportive with the challenges we continue to set ourselves. Working with Bruker has been a great experience – the team of application specialists has been very helpful and pushed us to try new ideas."

Gathering data, making predictions

Dr. Contreras explains that, initially, samples tested positive for *Candida auris* by PCR had isolates processed using the IR Biotyper. With the help of different statistical methods such as hierarchical clustering and principal component analysis in the software, she was then able to correlate those spectra with sequencing data – results that have recently been the subject of a paper published in 2022. The result of this, she says, is that they're able to make real-time genomic predictions on *Candida auris* isolates:
"We are creating an IR Biotyper database for Candida auris *comprised of strains circulating within our community and use it to predict genomic classifications that may be useful for understanding resistance or susceptibility patterns."*

Figure 2 shows how data from the IR Biotyper distinguishes *Candida auris* from other fungal species.

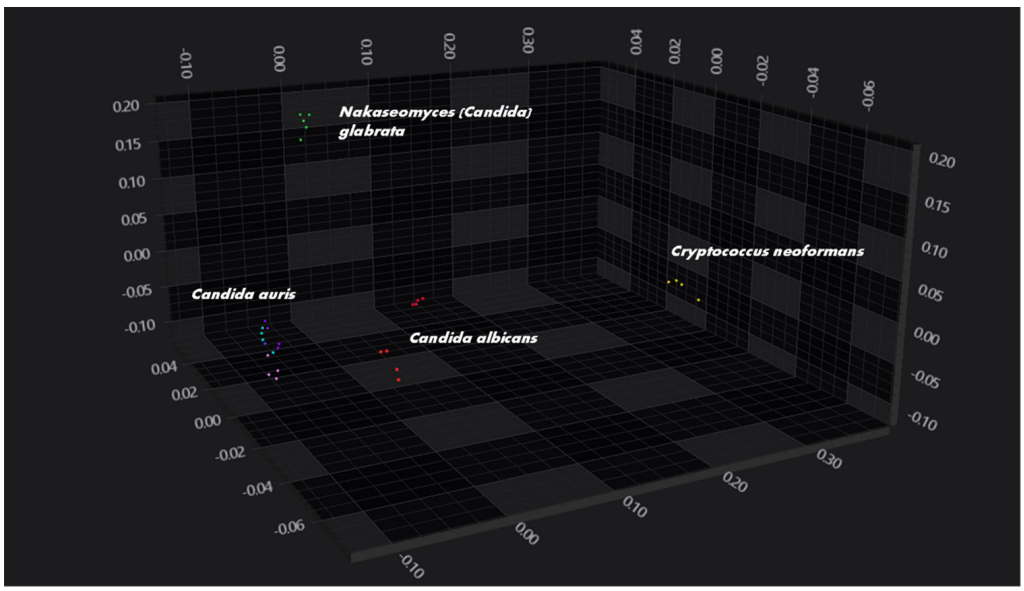

Figure 2:
3-D principal component analysis illustrating the distinction of clinically relevant yeast species from *Candida auris*.

"We're using the IR Biotyper not just for active surveillance, but for making predictions too – it's been a very, very useful technology for us."

Dr. Contreras cites an example:
"A recent literature publication suggested that the majority of Candida auris *strains circulating in the Los Angeles area were from Clade III (African lineage). We wanted to see if that was the case within our patient population and indeed found that over 95% of our identified* C. auris *positive patient strains also belonged to the African lineage (Figure 3). In addition, we were also able to identify* C. auris *isolates from South Asian lineage. Based on the discriminatory power observed, we were able to further use the IR Biotyper as a predictive modeling platform to monitor Clade distribution within our patient population."*

Dr. Morgan points out that the system is also useful for confirming when there isn't an outbreak:
"Sometimes we need to know whether a problem is genuine, and the IR Biotyper can help us in this situation too. It has been an incredibly useful technology for us."

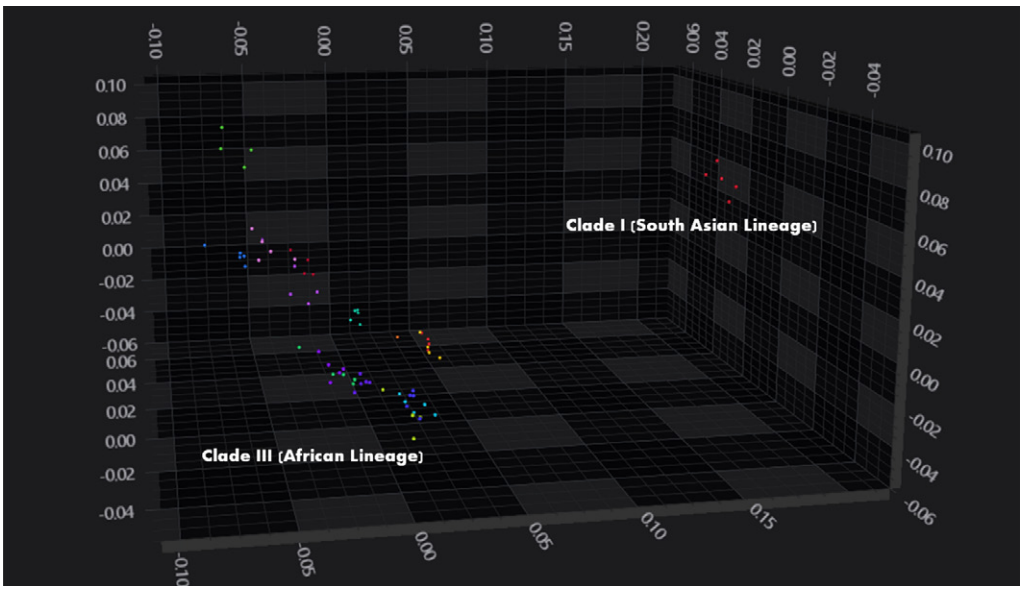

Figure 3:
3-D principal component analysis of a subset of identified *Candida auris* strains at Cedars-Sinai Medical Center demonstrating significant Clade distribution.

Fresh thinking on emerging challenges

Dr. Contreras gives one example of the team's boundary-pushing ethos:
"Because of the work with Candida auris *on the IR Biotyper, we were curious to see if this platform could be applied to other parts of the laboratory. A project we're currently in the early stages of is testing the discriminatory power of the IR Biotyper to aid in subspeciation of* Mycobacterium abscessus *complex. If we can subspeciate into the three subspecies, we can then use that to predict clarithromycin (CLA) resistance for* Mycobacterium abscessus *complex"* .
Full validation of this application by the Clinical Microbiology Laboratory would enable the team to significantly reduce the turnaround time for clarithromycin susceptibility results by real-time strain typing.

"Our clinical colleagues are both appreciative and amazed at what we've been able to do with the IR Biotyper."

Dr. Morgan outlines the views of her colleagues:
"I think they're both appreciative and amazed at some of the things that we have been able to accomplish with the IR Biotyper. To instill confidence in the results, we have to take care to explain what the system involves – because it's a relatively recent technology, many of our colleagues won't have encountered it during their training, so it definitely helps to reassure them on that point."

Dr. Contreras adds:
"Thinking outside the box, applying different instrumentation, and communicating the benefits is not just desirable for management of epidemiology and healthcare – it's essential."
Dr. Morgan agrees:
"When tackling emerging challenges in healthcare, you need to be prepared to look at all the tools available, try out ideas, and persevere – and sometimes you'll find you can achieve amazing results."

References

[1] J. Rhodes, M.C. Fisher, Global epidemiology of emerging *Candida auris*, Current Opinion in Microbiology, 52:84-89 (2019)
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[2] D. Contreras, M. Morgan, Surveillance diagnostic algorithm using real-time PCR assay and strain typing method development to assist with the control of *C. auris* amid COVID-19 pandemic. Front. Cell. Infect. Microbiol., 12:887754 (2022)
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About Cedars-Sinai Medical Center

Cedars-Sinai Medical Center is a nonprofit academic healthcare organization serving the diverse Los Angeles community and beyond. With pioneering medical research achievements, education programs defining the future of healthcare, and wide-ranging community benefit activities, Cedars-Sinai is setting new standards for quality and innovation in patient care.

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