Message from the President of the ESP

Prof. Pierre Bedossa

Dear colleagues, Dear friends,

I measure the great honor to be the new president of the ESP. Of course, this is an honor but also a challenge. It is a challenge because I have to take over from Prof Han van Krieken. I would like to congratulate him for his superb leadership. Everyone knew him already as an outstanding pathologist and scientist. We now know that Prof Han van Krieken is also a consummately diplomat, but, equally, that he has not been backward in confronting major issues of our society. As his predecessors, Fatima Carneiro, Fred Bosman, Mike Wells to name a few, Han van Krieken deployed tremendous energy to build a society which is now the home of any pathologist from Europe, at large.

I was a member of the executive committee more than 15 years ago. At that time the society was starting to rise. Prof. Manuel Sobrinho Simoes, Gunter Klöppel, Antonio Cardesa, to name a few, have laid the foundations of our home and it is impressive to look how fast the society has grown since that time, how many new initiatives have developed, and how much the society has increased its visibility around the world. This was because the foundations were very solid, thanks to these outstanding personalities.

But growing fast raises also threats. This needs a day by day management, a very professional office, the strict control of our budget, everything that have to be done without losing efficacy and attractiveness. Thanks to the safe structure of the society, we are in good shape, the office has been restructured with the arrival of our scientific director, Dr. Raed Al Dieri and the finances are on the safe side. I would like to specially thank Marco Santucci having accepted to be renewed a treasurer. With Ilmo Leivo as secretary, and Dina Tiniakos as president-elect, the dynamic is on.

Nothing would have been and will not be possible without the active participation of the various bodies of the ESP; the advisory board, the working groups, our journal Virchows Archiv and its dedicated editor-in-chief Fred Bosman, the education subcommittee and our website with a new educational portal that is expected to be launched very soon, thanks to the efforts of Helmut Popper. Recent initiatives such as the creation of the trainee subcommittee and the program of advanced training center and Giordano fellowship have been already successful. The trainee committee is part of our future and it is reassuring to observe how fast the residents and young trainees have been rapidly and deeply implicated. It is our aim to involve them even more. The first application for the Giordano’s fellowship has already been received in the office and I am pretty sure that it will be followed by many others. The ESP foundation will be ready to start soon and I am eager to discover the book on History of ESP, two initiatives launched by our past-president.

This will be probably too ambitious for a new president to launch additional initiatives without securing those that have emerged already. Nevertheless, we have to be ambitious and we have the capacity to do so. The office in Brussel has and will continue to be reshaped with new persons working on a very professional way and I am very confident that projects such as for example the junior pathologist academy can be launched very quickly. We have the ambition not to compete with the most famous scientific society around the world, but to develop common initiatives with the most visible one, looking for mutual benefit. The European Congress of Pathology, beside its payback in science, research and education for all of us is also a dedicated place for discussion, networking, sharing of experience and building new projects. With more than 2000 registrants from more than 80 different countries, the 2015 ECP in Belgrade was a great success. Next year, we will be in Cologne. This will be a joint congress between ESP and the German Division of the IAP. Strong and friendly relationships have been established between the two societies and thanks to the input of our dynamic working groups,
the program looks already very attractive. Preparation is underway, but any suggestion is welcome. Please do not hesitate to contact us to provide new ideas.

ESP has to be a living society!

Message from the Editor
Prof. Aurelio Ariza

The European Congress of Pathology (ECP) in Belgrade marked the end of Prof Han van Krieken’s presidency and the beginning of Prof Pierre Bedossa’s term. We thank our past president for his many achievements and wish the best to our new president.

From now on Prof van Krieken will chair the working groups (WGs), whereas Prof Fátima Carneiro, previously in charge of the WGs, will chair the advisory board, which is composed of the national societies’ presidents and has been masterly chaired by Prof Fred Bosman until now.

Also in Belgrade Prof Dina Tiniakos was approved by the ESP general assembly as president elect (please, don’t miss her third Tweet-the-Term instalment in this issue), while Prof Ilmo Levo and Prof Marco Santucci had their terms renewed as secretary and treasurer, respectively. Some changes have also taken place in the Newsletter editing team, where Ms Lora Kostova is now responsible for the tasks dutifully carried out by Dr Krasi Sergueieva until last September.

The rich diversity of Europe gives each ECP a distinctive flavor. At the Belgrade ECP it was, undoubtedly, Serbian hospitality. The figures proclaim by themselves the success of the congress: 1,886 registered participants, 107 accompanying persons, 317 sponsors, 1,100 persons at the opening ceremony, 1,306 submitted abstracts, 183 accepted oral presentations, and 920 accepted posters. The countries with more participants were the UK (119), Serbia (117), Greece (105), Turkey (98), Romania (81), Russia (80), Spain (78), The Netherlands (76), Italy (73), and Germany (67).

The scientific success of the 27th ECP was enhanced by its warm social atmosphere, which is vividly depicted in the following article by Prof Jovan Lole Vasiljević, president of the local organizing committee. Please, see some representative pictures at the end of the Newsletter.

The Belgrade congress has given a potent boost to Serbian pathologists, who contributed very significantly to the event. Prof Sanja Milenković, president of the Serbian Pathologists and Cytologists Association (SPCA), describes the main features of her national society and how the latter has been energized by the 27th ECP. Prof Milenković also shares with us her view of Art Paths Belgrade 2015, a special photograph exhibition that renews the quest of Art Paths Lisbon 2013 to bring to light the artistic facets of pathology.

In the article reserved for the ESP working groups, Prof Lina Carvalho, chair of the Pulmonary Pathology Working Group (PPWG), sketches the past, present and future of her group. To be commended is the creation of the ESP-PPWG Award for the residents’ best poster, an exemplary action to bring the young on board.

To conclude, Dr Loukas Kaklamenis offers us his selection of medical literature highlights (Analecta Medica) and Prof Gordan Vujanice, our associate editor, keeps us abreast of the recently published books and upcoming meetings of our specialty.

Enjoy!
The 27th European Congress of Pathology
Prof. Jovan Lole Vasiljević
Chair, Local Organizing Committee

The 27th ECP was held in Belgrade, Serbia, on 5th – 9th September 2015.

The Opening Ceremony was held in the Blue Hall of the Sava Center on Saturday, September 5th, at 19.00 h. Besides the usual address from the ESP President and the local organizers, including the Rector of Belgrade University, there was a wonderful musical performance.

First, the choir KUD LOLA sang some national and international songs. All participants were very satisfied with the choir’s superb quality.

In the second part, the folklore group of LOLA performed several traditional dances from Serbia and the Balkans.

After the official opening, all participants were invited to join the cocktail in the technical exhibit area. It was a very nice opening and many of the participants congratulated us.
The second day (the first working day), the real Congress started.

There were many interesting sessions and in the evening we had a Residents’ Party in Mikser House. For our residents and young pathologists, we had something really interesting. It was a live band, mainly blues, in the most popular new place in Belgrade – Mikser House!

On Monday, again, after many interesting sessions, we prepared a musical evening. The classical music concert was at the most prestigious concert hall in Belgrade – Kolarac. The very nice programme was performed by the St. George Strings Orchestra and the famous opera singers, Zoran Todorovith and Aneta Ilic. At the end, there were standing ovations.

Tuesday was also a very busy day. In addition to high-quality lectures and slide seminars, we had interesting organized tours and a free evening. Those invited to the Presidential Dinner had the chance to enjoy the evening in the White Royal Palace! It was a very nice dinner, with exquisite food and wine, followed by a performance by a St. George Strings Orchestra’s quintet that made the occasion very special.

And finally on Wednesday, the last day, after all sessions and the closing ceremony, we had the congress party at the Hyatt Hotel, next to the Sava Center. The room was full, the dinner was very good, and the music excellent! The DJ was really very good and the atmosphere was excellent.

At the end, I can only say it was a very successful congress, both scientifically and socially.
Pulmonary Pathology Working Group

Prof Lina Carvalho

Dear Colleagues,

The Belgrade Congress will stay in our minds for both its high scientific level and the hospitality of our Serbian host Prof. Jovan Vasiljević and collaborators. I thank all very much for their efforts in this particular time when in Europe we are seeing so many persons calling for an open world with more equality and understanding.

In the Belgrade Congress the Pulmonary Pathology Working Group (PPWG) made the more current classifications (such as the 2015 WHO Lung Tumors Classification and the 2013 Idiopathic Interstitial Pneumonias Update) available to general pathologists, who could listen to specialized lung pathologists explaining restrictions and parameters for reporting and had the opportunity to interact with radiologists and clinicians.

The group has developed step by step since the early nineties (the Heidelberg and Madrid meetings were held about twenty years ago) to become the European Group of Pulmonary Pathologists. We enjoyed the invaluable help of Prof Bryan Corrin, the teacher of a large number of pulmonary pathologists in Europe, including myself, who had the privilege of spending time with him in the Royal Brompton Hospital in London, many as residents. Also to be mentioned are Prof Klaus Keiser, who was our host twice, and Prof Emilio Alvarez-Fernandez, who hosted us in Madrid. Not to be forgotten is Prof Helmut Popper, who keeps the strong energy he has shown from the very beginning and holds the Graz meetings for rare(r) tumours of the lung, of great value for both residents and senior pathologists.

Molecular pathology has entered our routine work and I see it as a blessing transporting us beyond the limits of morbid anatomy. We are living a period with the challenge of attracting young colleagues who, beyond diagnosing and reporting, are prone to raise why and what for questions. They are part of the Gameboy Generation, with their senses wide opened to all aspects of a complex reality whose secrets they want to dig up. For now, let us start by jointly reporting morphological and molecular diagnoses!

Having had the privilege of being part of the group of pulmonary pathologists since the beginning, I take advantage of this opportunity to draw all pathologists and residents attention to the fact that participation in one or several ESP working groups considerably increases our knowledge and makes us much more efficient our important role in the diagnosis, prevention and screening of disease.

With this incentive in mind, the ESP-PPWG Award (300 euro) for the residents’ best poster was created this year. In Belgrade we had two best posters ex-aequo: Marc Rassy’s, from Lebanon, and Francesca Lunardi’s, from Italy. In this regard, Marc Rassy has sent us his moving remarks on how the experience gained from the whole Belgrade congress and, in particular, from his poster presentation, has whetted his appetite to come back for more next year. “Your mentoring and you stimulating us, residents, to push our research further will forge our education. The award will be used for new research projects and for covering part of next year’s trip. I cannot thank you enough for all your contribution,” wrote Marc Rassy. We’ll give this award again in Cologne and invite our colleagues to apply to the Pulmonary Pathology Working Group. The latter is a great forum to share opinions, ideas, projects, and knowledge within the ESP.

Cologne 2016, an event shared with the International Academy of Pathology, will also be a memorable congress. Preparations have already started to allocate as much time and content as possible to the field of diffuse pulmonary pathology, both in its morphologic and molecular aspects, so as to give patients the benefits of accurate diagnoses and personalized treatments.

I am confident that in Cologne we all will do our best to learn from others and spread our own work (no
matter how modest), in an effort to widen the future of European pathology.

All the best from Coimbra!

The Serbian Pathologists and Cytologists Association

Prof. Sanja Milenković
SPCA President

The Serbian Pathologists and Cytologists Association (SPCA) is a representative national society whose members are mostly Serbian pathologists. Currently, there are 134 pathologists and about 40 pathology residents in Serbia. The SPCA membership includes 84 pathologists (74 as collective members) and 32 residents.

Historically, the SPCA has continued the spirit and tradition of the Yugoslavian Society of Pathology, which was founded in 1967. In connection with our country’s turbulent historical events, our society changed its name in 2006, when the current SPCA designation was adopted.

According to its vision, the SPCA is a not-profit, voluntary, non-governmental association that establishes high professional standards and facilitates communication in the field of pathology and cytology.

As for its mission, the SPCA seeks to be a global community of professionals that advances excellence in the pathology laboratory practice through:

- Initiating, encouraging and developing professional contacts and cooperation of all interested professionals, institutions and organizations in Serbia.

- Activities that facilitate knowledge transfer and collaboration among professionals worldwide.

- Education programs and public programs that promote pathology laboratory testing of high quality and utility.

In order to improve communication and promote cooperation within the small community of Serbian pathologists and cytologists, the SPCA has actively participated in the organization of national congresses, continued education meetings, promotional events, and visits to centres of excellence. Since the beginning the SPCA joined the activities of the European Society of Pathology (ESP), founded in 1963, although as individual initiatives in limited contexts. Initially, the SPCA was represented in the ESP by Prof. Živojin Ignjačev, who was followed by the academician Vladimir Kanjuh.

Prof. Jovan Vasiljević was elected as member of the ESP Council in 2009 and developed the idea that Serbia should present its candidacy for the organization of a European Congress of Pathology (ECP). Obviously, at the time that idea was impossible to carry out for the pathologists and cytologists of a country with many problems, some of them still current (old equipment, few pathologists, slow modernization of educational curricula...). Nevertheless, the SPCA Executive Committee understood on time that that project was the best way to get things and people moving, change the usual points of view, and give an opportunity to the younger generations to look beyond the obvious.

Since 2011 the SPCA is represented in the ESP Advisory Board by the current president, Prof Sanja Milenković. Following numerous personal and collective meetings and individual visits by committee members even to the smallest pathology labs in Serbia, a new energy has been awakened among SPCA members, who have recognized the benefits of collective membership both for individuals and the whole community. The number of pathologists joining collective membership is increasing every year. An encouraging fact is that young pathologists and residents, with their active participation in the SPCA, are helping to overcome the generational gap created by a longstanding lack of pathology staff.
Since 2010 the SPCA has interacted with the Serbian government and state institutions and, as a result of these actions, the number of residents has significantly increased. After having completed their 4-year residency, there are now many young specialists in all parts of Serbia.

Under ESP auspices, the SPCA organized a national congress in 2012 for the first time. It was a big step. Then a decision was made in the ESP General Assembly in Prague in 2012 to hold a European Congress of Pathology (ECP) in Belgrade. It was an important moment and a boost for Serbian pathologists, who saw themselves as a significant part of the European pathology community and active participants in the 27th ECP.

In the 27th ECP Serbian pathologists have contributed three special sessions and organized and taken part in Art Paths Belgrade 2015. Particularly impressive was the very original presentation of activities addressed to the social promotion of pathology (Pathology and the Public Special Session). In the 27th ECP Serbia has been the second country by number of participants, which was very close to the number of attendees at Serbian national congresses. The energy infused into Serbian pathologists by the 27th ECP events has had many good effects.

The 15th Serbian National Congress, which is being enthusiastically prepared, will take place in Zlatibor on 21-23 April 2016, under the motto “Pathogenesis is the soul of pathology”. A residents’ session, held for the first time in the context of a Serbian national congress of pathology, will be the result of the current SPCA presidency’s firm decision to promote and educate young pathologists.

The motto of the much successful 27th ECP was “Breaking barriers in pathology.” Perhaps the effect intended by those words has been most spectacular on Serbian pathologists, among whom many barriers have been broken, a strong spirit of community has appeared, and the need to invest every atom of energy in the future has emerged.

I would like to conclude this brief review of the SPCA with the words of the 1961 literature Nobel prize winner, the Serbian writer Ivo Andrić: “Signs that we leave behind ourselves will not avoid the destiny of everything that is human: transience and oblivion. Maybe, it will pass unnoticed? Maybe nobody will understand it? However, they are necessary, as a mutual understanding and discovering among people. Even if these short and indefinite signs don’t save us from wandering and temptation, they can facilitate and help us to perceive that we are not alone, neither the first, nor the only.’
In order to continue the tradition of Art Paths Lisbon 2013, an Art Paths Belgrade 2015 ("The soul of laboratory life") exhibition was held during the 27th European Congress of Pathology. Numerous colleagues showed their hidden talents by actively participating in the presentation of their photographs and many others cooperated by selecting the best among them.

Twenty-three photographs were shown in the Dynamic Category and forty-five in the Artistic Category. Ten photographs from each of these two categories were chosen by online voting and finally the best picture from each category was chosen by on-site voting. The winner in the Dynamic Category was Maria Lambropoulou, from Greece, for her "Santa Claus is coming to the lab" photograph. AlekSandra Lovrenski, from Serbia, was the winner in the Artistic Category with her “Flying through pathology” picture.

The Dynamic Category was the favorite of young cheerful souls. Three thematic cakes gave a very sweet flavor to it: “The chocolate microscope... so delicious”; “Sweet flaring microscope for our 25th anniversary year”; “Sweet dreams of a histologist!” On the other hand, some authors caught artistic moments in their workplaces: “Game of lights and shadows near São José Hospital’s autopsy room”; “The game of light at the entrance of the pathology lab”; “Ladybird says where the love is?” Certainly, the art of living was well shown in this category.

Much talent was also displayed in the Artistic Category, which focused on the art contained in histology. Butterflies, hearts, smiles and flowers, previously hidden in histological slides, were given a chance to see the daylight by the authors. Other pathologists showed their abilities by combining different techniques and histological photographs. Among them there were painters (“Lymphoma flowers”; “Spirits of diagnosis”; “An invisible mirror reflects secrets hidden”), philosophers and writers (“The fifth element-pathologist”; “Soul’s palette”; “Rikki-Tikki”) and alternative artists (“Kolobov submarine”; “The galaxy of a canine tooth”).

Can a man, from this short time distance, duly evaluate the limits? And should he evaluate? “Thousand roads lead from the goal, but only one to it” (Michel de Montaigne).

It was a great pleasure to organize this exhibition with Dina Tiniakos and Anna Batistatou. The sight of every new picture was a delightful moment which strengthened our belief in doing a good job through pleasure.

Finally, there are inevitable conclusions to be drawn from the pictures shown in Art Paths: pathologists are artists and there is art in pathology.
Loss-of-function variants in ATM confer risk of gastric cancer

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Abstract

Gastric cancer is a serious health problem worldwide, with particularly high prevalence in eastern Asia. Genome-wide association studies (GWAS) in Asian populations have identified several loci that associate with gastric cancer risk. Here we report a GWAS of gastric cancer in a European population, using information on 2,500 population-based gastric cancer cases and 205,652 controls. We found a new gastric cancer association with loss-of-function mutations in ATM (gene test, $P = 8.0 \times 10^{-12}$; odds ratio (OR) = 4.74). The combination of the loss-of-function variants p.Gln852*, p.Ser644* and p.Tyr103* (combined minor allele frequency (MAF) = 0.3%) also associates with pancreatic and prostate cancers (OR = 3.81 and 2.18, respectively) and gives an indication of risk of breast and colorectal cancers (OR = 1.82 and 1.97, respectively). Cancers in those carrying loss-of-function ATM mutations are diagnosed at a significantly earlier age than in non-carriers. Our results confirm an association between gastric cancer in Europeans and three loci previously reported in Asians, MUC1, PRKAA1 and PSCA, refine the association signal at PRKAA1 and support a pathogenic role for the tandem repeat identified in MUC1.

Progesterone receptor modulates ERα action in breast cancer

Hisham Mohammed,1 I. Alasdair Russell,2 Rory Stark,3 Oscar M. Rueda,1 Theresa E. Hickey,2 Gerard A. Tarulli,2 Aurelien A. Serandour,1 Stephen N. Birell,2 Alejandra Bruna,3 Amel Saadil,1 Suraj Menon,1 James Hadfield,1 Michelle Pugh,1 Ganesh V. Raj,3 Gordon D. Brown,3 Clive D’Santos,3 Jessica L. L. Robinson,3 Grace Silva,4 Rosalind Launchbury,5 Charles M. Perou,4 John Stirling,1 Carlos Caldas,1, 5, 6, Wayne D. Tilley2, 9 & Jason S. Carroll1, 9

Abstract

Progesterone receptor (PR) expression is used as a biomarker of oestrogen receptor-α (ERα) function and breast cancer prognosis. Here we show that PR is not merely an ERα-induced gene target, but is also an ERα-associated protein that modulates its behaviour. In the presence of agonist ligands, PR associates with ERα to direct ERα chromatin binding events within breast cancer cells, resulting in a unique gene expression programme that is associated with good clinical outcome. Progesterone inhibited oestrogen-mediated growth of ERα+ cell line xenografts and primary ERα+ breast tumour explants, and had increased anti-proliferative effects when coupled with an ERα antagonist. Copy number loss of PGR, the gene coding for PR, is a common feature in ERα+ breast cancers, explaining lower PR levels in a subset of cases.

Our findings indicate that PR functions as a molecular rheostat to control ERα chromatin binding and transcriptional activity, which has important implications for prognosis and therapeutic interventions.

Tumor necrosis factor-α confers cardioprotection through ectopic expression of keratins K8 and K18

Stamatis Papathanasiou, Steffen Rickelt, Maria Eugenia Soriano, Tobias G Schips, Harald J Maier, Constantinos H Davos, Aimilla Varela,

Loukas Kaklamanis, Douglas L Mann & Yassemi Capetanaki

Nature Medicine,21,1076-1084 (September 2015) doi:10.1038/nm.3925

Abstract

Tumor necrosis factor-α (TNF-α), one of the major stress-induced proinflammatory cytokines, is upregulated in the heart after tissue injury1, 2, and its sustained expression can contribute to the development of heart failure1, 3, 4. Whether TNF-α also exerts cytoprotective effects in heart failure is not known. Here we provide evidence for a cardioprotective function of TNF-α in a genetic heart failure model, desmin-deficient mice. The cardioprotective effects of TNF-α are a consequence of nuclear factor-κB (NF-κB)-mediated ectopic expression in cardiomyocytes of keratin 8 (K8) and keratin 18 (K18), two epithelial-specific intermediate filament proteins5, 6. In cardiomyocytes, K8 and K18 (K8/K18) formed an alternative cytoskeletal network that localized mainly at intercalated discs (IDs) and conferred cardioprotection by maintaining normal ID structure and mitochondrial integrity and function. Ectopic induction of K8/K18 expression in cardiomyocytes also occurred in other genetic and experimental models of heart failure. Loss of the K8/K18 network resulted in a maladaptive cardiac phenotype following transverse aortic constriction. In human failing myocardium, where TNF-α expression is upregulated2, K8/K18 were also ectopically expressed and localized primarily at IDs, which did not contain detectable amounts of desmin. Thus, TNF-α- and NF-κB-mediated formation of an alternative, stress-induced intermediate filament cytoskeleton has cardioprotective function in mice and potentially in humans.
RAS-MAPK dependence underlies a rational polytherapy strategy in EML4-ALK–positive lung cancer

Gorjan Hrustanovic,1, 2 Victor Olivas,1, 2 Evangelos Pazarentzos,1, 2 Asmin Tulipule,1, 2 Saurabh Asthana,1, 2 Collin M Blakely,1, 2 Ross A Okamoto,1, 2 Luping Lin,1, 2 Dana S Neel,1, 2 Amit Sabnis,1, 2 Jennifer Flanagan,1, 2 Elton Chan,1, 2 Marileile Varella-Garcia,3, 4 Dara L Aisner,4 Aria Vaishnavi,3 Sai-Hong I Ou,5, 6 Eric A Collisson,1, 2 Eiki Ichihara,7 Philip C Mack,8, 9 Christine M Lovly,7 Niki Karachaliou,10 Rafael Rosell,10 Jonathan W Riess,8, 9 Robert C Doebele3 & Trever G Bivona1, 2.


Abstract
One strategy for combating cancer-drug resistance is to deploy rational polytherapy up front that suppresses the survival and emergence of resistant tumor cells. Here we demonstrate in models of lung adenocarcinoma harboring the oncogenic fusion of ALK and EML4 that the GTPase RAS–mitogen-activated protein kinase (MAPK) pathway, but not other known ALK effectors, is required for tumor-cell survival. EML4-ALK activated RAS-MAPK signaling by engaging all three major RAS isoforms through the HELP domain of EML4. Reactivation of the MAPK pathway via either a gain in the number of copies of the gene encoding wild-type K-RAS (KRAS(WT)) or decreased expression of the MAPK phosphatase DUSP6 promoted resistance to ALK inhibitors in vitro, and each was associated with resistance to ALK inhibitors in individuals with EML4-ALK–positive lung adenocarcinoma. Upfront inhibition of both ALK and the kinase MEK enhanced both the magnitude and duration of the initial response in preclinical models of EML4-ALK lung adenocarcinoma. Our findings identify RAS-MAPK dependence as a hallmark of EML4-ALK lung adenocarcinoma and provide a rationale for the upfront inhibition of both ALK and MEK to forestall resistance and improve patient outcomes.
Abstract

The International Consultations on Urological Diseases are international consensus meetings, supported by the World Health Organization and the Union Internationale Contre le Cancer, which have occurred since 1981. Each consultation has the goal of convening experts to review data and provide evidence-based recommendations to improve practice. In 2012, the selected subject was bladder cancer, a disease which remains a major public health problem with little improvement in many years. The proceedings of the 2nd International Consultation on Bladder Cancer, which included a 'Pathology of Bladder Cancer Work Group,' have recently been published; herein, we provide a summary of developments and consensus relevant to the practicing pathologist. Although the published proceedings have tackled a comprehensive set of issues regarding the pathology of bladder cancer, this update summarizes the recommendations regarding selected issues for the practicing pathologist.

These include guidelines for classification and grading of urothelial neoplasia, with particular emphasis on the approach to inverted lesions, the handling of incipient papillary lesions frequently seen during surveillance of bladder cancer patients, descriptions of newer variants, and terminology for urine cytology reporting.

6.

Carboxylesterase 2 as a Determinant of Response to Irinotecan and

Neoadjuvant FOLFIRINOX Therapy in Pancreatic Ductal Adenocarcinoma

Michela Capello, Minhee Lee, Hong Wang, Ingrid Babel, Matthew H. Katz, Jason B. Fleming, Anirban Maitra, Huamin Wang, Weihua Tian, Ayumu Taguchi and Samir M. Hanash


Abstract

Background: Serine hydrolases (SHs) are among the largest classes of enzymes in humans and play crucial role in many pathophysiological processes of cancer. We have undertaken a comprehensive proteomic analysis to assess the differential expression and cellular localization of SHs, which uncovered distinctive expression of Carboxylesterase 2 (CES2), the most efficient carboxyl esterase in activating the prodrug irinotecan into SN-38, in pancreatic ductal adenocarcinoma (PDAC). We therefore assessed the extent of heterogeneity in CES2 expression in PDAC and its potential relevance to irinotecan based therapy.

Methods: CES2 expression in PDAC and paired nontumor tissues was evaluated by immunohistochemistry. CES2 activity was assessed by monitoring the hydrolysis of the substrate p-NPA and correlated with irinotecan IC₅₀ values by means of Pearson’s correlation. Kaplan-Meier and Cox regression analyses were applied to assess the association between overall survival and CES2 expression in patients who underwent neoadjuvant FOLFIRINOX treatment. All statistical tests were two-sided.

Results: Statistically significant overexpression of CES2, both at the mRNA and protein levels, was observed in PDAC compared with paired nontumor tissue (P < .001), with 48 of 118 (40.7%) tumors exhibiting high CES2 expression. CES2 activity in 11 PDAC cell lines was inversely
Correlated with irinotecan IC50 values (R = -0.68, P = .02). High CES2 expression in tumor tissue was associated with longer overall survival in resectable and borderline resectable patients who underwent neoadjuvant FOLFIRINOX treatment (hazard ratio = 0.14, 95% confidence interval = 0.04 to 0.51, P = .02).

Conclusion: Our findings suggest that CES2 expression and activity, by mediating the intratumoral activation of irinotecan, is a contributor to FOLFIRINOX sensitivity in pancreatic cancer and CES2 assessment may define a subset of patients likely to respond to irinotecan based therapy.

7.

Comparison of the Genomic Landscape Between Primary Breast Cancer in African American Versus White Women and the Association of Racial Differences With Tumor Recurrence

Tanya Keenan, Beverly Moy, Edmund A. Mroz, Kenneth Ross, Andrzej Niemierko, James W. Rocco, Steven Isakoff, Leif W. Ellisén and Aditya Bardia

Abstract

Purpose African American women are more likely to die as a result of breast cancer than white women. The influence of somatic genomic profiles on this racial disparity is unclear. We aimed to compare the racial distribution of tumor genomic characteristics and breast cancer recurrence.

Methods We assessed white and African American women with stage I to III breast cancer diagnosed from 1988 to 2013 and primary tumors submitted to The Cancer Genome Atlas from 2010 to 2014. We used Cox proportional hazards models to evaluate the association of race and genetic traits with tumor recurrence.

Results We investigated exome sequencing and gene expression data in 663 and 711 white and 105 and 159 African American women, respectively. African Americans had more TP53 mutations (42.9% v 27.6%; P = .003) and fewer PIK3CA mutations (20.0% v 33.9%; P = .008).

Intratumor genetic heterogeneity was greater in African American than white tumors overall by 5.1 units (95% CI, 2.4 to 7.7) and within triple-negative tumors by 4.1 units (95% CI, 1.4 to 6.8). African Americans had more basal tumors by the 50-gene set predictor using the predication analysis of microarray method (PAM50; 39.0% vs 18.6%; P < .001) and fewer PAM50 luminal A tumors (17.0% vs 34.7%; P < .001). Among triple-negative subtypes, African Americans had more basal-like 1 and mesenchymal stem-like tumors. African Americans had a higher risk of tumor recurrence than whites (hazard ratio, 2.22; 95% CI, 1.05 to 4.67). Racial differences in TP53 mutation, PAM50 basal subtype, and triple-negative tumor prevalence but not intratumor genetic heterogeneity influenced the magnitude and significance of the racial disparity in tumor recurrence.

Conclusion African Americans had greater intratumor genetic heterogeneity and more basal gene expression tumors, even within triple-negative breast cancer. This pattern suggests more aggressive tumor biology in African Americans than whites, which could contribute to racial disparity in breast cancer outcome.
Some Recently Published Books
Prof. Gordan Vujanic

Keeling’s Fetal and Neonatal Pathology
T. Yee Khong and Roger Malcomson
2015 (5th ed), 882 pages, 300+ illus, ~€300
A new feature of this edition is an emphasis on the molecular aspects of pathology in the perinatal setting. There are four new chapters, including one on the genetic and epigenetic basis of development and disease, and over 300 new illustrations. The format of the book remains the same as previous editions with the first half covering general areas in perinatal pathology. The second half is based on organ systems and covers specific pathological entities, now including discussion of the relevant molecular pathology. There is extensive cross-referencing between chapters.

Dorman and Czerniak’s Bone Tumors
Bogdan Czerniak
2015 (2nd ed), 1,520 pages, ~€310
The second edition of Dorman and Czerniak’s Bone Tumors brings together the latest data available on bone tumor pathology, making it the most comprehensive and encyclopedic reference on the epidemiology, clinical, pathologic, and molecular aspects of bone tumors. Now offered in full color and featuring updated imaging throughout, this one-of-a-kind resource provides a highly visual review of every disorder - from the common to the rare.

Atlas of Intraoperative Frozen Section Diagnosis in Gynecologic Pathology
Pei Hui and Natalia Buza
2015, 329 pages, 271 illus, ~€90
This atlas is dedicated specifically to gynecologic frozen section diagnosis and addresses professional practice gaps such as high diagnostic error rate, slow turnaround time, and inefficient communication between surgeons and pathologists at the time of intraoperative frozen section consultation of gynecologic specimens. The format of the volume is a combination of concise text and high quality gross and frozen section microscopic images, meticulously selected from the superb collection of pathology specimens of gynecologic tumors provided at Yale-New Haven Hospital in the past decades.

Karch’s Pathology of Drug Abuse
By Steven Karch and Olaf Drummer
2015 (5th ed), 906 pages, ~€145
Written in the same accessible manner as previous editions, the fifth edition of Karch’s Pathology of Drug Abuse is an essential guide to the pathology, toxicology, and pharmacology of commonly abused drugs. The book focuses on the investigation of drug-related deaths, practical approaches to the detection of drug abuse, and discussions of medical complications associated with each of the abused drugs.

Pancreatic Neuroendocrine Neoplasms
Stefano La Rosa and Fausto Sessa
2015, 195 pages, 12 illus, ~€90
This book provides a broad overview of pancreatic neuroendocrine neoplasms, focusing on the most important developments in the technologies used to diagnose, classify and treat them. After a historical and epidemiological overview, the opening chapters examine the various diagnostic approaches (radiology, nuclear medicine, endocrinology, cytology and immunohistochemistry) and discuss the WHO classification. The functioning and nonfunctioning tumor types are then fully discussed, covering epidemiology, diagnosis, morphology and prognosis of each entity.

Intraocular Tumors
Jerry Shields and Carol Shields 2015 (3rd ed), 608 pages, ~€300
In this updated and revised third edition, world-renowned authorities at the Wills Eye Hospital provide outstanding guidance on recognition, evaluation, and treatment of ocular tumors, highlighted by more than 2,500 stunning photographs and surgical drawings. This unsurpassed ocular oncology resource is a comprehensive guide to the clinical features, diagnosis, management, and pathology of intraocular tumors and pseudotumors, depicting clinical variations, treatment, and histopathologic characteristics of the many varied benign and malignant lesions that affect the uveal tract, retina, and other intraocular structures.

Diagnostic Pathology: Kidney Diseases
Robert Colvin, M.D. and Anthony Chang, M.D. 2015 (2nd ed.), 1,144 pages, ~€260
Part of the highly regarded Diagnostic Pathology series, this updated volume is a visually stunning, easy-to-use reference covering all aspects of common and rare renal diseases and their variants. Outstanding images—including gross and microscopic pathology, a wide range of stains, and detailed medical illustrations—make this an invaluable diagnostic aid for every practicing pathologist, resident, or fellow. Written by leading pathologists, this second edition presents an up-to-date, concise presentation of major pathological, clinical, pathophysiological, and genetic information for over 240 diagnoses.

Soft Tissue Pathology: Diagnostic Challenges
Leona Doyle 2015, 1,500 illus, ~€90
This issue of Surgical Pathology Clinics is devoted to Soft Tissue Tumors, the first in this series was presented in 2011. This issue addresses the most difficult diagnostic challenges and focuses on differential diagnosis in soft tissue tumors. Each presentation is accompanied by abundant histologic slides to display the diagnostic differences. Additionally, authors selected two to five diagnoses they find can be particularly difficult, with an emphasis on how to approach such lesions on biopsy samples where relevant and the role of ancillary studies.

Diagnostic Pathology: Gastrointestinal
Joel Greenson 2015 (2nd ed.), 800 pages, 2,500+ illus, ~€200
Part of the highly regarded Diagnostic Pathology series, this updated volume by Joel K. Greenson, MD, is a visually stunning, easy-to-use reference covering all aspects of gastrointestinal pathology. Outstanding images—including gross pathology, a wide range of pathology stains, and detailed medical illustrations—make this an invaluable diagnostic aid for every practicing pathologist, resident, or fellow.

Molecular Oncology Testing for Solid Tumors
Michael Idowu, Catherine Dumur, and Carleton Garrett, 2015, 742 pages, 3 illus, ~€135
Familiarity with and understanding molecular testing is becoming imperative for practicing physicians, especially pathologists and oncologists given the current explosion of molecular tests for diagnostic, prognostic and predictive indications.

Molecular Oncology Testing for Solid Tumors is designed to present an up to date practical approach to molecular testing in an easy to understand format.

Precision Molecular Pathology of Breast Cancer
Ashraf Khan, Ian Ellis, Andrew Hanby, Ediz Cosar, Emad Rakha and Dina Kandil 2015, 338 pages, ~€100
This volume provides a comprehensive review of the molecular mechanisms involved in precancerous lesions and benign and malignant breast tumors. Given the complex molecular pathways in breast cancer biology, the book simplifies these complex mechanisms and highlights the practical issues important for daily practice. Sections are structured to review breast carcinogenesis and the role of familial predisposition and stem cells in initiation and progression of breast cancer. In-depth chapters present mor-
phologic and molecular correlations in precancerous and malignant breast lesions, while outlining highly practical issues that are in practice today in breast pathology, such as evaluation of estrogen, progesterone receptors, and HER-2.

**Diagnostic Pathology: Soft Tissue Tumors**
Matthew Lindberg
2015 (2nd ed), 800 pages, 2,000+ illus, ~€270
Part of the highly regarded Diagnostic Pathology series, this updated volume by Matthew Lindberg, MD, is a visually stunning, easy-to-use reference covering all aspects of soft tissue pathology. Outstanding images - including gross pathology, a wide range of stains, and detailed medical illustrations - make this an invaluable diagnostic aid for every practicing pathologist, resident, or fellow. Packed with even more high-resolution images than the previous edition - more than 2,000 images in all - it clearly depicts not only the key features of each tumor, but also the wide array of histologic variants.

**Neuroendocrine Tumors**
M. Papotti, W.W. de Herder, E. Ghigo, F. Guaraldi and A. Benso
2015, 270 pages, 51 illus., ~€230
The term ‘carcinoid’ entered medical literature over 100 years ago to describe a peculiar intestinal epithelial neoplasm. Since then, a large body of literature has expanded the concept of carcinoid, later replaced by the term ‘Neuroendocrine Tumor’ (NET), defining a wide spectrum of peculiar tumors, potentially affecting all organs and tissues, originating from neuroendocrine cells, sharing, but, at the same time, keeping, pathognomonic pathological, radiological and clinical features.

**Atlas of Cutaneous Lymphomas**
Joi B. Carter, Amrita Goyal and Lyn McDivitt Duncan
2015, 214 pages, ~€180
This atlas contains excellent clinical and histopathologic images and text of each of the types of cutaneous lymphoma (around 25 entities). It is the first go-to text for those who are considering a diagnosis of cutaneous lymphoma in their differential diagnosis. The text also includes diagnostic mimics of lymphoma and differential diagnosis tables and algorithms. The target audience is general practitioners, dermatologists, pathologists and students, residents and fellows.

**Neoplastic Gastrointestinal Pathology**
Laura Lamps, Andrew Bellizzi, Wendy Frankel, Scott Owens and Rhonda Yantiss
2015, 408 pages, 600+ illus, ~€120
Approximately 20 million gastrointestinal tract biopsies are performed each year in the United States. While many of these are straightforward, some are; histologically subtle or involve a complex differential diagnosis. This concise visual guide to the full range of neoplastic gastrointestinal specimens; provides the practicing pathologist or trainee with a clear analysis and diagnosis of both common and potentially misleading variants of disease.

**Scheuer’s Liver Biopsy Interpretation**
Jay Lefkowitch
2015 (9th ed), 440 pages, ~€155
For more than 40 years, Scheuer’s Liver Biopsy Interpretation has been the pathologist’s go-to resource for help in solving diagnostic problems at the microscope. The 9th Edition brings you fully up to date in the field, with coverage of new diagnostic tools, new information on drug-induced liver injury and cytopathology, and many new high-quality illustrations.

**Carlson: Salivary Gland Pathology Diagnosis and Management**
Eric Carlson and Robert A. Ord
2015, 392 pages, ~€180
Salivary Gland Pathology: Diagnosis and Management, Second Edition, updates the landmark text in this important discipline within oral and maxillofacial surgery, otolaryngology/head and neck surgery, and general surgery. Written by well-established clinicians, educators, and re-
searchers in oral and maxillofacial surgery, this book brings together information on the etiology, diagnosis, and treatment of all types of salivary gland pathology. Clear and comprehensive, Salivary Gland Pathology: Diagnosis and Management offers complete explanation of all points, supported by a wealth of clinical and surgical illustrations to allow the reader to gain insight into every facet of each pathologic entity and its diagnosis and treatment.

**Biopsy Interpretation of Soft Tissue Tumors**
Cyril Fisher, Elizabeth Montgomery and Khin Thway
2015, 544 pages, ~€150
Part of the popular Biopsy Interpretation Series, the second edition of Biopsy Interpretation of Soft Tissue Tumors provides an easy-to-follow, practical approach to the interpretation of soft tissue biopsies, including open and percutaneous core needle biopsies. Covering both common and rare soft tissue tumors, this up-to-date bench reference parallels the diagnostic process, detailing key differential diagnostic features of specific tumors using morphologic, immuno-histochemical, ultrastructural, and genetic data. A pattern-based approach ensures that you can quickly find the information you need, in the format most useful to everyday practice.

**Diagnostic Pathology: Infectious Diseases**
Danny A. Milner
2015, 440 pages, ~€195
Diagnostic Pathology: Infectious Diseases takes a comprehensive look at infectious diseases, their anatomic manifestations, and how to ensure a complete and accurate sign out at the microscope. A user-friendly chapter landscape and thousands of high-quality images combine to make this medical reference book a key companion for the general surgical pathologist or resident in training.

**Pathology Informatics, An Issue of Surgical Pathology Clinics**

Anil V. Parwani, M.D.
2015, ~€90
This issue of Surgical Pathology Clinics takes a departure from its presentation of Differential Diagnosis, Histopathology, Staging, and Prognosis of tumors in different anatomic sites. This special issue is devoted to topics in pathology informatics as they relate to the practice of surgical pathology. Topics include: Basics of Information Systems (Hardware, Software); Networks, Interfaces and Communications; Databases; Data Representation, Coding and Communication Standards; Laboratory Information Systems; Enhancing and Customizing Laboratory Information Systems to Improve/Enhance Pathologist Workflow; Laboratory Management and Operations; Specialized Laboratory Information Systems; Middleware and Laboratory Automation; Synoptic Reporting in Anatomical Pathology; Bar Coding and Tracking; Molecular Pathology Informatics; Informatics and Autopsy Pathology; Pathology Informatics and Project Management; Digital Imaging Basics; Use of Digital Images in Clinical Practice; Whole Slide Imaging; Telepathology; Mobile Technologies for the Surgical Pathologist; Image Analysis; Advanced Imaging Techniques; Healthcare Information Systems; Data Security and Reliability; Role of Informatics in Patient Safety and Quality Assurance; Role of Pathology Informatics in IT Leadership; Selection and Implementation of New Information Systems; Biomedical Informatics and Research Informatics; Training in Pathology Informatics; and Building Tools for the Surgical Pathologist: Next Generation Pathologist.

**Atlas of Mediastinal Pathology**
Saul Suster
2015, 225 pages, ~€145
The mediastinum is a virtual compartment in the chest cavity that is the seat of several vital organs and structures that can be involved in a variety of pathologic processes, including congenital and developmental abnormalities, inflammatory conditions, and benign and malig-
nant neoplasms. The Atlas of Mediastinal Pathology provides a pictorial survey of the major disease processes that can affect this anatomic compartment, including congenital and acquired cysts, benign hamartomatous processes, inflammatory processes involving the mediastinum, and benign and malignant neoplasms. The latter includes tumors of the thymus (thymoma and thymic carcinoma), neuroendocrine neoplasms, germ cell tumors, mesenchymal neoplasms, and hematolymphoid malignancies. The use of ancillary diagnostic methods is illustrated, where appropriate, providing assistance for pathologists in arriving at the correct diagnosis.

Orthopaedic Pathology
By Vincent J. Vigorita M.D.
2015, 912 pages, ¬€310
Ideal for orthopaedic, pathology, and radiology residents and practitioners, the updated third edition of Orthopaedic Pathology is a comprehensive, practical guide to diagnosing musculoskeletal disorders, offering details on the pathologic and radiologic characteristics of all bone and joint diseases. Highlighted by more than 1,700 high-quality illustrations, it focuses on helping you reach an accurate diagnosis for virtually any orthopaedic disorder you’re likely to encounter, including cysts, arthritis, synovial lesions, fibrous lesions, metastatic cancer, metabolic bone disease such as osteoporosis and Paget’s disease, fractures, osteomyelitis, tumors and tumor-like lesions and developmental bone disorders. A separate section on soft-tissue pathology discusses meniscal injuries, bursa, ligaments, and tendons.

WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart
By International Agency for Research on Cancer 2015, 410 pages, ¬€140
WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart is the seventh volume in the Fourth Edition of the WHO series on histological and genetic typing of human tumors. This authoritative, concise reference book provides an international standard for oncologists and pathologists and will serve as an indispensable guide for use in the design of studies monitoring response to therapy and clinical outcome.

Advances in Surgical Pathology: Bladder Cancer
Qihui “Jim” Zhai and Dr. Jae Y. Ro
2015, 272 pages, ¬€135
Apply a state-of-the-art, integrated approach to bladder cancer diagnosis and staging with Advances in Surgical Pathology: Bladder Cancer. Distinguished experts provide you with concise, current, and well-rounded guidance on all forms of bladder cancer, with an emphasis on practical issues and new developments. This cutting-edge surgical pathology reference is an ideal tool to help you update your knowledge and skills and solve difficult diagnostic dilemmas, as well as a valuable resource for certification and recertification preparation.

Forthcoming Meetings in 2015

AMP: Molecular Pathology Outreach Course
Association of Molecular Pathology (AMP)
4 November 2015
Austin, USA

Association for Molecular Pathology Annual Meeting 2015
5 - 7 November 2015
Austin, USA

HNIAP Silver Jubilee Congress
International Academy of Pathology – Hing Kong Division
6 – 8 November 2015
Kowloon, Hong Kong, China

Paediatric Pathology Society and ANZ Paediatric Pathology Group Joint Scientific Meeting
The Royal College of Pathologists of Australasia
19 – 21 November 2015,
Perth, Australia
The 37th Meeting of the French Society of Breast Pathology Sénologie
French Society of Senology and Breast Pathology
11 – 13 November 2015
Bordeaux, France

SSP: 81st Annual Meeting
Swiss Society of Pathology
12 – 14 November 2015
Basel, Switzerland

IAP-BD: 110th Symposium on Uropathology
International Academy of Pathology – British Division
20 – 21 November 2015
London, U.K.

2nd Digital Pathology Congress
“Understanding & Utilizing Digital Pathology as a Tool for Advancing Pathology Practice”
3 – 4 December 2015
London, U.K.
(http://www.globalengage.co.uk/digital-pathology.html)

International Society of Dermatopathology (ISDP) 19th Joint Meeting
The International Society of Dermatopathology
2 – 3 March 2015
Arlington, USA

Society for Pediatric Pathology Spring Meeting 2016
11 – 13 March 2016
Seattle, USA

USCAP: 105th Annual Meeting 2016
United States & Canadian Academy of Pathology (USCAP)
12 – 18 March 2016
Seattle, USA

100th conference of the German Society of Pathology
19-21 Mai 2016
Berlin, Germany