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Connections

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You can run but you can't hide

CMPT's goes through assessment for ISO17043 accreditation

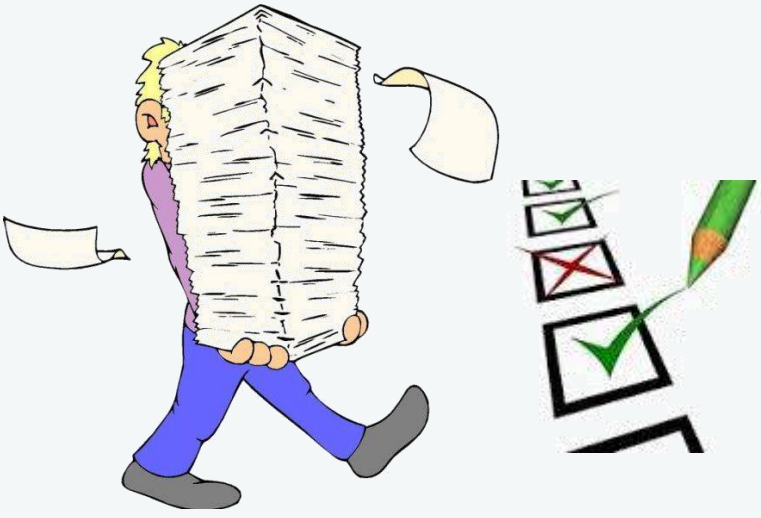
In 1941, world champion boxer Joe Louis was matched with boxer Billy Conn, the champion in a lighter weight class known for quick moves and fast punches. The press questioned Louis how he was going to deal with Conn in the ring, to which he disdainfully and famously replied "he can run but he can't hide". I raise the story because it very much applies to going through our international accreditation assessment to the standard ISO/IEC 17043: "Conformity assessment - General requirements for proficiency testing."

Last week we had our assessment audit by representatives of the American Association for Laboratory Accreditation (A2LA). The site visit took almost two and a half days (close to 20 hours) to complete. A good term to describe the assessment is '*thorough*'.

In any audit that is thorough and complete we, as the subject of the assessment, have ample opportunity to show off all the things that we do well. That is the point of the accreditation exercise. But at some point, the areas where we are not quite as strong will start to appear as well. You can try to distract and bring the subject back to areas of strength, but sooner or later one has to confront the weaker points; it all comes out in the wash.

After the going through the whole exercise, we are quite pleased with how the whole experience went. Clearly, we do have some issues to address, all of them of a documentation nature, but overall the assessors were very complementary about our programs, the samples that we create, and our approach to both planning and grading.

While the A2LA approach does not differentiate between "major" and "minor" deficiencies, we did not see any of their findings as a significant deterrent to our eventual success.



IN THIS ISSUE

The A2LA assessment is completely objective. The assessors that came to CMPT were professionals, a microbiologist and a statistician, with a lot of experience and expertise in appraising against this standard. It was clear that we were not being assessed against practices as they had seen in other laboratories or proficiency testing programs; we were being assessed against the standard, and the official interpretations as expressed by the organization. It may be tough, but it is truly fair.

At this point we have seen and received the auditors' report, and we are now awaiting the "official" report from the organization. In the meantime we have already addressed most of the issues raised during the assessment.

A common question asked often at this point is 'Why do we seek official external validation?' It is certainly not required by any jurisdiction in which we provide our services and it has never been raised as a point of contention by our participants.

We do this because we believe in the concept of Quality and understand that external assessment is an essential component of that concept. We can (and do) go through the process of setting up our Quality Management System, and perform our internal audits, and management review, and customer satisfaction surveys, and we can (and do) point to the transparency of our reporting, to our strengths and also our weaknesses. However, until we go through the true exercise of external review, we cannot definitively argue that we truly meet the internationally accepted meanings of Quality and Performance.

And that is our goal.

Michael Noble, CMPT Chair

Proficiency Testing … A Focus on 16S rRNA gene sequencing and MALDI-TOF

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The National Molecular Microbiology Diagnostics Users Group, commonly called the National Molecular Group (NMG), has met annually since 2006 to provide a forum for bench technologists, supervisors or other interested parties to meet and discuss molecular diagnostics pertaining to the detection of infectious disease agents.

One of the common subjects of discussion for this group has been the difficulties which laboratories have in accessing comprehensive but cost-effective proficiency test (PT) programmes which target specific esoteric or rare diseases (for Canada). In 2010, it was suggested that the NMG take the lead to create a PT for 16S rRNA gene sequencing. The Special Bacteriology Unit at the National Microbiology Laboratory (NML) agreed to assist with organizing such a test.

In 2012, the first proficiency test for 16S rRNA gene sequencing, consisting of two pure cultures of isolates sent to 13 participant sites, was sent out. The NML selected, prepared, and shipped strains on blood agar plates. Results were summarized at the October 2012 NMG meeting (available at the NMG website:www.nmgroup.ca). Readers are invited to look at those postings to view specific details for each proficiency test.

By 2012, it became apparent that identification of bacteria using Matrix-Assisted Laser Desorption – Time of Flight (MALDI-TOF) mass spectroscopy systems was being widely adopted by laboratories in Canada and other countries. The simplicity for preparation of isolates, the rapid turnaround times achieved for microbial identification and the cost-effectiveness of this technology after initial expenditure to acquire a system, have been outlined over two issues of the CMPT Newsletter by the editor V. Restelli. This technology and its implementation have been the subject of several recent reviews (1, 2).

In Canada, new users to this technology may purchase systems from two different companies: the Bruker system (Bruker) and the Vitek MS system (Biomérieux), for a similar outlay of up front capital costs. The instrumentation and a number of common pathogens from highly curated databases attached to each system, namely, the Biotyper (Bruker) and In Vitro Diagnostics (IVD, Biomérieux) are Health Canada and FDA approved. The Vitek MS also provides a 'research use only' (RUO) database, called Saramis in older literature. These databases together are called the Vitek MS Plus (IVD Plus RUO).

A Canadian MALDI-TOF User's group (CMUG) headed by Dr. Michelle Alfa (DSM Winnipeg) and Kathy Bernard (NML, Winnipeg) was created in 2012 in response to the heightened interest in this new technology. This group had its first meeting as part of the AMMI-CACMID conference held that year in Vancouver, BC. Subsequent meetings co-chaired by Dr. Philippe Legacé-Wiens (DSM Winnipeg) and K. Bernard, have been held attached to the above named conference in 2013 (in Quebec City) and 2014 (in Victoria BC); a new meeting is being planned for the upcoming 2015 AMMI-CACMID meeting (see 'Get Connected').

The intent of this group is to provide an informal forum for discussion of MALDI systems for new or potential users, to highlight issues which have been encountered after extensive use of MALDI-TOF systems, to examine workflow adjustments after introduction of this technology within the work site and other topics of interest. Vendors also attend and are available to briefly describe any new lines of research or changes to their products which may have occurred in the past year.

In 2013 it was decided that the NMG-NML 16S rRNA proficiency test could be extended to include MALDI-TOF users. Beginning in that year, participants had the choice of doing 16S rRNA gene sequencing only, MALDI-TOF testing only, or both assays. If the laboratory site elected to do both, they were asked to have different people perform the 16S or MALDI testing and to refrain from discussing results. Participant sites could also elect to have more than one technologist work on the same PT panel, and if so, submit individual results from the same site, for example, results from: <laboratory X> - technologist 1 and <laboratory X> - technologist 2. Each set of results was individually evaluated after being sent back to K. Bernard at the NML for review; in this way, results obtained by individual technologists could be applied towards quality management / accreditation requirements.

Laboratories were given 2-3 weeks to return a report and results for each site were coded prior to further discussion. Each manager or contact could request a formal letter which described how well their specific laboratory results fared in the test but otherwise, each participant received results as part of a detailed email.

Participants were asked to provide the following information:

16S rRNA gene sequencing:

- If the sequencing step was done in house or sent outside to another site
- How many base pairs were obtained
- What criteria/scoring system were used to support the identification. For example, in our laboratory, we report 16S results using the following format: 'Bacterium identified as *Corynebacterium amycolatum,* 99.7% identity to *C. amycolatum* CCUG 35685^T [with GenBank accession no.] NR_117030'. There are a number of ways to express this type of information.
- Based on the identification obtained, would the participant report this information as a definitive result.

Similarly, MALDI-TOF users were asked to provide:

- Which MALDI system was used (Bruker or Vitek)
- Were panel strains tested after using a 'direct' or 'extracted' method (or both)
- What identification and score(s) were obtained
- If based on the MALDI result, would the user report the identification of the isolate as definitive.

Strains from our contemporary or historical culture collection were selected for each panel, ensuring that the identity of the organism was unapparent to Special Bacteriology staff, so they too could participate in the proficiency test. Staff from three other laboratories at the NML also participated in these proficiency tests.

Each strain had had at least 16S and some biochemical testing done. Some strains had also had an extensive slate of biochemical, chemotaxonomic, or other tests done. Isolates were selected and degree of difficulty established on the basis that if, after use of 16S rRNA gene sequencing or by the MALDI system, could the bacterium be unambiguously identified and if that genus and species would be reported definitively. If not, it was suggested that participants report caveats observed and/or comments. For example, if two or more species from the same genus were observed to give rise to similar 'high scores', regardless of method, it was intended that the participant should discuss this observation and provide a comment as to which genus and species / other wording, would ultimately be used to report the result.

Some participants provided substantial information as to how they came to derive a decision on reporting the result, especially for the more 'difficult to identify' samples sent out. Other laboratories did not provide any or minimal information as to how they came to their conclusions.

In 2013, three pure cultures of bacteria were sent on sheep blood agar plates to 29 participants located at 25 sites. The bacteria were selected to represent, by both 16S rRNA gene sequencing and by MALDI-TOF, different degrees of difficulty in providing a definitive, unambiguous identification of the isolate. Bacteria selected were: *Streptococcus suis* (deemed to provide an easy, unambiguous identification regardless of method used), *Klebsiella pneumoniae* (with a subtle identification ambiguity, for both approaches) and an unidentifiable bacterium (by the Special Bacteriology laboratory) which best fit the family *Aerococcaceae*, and so by both 16S rRNA gene sequencing and MALDI should give rise to an unidentifiable result.

A similar selection and triage process was used for the October 2014 test. In this round, the panels consisted of four strains rather than three and were shipped in transport media rather than on blood agar plates. Thirty four sites participated in the 2014 test; 11 of these did both 16S and MALDI testing, 9 sites did 16S only and 11 sites did MALDI-TOF only. Among MALDI-TOF users, 16 used Bruker and 13 sites used Vitek MS systems.

There was an intended but subtle attempt here to solicit for certain information or comments as invoked by the results. The bacteria selected here were: *Bacteriodes fragilis* (deemed to provide an easy, unambiguous identification regardless of method used); *Corynebacterium propinquum* (moderate complexity, as this species is not easy to discern from *C. pseudodiphtheriticum* by either method, based on recent literature) (3); *Burkholderia thailandensis* (discussed further below) and an unidentifiable bacterium from the family *Propionibacteriaceae.*

Inclusion of *B. thailandensis*, a risk Level 1 bacterium and exceedingly rare human pathogen (4) to the panel, merits discussion. This bacterium cannot be unambiguously differentiated from two risk level 3 bacteria, *B. pseudomallei* and *B. mallei,* by 16S sequencing alone.

All laboratories in Canada should be aware that if an isolate identified in their facility has features suggestive of a risk level 3 pathogen regardless of whether results were generated by an automated identification system, by 16S rRNA gene sequencing, or by manual biochemical methods, they should send or consider sending the strain to a reference centre for definitive identification. For this proficiency test, it was anticipated that participant laboratories which are also members of the Canadian Laboratory Response Network (CLRN), would (possibly) indicate that they would definitively rule out / rule in the risk level 3 species within the confines of a containment level 3 setting. That being said, inclusion of this bacterium in the 2014 panel carried a significant caveat: as shipper, we must truthfully declare the risk level of the bacteria included in the panel, so participants had a clue at the front end of the type of bacteria being assessed.

Among 16S rRNA gene sequence test results, all 22 participants from 20 sites identified this bacterium as *B. thailandensis* but only 36% of these commented on detecting high degree of identification/scores towards both *B. thailandensis* as well as *B. pseudomallei* and would consider sending the isolate to a reference centre for definitive identification.

It was anticipated that results from MALDI users would be problematic. Bruker's Biotyper database LACKS entries for *B. pseudomallei* and *B mallei,* but does have a single entry for *B. thailandensis*. Spectra for the risk Level 3 agents are only located in a separate database called the 'Security Relevant' or SR database; Bruker users would have to have purchased and then accessed this second database, in parallel to the Biotyper, to infer any close relationship between *B. thailandensis* and *B. pseudomallei*. In fact, when this was done (as tested here at the NML), the *B. thailandensis* reference strain gave rise to significant Bruker scores (2.0-2.1) towards entries for both *B. thailandensis* and *B. pseudomallei,* suggesting that those species could not be differentiated by the Bruker MALDI system alone. Issues pertaining to accessing a separate Bruker database to screen strains for potential identification as risk level 3 bacteria has been described recently (5) .

In this PT, only 37% of Bruker users identified the bacterium as *B. thailandensis* and also inferred that they would send the strain to a reference centre to rule out risk level 3 agents or to provide final identification. None of the 13 Vitek MS users provided the correct identification.

The Vitek MS IVD database appears to lack spectra for both *B. thailandensis* and *B. pseudomallei*; the RUO database has at least one entry for both, but neither species was reported by participants in this PT from any site. As a result, most Vitek users gave responses of low to high type scores towards a variety of *Burkholderia* species, such as those in the *B cepacia* group. Although this test was flawed due to the shipper declaration issue, the following comments can be made from the results:

- When one suspects or encounters strains which by their usual identification system have features of a risk level 3 agent, all

work should cease and the bacterium should be discussed with and sent to the nearest CLRN laboratory or to the NML for definitive identification and molecular typing, as required. Contact at the NML for further information at: BADD.NML@phac-aspc.gc.ca or call 1-204-784-5928

- 16S rRNA gene sequencing alone cannot be used to discern: *B. thailandensis* from *B. pseudomallei* or *B. mallei; Bacillus anthracis* (risk level 3) from other members of the *Bacillus cereus* group, or (risk level 1) *Yersinia pseudotuberculosis* from (risk level 3) *Y. pestis.*
- Anecdotally, bacteria which cannot be readily resolved by 16S rRNA gene sequencing alone will probably not be resolved by the MALDI system alone.
- Users must be aware of the limitations of the databases provided by the vendors to correctly identify pathogens as risk level 3 agents, as outlined here or as described in recent literature.

Genomic Research and Development Initiative funded MALDI-TOF Project

In 2013-2014 staff at the NML with K. Bernard as principal investigator, in partnership with a number of other Canadian laboratories, successfully competed for 2.5 years of funding from the (GRDI, http://grdi-irdg.collaboration.gc.ca/eng/about/index.html) on a project to create MALDI-TOF spectra for 'rare or unusual or difficult to identify' pathogens, which are poorly represented or absent from the Bruker Biotyper database.

The intended result of this project is to create a Canadian 'National MALDI Database', consisting of curated entries of such taxa, beta-test their quality by sending the new database / panels of live bacteria for blind testing by external partners and then make this database freely available to members of a consortium of Canadian MALDI users.

Criteria for membership in the consortium of MALDI-TOF users will be announced at a future date, closer to the end of this project.

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Interested readers can join CMUG by filling out the 'new members' form located at: www.dsmanitoba.ca/CMUG.

Part III: MALDI-TOF; other applications in the Clinical Microbiology Laboratory

In our previous articles we discussed how MALDI-TOF MS has helped with the rapid identification of commonly isolated organisms in the clinical microbiology.

However, MALDI-TOF MS has special importance in routine identification of pathogens that require long incubation times and complex culture conditions such as anaerobic bacteria, mycobacteria, and fungi. Significant reduction in time to diagnostic and to laboratory costs that this technology offers could significantly change the management of these infections.

Anaerobes

Anaerobes identification by MALDI-TOF MS has shown some promising results and reliable identification is usually achieved for frequently isolated clinical bacteria, such as *Bacteroides fragilis*, *Clostridium perfringens*, and *Finegoldia magna*. However, the ability of MALDI-TOF MS to identify anaerobic species is not as robust as it is for more commonly isolated bacteria.

Mycobacteria

Rapid identification of mycobacteria is essential for the prompt management of infected patients. Species identification has relied on phenotypic tests that require long incubation periods and usually require specialized laboratories.

Although some success in the identification of mycobacteria has been achieved with whole cells, several protein extraction protocols have been developed in order to increase the quality of the MALDI-TOF spectra and also to address biosafety concerns.

Unfortunately, significant amount of material or biomass has been reported to be needed for the proper identification of mycobacteria and this process may take several days of culture.

Fungi

As with mycobacteria, MALDI-TOF MS has the potential to significantly impact the identification of fungi and the management of fungal infections.

Reproducible MALDI-TOF spectra are usually obtained for yeasts as their growth is rapid and homogeneous on agar plates. Promising results have been achieved with whole cell, direct on-plate methods.

Molds have been proven to be more difficult to analyze as their variable growing patterns, their diverse morphology, and different structures affects spectra reproducibility. Protein extraction protocols are needed as their stronger cell walls prevent proper lysis; additionally grow conditions and difficulty to obtain a standardized inoculum all affect spectra reproducibility. Furthermore, the presence of melanin has been shown to inhibit ionization during the MALDI-TOF MS process.

Direct detection of organisms from clinical samples

The ability of MALDI-TOF MS to detect organisms directly from clinical samples is determined by several factors:

- Type of infection: current MALDI-TOF MS data software analysis is not able to reliably identify all microorganisms present in mixed cultures therefore, is only applicable to infections that are typically monomicrobial.
- Concentration of microorganisms in the clinical sample: the most promising results have been obtained when bacteria are present in concentrations > 10^5 cfu/mL
- The presence of host proteins: the presence of host proteins (serum) interferes with the analysis by introducing unexpected peaks into the mass spectra.

Taking into account all these factors, two clinical samples are good candidates for the direct detection of organisms by MALDI-TOF MS:

- *Urine* is considered a good candidate for as urinary tract infections are generally monomicrobial and clinically significant infections generally have a high number of bacteria (>10^5 cfu/mL). Furthermore, there are almost no host proteins in the sample that would interfere with the identification spectrum.

  Studies have shown excellent positive predictive value although sensitivity could be improved, especially for gram positive bacteria

- *Blood cultures* are also good candidates for direct identification of organisms by MALDI-TOF MS. Unfortunately, because the organism load in bacteremias can be as low as 1 cfu/mL, identification of organisms is restricted to positive blood cultures instead of directly from the patient's blood.

  Organism concentration in positive blood cultures easily reach >10^7 cfu/mL, well within the detection limits of MALDI-TOF. However, unlike urine samples, separation protocols need to be applied to separate bacterial proteins from host proteins (serum) as human proteins will interfere with the analysis.

Detection of antimicrobial resistance

MALDI-TOF MS has also been applied for the analysis and detection of antibiotic resistance mechanisms. Although methods have been developed to detect all types of resistance mechanisms, the most common approach has been the detection of resistance based on the modification of target antimicrobials.

In this approach, the bacterial culture is incubated in the presence of the antimicrobial for 1-3 hours and the sample is then analyzed by MALDI-TOF MS. The spectrum obtained is analyzed for the modification of the antimicrobial compound. Figure 1 shows a representation of a carbapenemase detection method.

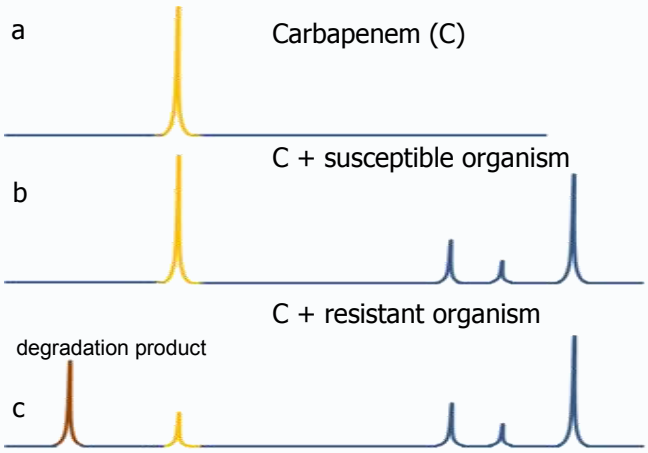

Figure1. Schematic representation of a cabapenemase detection method by MALDI-TOF MS. a: carbapenem peak without the organism; b: susceptible organism with the intact carbapenem peak; c: carbapenemase producing organism, the carbapenem peak disappears and degradation products are observed.

A very interesting approach using labelled isotopes has been recently developed. The method consists on growing the organisms in a medium containing nutrients labelled with stable isotopes (e.g. 90% C^{13}). Organisms growing in this medium will incorporate the label and their protein spectrum will shift in mass in a predictable way. When incubated with an antibiotic, resistant organisms will grow, showing the expected shift in the spectrum, while sensitive organisms will not grow showing the original spectrum (Figure 2).

The advantage of this method is that it can potentially detect any kind of resistance mechanism.

Conclusion

In this three part series on MS in the microbiology laboratory we have reviewed the actual and potential applications of this technology and the benefits this technology could bring to the microbiology laboratory.

Although applied very successfully to the identification of certain organisms, the technology is not without limitations.

Most of the problems encountered are due to the lack of reliable databases, an issue that is expected to be improved as more organisms are tested and analysed so databases can be strengthened.

Some organisms are, however, too similar to be differentiated by MALDI-TOF MS and thus, confirmation assays need to be performed until new protocols are developed that allow for their definitive identification.

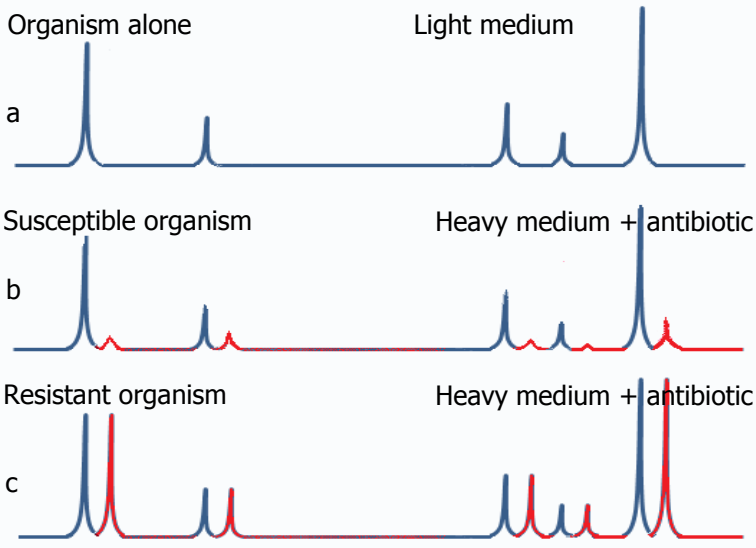

Figure 2. Schematic representation of detection of antimicrobial resistance by stable isotope labelling; a: bacteria grown in normal (light) medium; susceptible (b) and resistant (c) bacteria grown in isotope labelled (heavy) medium in the presence of the antibiotic (Demirev, 2013)

Although MALDI-TOF MS has had a lot of progress in the field of mycobacteriology, mycology, and antimicrobial resistance detection, there is still a long way to go for these tests to become part of the routine analysis in the clinical microbiology.

The continuous development of new and creative protocols speaks of the great versatility of this technology, which explains why many laboratories have already embraced it for their routine identification of organisms.

Veronica Restelli, Editor

Suggested readings

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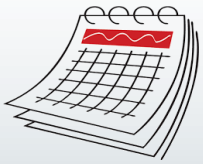
Upcoming Events

MARCH 2015

51st British Society for Medical Mycology 51st Annual Scientific Meeting

March 8-10, Aberdeen, Scotland

More info: http://www.bsmm.org



APRIL 2015

AMNI Canada - CACMID 2015

April 16-18, Charlottetown, PEI

More info: http://www.ammi.ca/annual-conference/2015/

European Congress of Clinical Microbiology and Infectious Diseases

April 25—28, Copenhagen, Denmark

More info: http://2014.eccmid.org/eccmid_2015/#c11979

JUNE 2015

2nd Annual Microbiology and Infectious Diseases Asia Congress

June 2015, Singapore

More info: http://www.microbiologyasia-congress.com/

ABOUT CONNECTIONS

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