Year 2, No. 1, June 2015

Auto-immunity

CLOSE UP

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A.MENARINI diagnostics

Auto-immunity CLOSE UP

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Aims & Scope
Autoimmunity Close Up is the new A. Menarini Diagnostics publication in the field of autoimmunity. The magazine establishes an interdisciplinary forum connecting experts involved in all aspects of the complex world of autoimmunity diagnosis.
Autoimmunity Close Up provides our customers and colleagues with important product information and updates, insights into issues of general interest in autoimmunity and the latest findings in autoimmune diseases.
The magazine encompasses a wide range of topics including connective tissue diseases, rheumatoid arthritis, antiphospholipid syndrome, celiac disease, IBD, vasculitis, autoimmune thyroid and liver diseases, as well as POCT, ITC & health economics.
Each issue features reviews, editorials, and interviews with leading scientists who actively participate in building the content.
If you have any questions or require further information about *Autoimmunity Close Up*, please contact your local A. Menarini Diagnostics Affiliate or Distributor.

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In this issue:

EDITOR'S NOTE

Welcome Back, AICU!

After our first issue, this edition confirms our traditional format of a mix of articles that we hope will prove useful for work in your autoimmunity laboratories.

This issue contains contributions related to the diverse group of autoimmune vasculitides and the use of methods recognised as the state of art, namely, IIF and the ANCA substrate. The term "vasculitis" refers to a large variety of diseases, among them Takayasu's arteritis, cutaneous vasculitis, Kawasaki disease, polyarteritis nodosa, Churg–Strauss syndrome, microscopic polyangiitis, and granulomatosis with polyangiitis, also known as Wegener's granulomatosis. Often, these diagnoses are closely dependent on the laboratory results and then, of course, on the clinical picture; this explains why the reading, interpretation, and standardisation of the detection of MPO and PR3, or the ANCA-related antibodies, is so important.
Immunoassays used for the measurement of autoantibodies should be sensitive and specific, and their use is cost-effective in the clinical setting as they significantly and rapidly complete the picture. These results are dependent on a large number of factors such as antibody specificity, reaction kinetics, multimeric state of the proteins, matrix effects, etc. Furthermore, quantification with immunoassays requires the use of a proper calibrator. In fact, the EU Directive on In Vitro Diagnostic Medical Devices (IVD-MD) (Directive 98/79/EC) requires traceability of calibrators and control materials to reference measurement procedures and/or reference materials of higher order. As regards traceability, for example, many steps forward have been made, mostly thanks to the advent of information technology. A practical effect in the daily lab routine is the use of a barcode (2D BarCode) over the surface of the IFI slides; this will eventually supplant the traditional use of pencils or similar to mark the slides, a major source of error in the identification of the slides and samples.
A general standardisation system is, realistically, still a long way away in autoimmunity; nevertheless some initiatives have been particularly well received such as, for example, the setting up in 2009 of a new working group with a mandate for the Harmonisation of Autoantibody Tests (WG-HAT) by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). The example of the production and certification of ERM-DA476/IFCC, a new serum protein reference material intended for the standardisation of measurements of antimyeloperoxidase immunoglobulin G (anti-MPO IgG) antibodies, is a brilliant solution to the historical lack of standardisation. In this initiative, the European Commission, through the Joint Research Centre of the Institute for Reference Materials and Measurements (IRMM) in Geel, Belgium, has played a pivotal role.

Coming back to the contents of this issue, the first contribution is related to the technologies used for the automated microscopes and scanners for indirect immunofluorescence, which allow an improved standardisation in this field, typically poor on this respect.
We then turn to Filippo Nencini, Project Leader at Visia Imaging, who has released a very practical solution to aid the reading, interpretation and diagnosis of vasculitis on the ANCA IIF substrate. In this section, he presents the preliminary results obtained with this novel approach.
In "Autoimmunity Lab", we focus on a selection of publications about the use of automated computer-aided diagnostic systems for antinuclear immunofluorescence antibody screening. The literature clearly shows that all systems on the market, including the Zenit G-Sight series, perform very well in the task for which they were created. Indeed, the automatic discrimination between positive and negative samples had an accuracy tending to 100%. Sophisticated new software applications are now available allowing better definition in the automatic recognition of patterns and light signal conversion to end-point titer. In the future, this may avert the need to dilute serum for titration, which will result in significant economic advantages as well as saving time.

Finally, we round up this issue with a section introduced in the previous edition – "Company Pinboard" – where we highlight forthcoming events in autoimmunity, such as a workshop in Vienna and the EuroMedLab congress in Paris.

Massimo Donnini
International Product Manager Autoimmunity
A. Menarini Diagnostics

A.MENARINI diagnostics

TECHNICAL INSIGHTS

Standardisation and Traceability in the Immunodiagnostics Lab

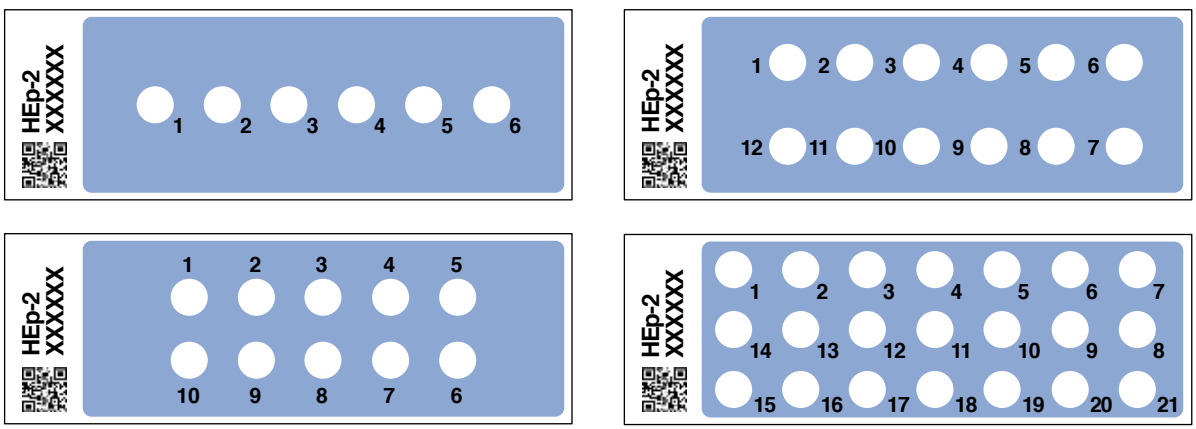
The detection and quantification of antibodies to autoantigens are important for the diagnosis and monitoring of a number of autoimmune diseases. The increasing volume of tests ordered for these purposes, their labour-intensity, and, above all, the large variability of results, potentially leading to diagnostic and follow-up delays or misdiagnosis, call for a standardisation process, whereby different immunoassays allow intra- and inter-laboratory comparisons.

In 2009, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established a working group with a mandate for the Harmonization of Autoantibody Tests (known as WG-HAT), and considerable efforts are being made to address the issue of standardisation and harmonisation in the field of immunodiagnostics. Concerning specifically the field of antinuclear antibody (ANA) testing, an international group of experts pointed out that '*while it* [indirect immunofluorescence] *is considered the 'gold' standard, it is only as good as the laboratory that performs this assay*'. Those experts therefore undertook a three-step process followed by a Delphi exercise with closed voting and issued 25 recommendations for the appropriate assessment and interpretation of anticellular antibodies of the ANA family.[1] Additionally, they recognized that, in parallel to defining new autoantibodies and developing new platforms, there is an urgent need for training programmes for clinicians, technicians and the industry, and mentioned some issues needing further studies, such as the local validation of platforms, significance of titres and patterns between different populations and stages of diseases, and the role of automated methods for indirect immunofluorescence assays that may overcome the many limitations of the manual assays.[1]

The issue of standardisation is also discussed in a paper by Beck and Lock[2], focusing on measurement uncertainty from the perspective of an immunology laboratory. As the authors recall, the measurement uncertainty principle is that systematic error (bias) should be corrected for by reference to standards, leaving random error (measured by the standard deviation) as the basic parameter for measuring uncertainty. However, because of the lack of standards, it is hard to isolate random error as the sole source of error. At present, there is no unified international solution to standardisation issues; therefore, in order to minimise assay uncertainty, maximum adherence to quality control measures has to be ensured.[2]

As discussed by Beck and Lock, the availability and use of *standards* is a crucial point. At present, there is a limited number of specific autoantibody standards made available

Examples of bar-coded substrate slides



Actions to increase the accuracy and reliability of immunology assays

Action	Qualitative assays	Semi-quantitative assays	Quantitative assays
Validation methods including confirmation of clinical sensitivity and specificity, where possible	✔	✔	✔
Use of **internal quality control** (IQC) material	✔	✔	✔
Enrolment in **external quality control** (EQC) schemes, where possible, or in alternative mechanisms of comparisons should be employed	✔	✔	✔
Scrutiny of IQC performance to accept assay runs with appropriate use of **Westgard rules**	–	–	✔
Root cause analysis investigations of IQC/EQA failure	–	–	✔
Clinical authorisation and clinical commentary of results	✔	✔	✔
Use of **CE marked reagents** not necessarily as part of a standard kit	✔	–	–
Use of **CE marked commercial kits**. It is possible to use non-CE marked kits provided that adequate evidence of assay maintenance is available	–	✔	✔
Use of **manufacturer-validated reference ranges**, internally verified as appropriate	–	–	✔
Expertise in IIF reading	✔	–	–
Audit of IIF reading with comparison of user agreement and regular revalidation of competency exercises. **Definition of "correct result" must be established** whether this be based on an expert opinion or on consensus. **Re-education** of any out-of-consensus reader is critical for quality improvement	✔	–	–
Regular maintenance of analysers, diluters and UV microscope	✔	✔	✔

by the World Health Organization (WHO) and the Centers for Disease Control (CDC), many of which do not allow quantitative assessment. Therefore, standards for specific proteins are mostly derived from international calibration material, such as ERM-DA470k/IFCC, a serum protein standard which is available for the calibration for 12 serum proteins, including immunoglobulins G, A and M. However, even with certified reference preparations harmonisation of results among manufacturers may not be achievable.[2]

Traceability is another critical issue for standardisation: for many autoantibody methods, it is limited to in-house procedures or calibrators that are often assigned an arbitrary value, and even when there is a good traceability there is often no agreed standard.[2]

Concerning *methodological standardisation*, understanding of the analytical aspects of assays – including the biology of the target antibodies and the clinical significance of the results – is imperative in ensuring that results are correctly interpreted.[2]

Given that qualitative, semi-quantitative and quantitative immunoassays all suffer from analytical variability, the authors provide some examples of measures they believe would maximise the accuracy and reliability of assay results.[2]

Because of the current lack of standardisation, all data should be scrutinised to minimise the potential risk, and *sense checking* of results in relation to a known clinico-epidemiological context is fundamental. In fact, although clinical sensitivity and specificity provide good indications as to the clinical significance of results, no immunology test result alone should be used to make a definitive diagnosis without correlation with the clinical context.[2]

Besides the abovementioned uncertainty and standardisation issues, a key element is the ability to trace each single specimen. In fact, specimen (tissue sections, wells, slides)

tracing could possibly be viewed as a further step in the traceability pathway.

Bar-coding can be one valuable tool for specimen traceability. In a systematic review and meta-analysis of 17 observational studies (10 studies for bar-coding of patient specimens and 7 for bar-coding of point-of-care testing),[3] each comparing bar-coding to non-bar-coding identification systems, patient specimen bar-coding statistically significantly reduced the error rate compared to rates before the introduction of bar-coding practices (OR 4.39, 95% CI 3.05 to 6.32 nine studies). Similarly, bar-coding of point-of-care testing statistically significantly reduced error rates compared to rates prior to the introduction of this practice (OR 5.93, 95% CI 5.28 to 6.67 seven studies).[3]

Bar-coding therefore proved to be effective for reducing patient specimen and laboratory testing identification errors in diverse hospital settings and was recommended by the authors as an evidence-based "best practice".[3]

Immunodiagnostics is one of the several fields where bar-coding can improve specimen processing as well as laboratory workflow. In order to support bar-coding in the immunodiagnostics laboratory, A. Menarini will soon make available bar-coded immunofluorescence slides. These will represent an additional tool for improving patient safety and facilitating technical work.

Take home message

- Current issues in the field of immunodiagnostics underscore the importance of standardization
- Standards are crucial to correct for systematic errors. The use of standards must be backed by traceability
- Sense checking of results in relation to a known clinico-epidemiological context is fundamental
- Specimen tracing (e.g., through bar-coding) could possibly be viewed as a step in the traceability pathway

1. *Agmon-Levin N, Damoiseaux J, Kallenberg C, et al. International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. Ann Rheum Dis. 2014;73(1):17-23.*
2. *Beck SC, Lock RJ. Uncertainty of measurement: an immunology laboratory perspective. Ann Clin Biochem. 2015;52(Pt 1):7-17.*
3. *Snyder SR, Favoretto AM, Derzon JH, et al. Effectiveness of barcoding for reducing patient specimen and laboratory testing identification errors: a Laboratory Medicine Best Practices systematic review and meta-analysis. Clin Biochem. 2012;45(13-14):988-98.*

RESEARCH UPDATES

Evaluation of the Zenit G-Sight for the Automatic Identification and Interpretation of ANCA Patterns

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Introduction

The indirect immunofluorescence technique on ethanol-fixed neutrophils is still the method of choice to detect antineutrophil cytoplasmic antibodies (ANCA) in ANCA-related vasculitis. The objective of the study was to evaluate the Zenit G-Sight system (A. Menarini Diagnostics, Florence, Italy) for the automated interpretation of ANCA patterns.

Method

The Zenit G-Sight system is a microscope equipped with a motorized precision stage that holds up to 8 slides. The acquisition source features a 450 nm-490 nm wavelength LED and a colour camera. Well plate acquisition is performed using a 40x lens or optionally a 20x lens. The system is designed to acquire the entire well plate and to view it through the virtual microscope. The software was developed for the automated reading and interpretation of HEp-2 cells and ANCA patterns. For each well, the fluorescent intensity of the cells is measured and the pattern is classified. The system was trained on a set of sera previously classified so as to optimise the recognition algorithm response. A positive probability measure is used to classify the well as positive, negative or uncertain and to set two discrimination thresholds between the three responses. The system also allows recognition of P-ANCA, C-ANCA and other- ANCA patterns (not P, not C) (Figure 1). To enable pattern identification, the system performs the following steps: it applies techniques to separate the cells from the background; it calculates texture parameters and uses them as descriptors of a

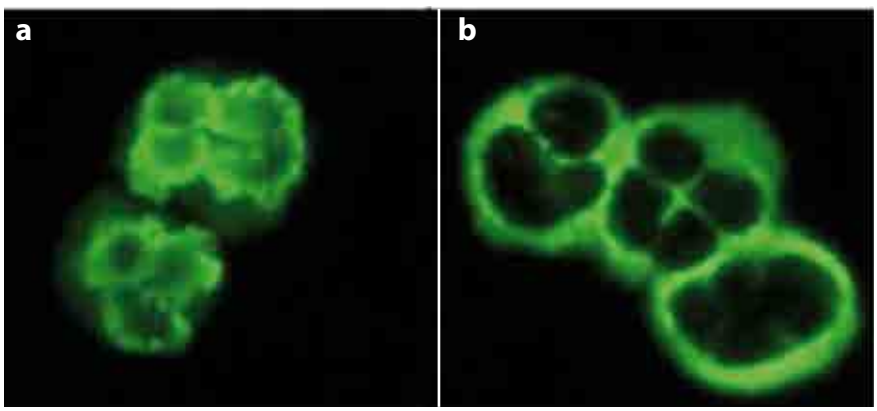

Figure 1: a. Detail of P-ANCA pattern; b. Detail of C-ANCA pattern

Table 1: Concordance of positive/negative response between observer and Zenit G-Sight

	Human observer	G-Sight	Concordance (%)
Tot Neg.	**19**	19 (0 false pos.)	**83**
Tot Pos.	**16**	10 (6 false neg.)	
P-ANCA	10	7	70
C-ANCA	4	2	50
Other-ANCA	2	1	50

supervised classifier so as to provide the relevant pattern for each cell.

Results

The Zenit G-Sight system was evaluated for the identification of ANCA patterns on 35 sera, of which 16 positive and 19 negative samples. The positive samples showed the following patterns: 10 P-ANCA, 4 C-ANCA and 2 other-ANCA. The concordance of positive/negative response (considering uncertain response as negative) between the system and the human observer was 83% with 0 samples classified as false positive and 6 as false negative. The Zenit G-Sight system assigns a P-ANCA pattern in 7 out of 10 samples (70%), C-ANCA in 2 samples out of 4 (50%) and other-ANCA in 1 sample out of 2 (50%). If the response is not positive, the system provides no pattern indication. Table 1 summarizes the findings.

Conclusions

Automated reading with the Zenit G-Sight system demonstrated reliable results consistent with visual assessment. The results show that the system can be used to assist in ANCA pattern interpretation.

An old approach for an advanced technology

Immunofluorescence (IF) is still the reference standard for ANA screening. However, despite the availability of screening techniques using automated EIA, chemiluminescence or Luminex methods, immunofluorescence test volumes are not increasing but remain stable.

The main driving force away from IF have been the shortage of skilled technologists (smaller numbers of well-trained immunologists along with retirement of the older generation) to read the microscopic IF tests, and the greater manual labour time. The need to avoid manual procedures has been made more urgent by the current scenario where there is a tendency to concentrate autoimmune testing in fewer labs with increased workload volumes. Thus, these large labs have become interested in using automated microscope systems with pattern recognition which can eliminate the large number of negative specimens. In this context, the **Zenit G-Sight** automated IF scanner appears to have more placements than any of the other competitors in Europe.

The importance of standardisation stimulates the introduction of new methods to perform calibrations on these particular automated microscope systems. In this respect, the **Zenit G-Sight uses calibration slides**, which are designed for the routine calibration of confocal fluorescent microscopes and other systems for fluorescence image acquisition.
The slides are prepared by mounting statistically distributed monodisperse PMMA (polymethylmethacrylate) particles, containing ultra-stable fluorophores on slides of a standard size of 75 x 25 x 1 mm.
These calibrations are useful tools for checking the calibration of the lighting path, to enable the LED lighting value to be self-regulated or, where necessary, to identify any defects or malfunctions. However, they are chiefly useful because these optical standards nowadays represent the unique and irreplaceable tool to ensure that the lab produces consistent results.

With a view to offering a valid tool to minimise the effect of the retirement of immunologists and consequently the need for enhanced technologist skill in reading the microscopic IF tests through scanners, **Zenit G-Sight** uses the JPEG2000 format to generate files that contain a whole "digitized" well.

The JPEG2000 is a format that, compared with standard compression formats (such as JPEG), has the following advantages:

- better image quality used in the compression: this allows for the same compression ratio to provide a better visual quality of the images
- creation of an image "pyramid" (from high to low resolution): this allows the advantage of efficiently creating the virtual microscope (navigation at different magnifications)
- image creation and storage for a single slide: this enables the user to navigate very large images in an optimal manner
- altogether, the above points allow for better and more efficient remote viewing of images

This latter feature opens up new perspectives with respect to second opinions, as it allows users at two remote locations to exchange views on specific IFA results, thus facilitating their interpretation.

Massimo Donnini

AUTOIMMUNITY LAB

Automation in Indirect Immunofluorescence

Indirect immunofluorescence (IIF) is the standard screening method for the detection of antinuclear antibodies (ANA). Several automated IIF systems have been implemented to relieve IIF from the need for expert morphologists, the subjectivity of interpretation, and a low degree of standardisation and automation.

A retrospective study by **Bossuyt et al.**,[1] from the Catholic University and the University Hospitals in Leuven, and Menarini Benelux in Zaventem, Belgium, **tested the diagnostic performance** of one such automated system (**G-Sight, Menarini**) in estimating fluorescence intensity and classifying fluorescence patterns.

Image acquisition by G-Sight, performed on 268 consecutive samples, indicated a good agreement between results obtained with two cell substrates (HEp-2 and HEp-2000), except for the nucleolar pattern. Agreement for positivity/negativity was 0.85 (statistics 0.81, 2-tailed p value <0.0001) for cutoff at dilution 1:80, and 0.91 (statistics 0.81, 2-tailed p value <0.0001) for cutoff at dilution 1:160.

In 259 consecutive samples, there was a significant correlation between the end-point titer and the probability index (i.e., the probability measure of positivity) (Spearman's rho [95% CI]: 0.77 [0.71–0.81], 2-tailed p<0.0001). The increase in likelihood ratios (i.e., the likelihood in patients divided by the likelihood in controls) for systemic rheumatic disease with increasing probability index indicates that the G-Sight automated system offers clinically useful information and facilitates standardised interpretation.

The accuracy of pattern assignment was limited and dependent on the pattern and the substrate used; the highest percentage of correct assignment was attained for the centromere pattern.

A broader study by **Bizzaro et al.**,[2] a Study Group on Autoimmune Diseases of the Italian Society of Laboratory Medicine, assessed six IIF automated systems – Aklides, EUROPattern, Helios, Image Navigator, NovaView and G-Sight (I-Sight-IFA) – through the analysis of 92 ANA-positive and 34 ANA-negative sera. Overall, at the cutoffs suggested by manufacturers, sensitivity was 96.7% and specificity was 89.2% (Table 1). For the five systems giving a quantitative value of the light signals, the signal intensity showed a good correlation with the titer obtained by manual reading (Table 1) (Spearman's rho between 0.672 and 0.839; p <0.0001 for all systems). Intra-assay imprecision, as measured in five aliquots of the same sample serum, was 39.12% for the manual method and ranged from 1.99% for G-Sight to 25.26% for Aklides (Table 1). Accuracy in the recognition of the most typical patterns was limited, ranging from 52% with Aklides to 79% with EUROPattern (Table 1). Overall, accuracy in recognition ranged from 70 to 85% for the classic nuclear and nucleolar patterns, and from 20 to 50% for the rarer patterns.

Overall, the results of these two studies indicate that using an **IIF automated system in (auto)immunodiagnostics can improve harmonisation** by reducing intra- and inter-laboratory variability. Besides improving the clinical efficacy of the autoimmunology laboratory, the use of an automated system could have a remarkable impact on laboratory work-flows.

Table 1: Comparison of six immunofluorescence automated systems based on their performance characteristics

	Aklides	EUROPattern	Helios	Image Navigator	NovaView	G-Sight	Total
Sensitivity* (%)	97.8	96.7	97.8	95.7	93.5	98.9	96.7
Specificity¶ (%)	88.2	85.3	94.1	94.1	94.1	79.4	89.2
Correlation between light intensity and titer^	0.672 (0.560–0.760)	0.754 (0.664–0.822)	–	0.831 (0.766–0.879)	0.839 (0.773–0.885)	0.822 (0.754–0.873)	n.a.
Imprecision (%)	25.26	23.76	–	15.06	7.98	1.99	n.a.
Accuracy (%)	52	79	n.a.§	n.a.§	54	63	

*Positive samples on automated assessment over positive samples on manual assessment
¶Negative samples on automated assessment over negative samples on manual assessment
^Spearman's rho (95% CI) for the correlation between light-intensity value and manually assigned titer; p<0.001 for all the systems
§The system does not provide data on fluorescence pattern

1. *Bossuyt X, Cooreman S, De Baere H, Verschueren P, Westhovens R, Blockmans D, Mariën G. Detection of antinuclear antibodies by automated indirect immunofluorescence analysis. Clin Chim Acta. 2013 Jan 16;415:101-6.*
2. *Bizzaro N, Antico A, Platzgummer S, Tonutti E, Bassetti D, Pesente F, Tozzoli R, Tampoia M, Villalta D; Study Group on Autoimmune Diseases of the Italian Society of Laboratory Medicine, Italy. Automated antinuclear immunofluorescence antibody screening: a comparative study of six computer-aided diagnostic systems. Autoimmun Rev. 2014 Mar;13(3):292-8.*

COMPANY PINBOARD

Latest Marketing & Scientific Events

2015 EuroMedLab is about to start!

The 21st IFCC-EFLM European Congress of Clinical Chemistry and Laboratory Medicine (EuroMedLab), will take place in Paris, France, on 21-25 June 2015 in the Palais des Congrès and will cover both the basic science in laboratory medicine and the applications of this ever-evolving field in academia, industry and laboratory practice. Through plenary lectures, symposia, educational workshops, and poster sessions participants will have the opportunity to update and share their knowledge and establish partnerships.

The EuroMedLab Paris 2015 will also feature educational workshops, which will be held in cooperation with in vitro diagnostic industries.

A. Menarini Diagnostics will hold the educational workshop ***Novel diagnostic tools for the diagnosis of autoimmunity liver diseases***, which will be chaired by Xavier Bossuyt and will feature the following:

- **Introduction to autoimmune liver disease testing**
  Xavier Bossuyt
  University of Leuven, Leuven (Belgium)
- **Role of autoantibodies in primary biliary cirrhosis**
  Pietro Invernizzi
  Humanitas Clinical and Research Center, Rozzano (Italy)
- **Diagnostic and prognostic significance of autoantibodies in autoimmune hepatitis**
  Luigi Muratori
  Sant'Orsola-Malpighi Hospital, Bologna (Italy)

A. Menarini Diagnostics will also have a stand at EuroMedLab Paris 2015: in depth information on the company's latest products will be provided to visitors.


By Myrabella

A prestigious venue for the next Austrian Autoimmunity Symposium

A. Menarini Autoimmunity Symposium will take place in Vienna, Austria, on June 12-13 2015, at the Apothekertrakt, on the east side of the Schönbrunn palace grounds.

The workshop will feature:

- **A technical session on autoimmunodiagnostics, the use of automated systems and their impact on the diagnostics of antinuclear antibodies, and fluorescence pattern recognition in Hep-2 cells.**
  Werner Klotz, Innsbruck (Austria)
- **Anti-neuron antibodies, their use and interpretation of test results, as well as a comparison of visual versus automated analysis.**
  Manfred Herold, Innsbruck (Austria)
  Xavier Bossuyt, Leuven (Belgium)
  Romana Höftberger, Vienna (Austria)
  Jörg Hofmann, Vienna (Austria)


By Jebulon

ZENIT·GSIGHT

Three models. Three targets. One high-quality standard

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