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### Word from the President Prof. M. Wells

It has been many years since the United Kingdom experienced as much snow so early in the winter as we have experienced in the last four weeks and there has been widespread chaos here. Thankfully, much of the snow had gone by Christmas and we were able to have a more restful time over Christmas and New Year.

The Intercongress Meeting in Krakow was very special and I am most grateful to my Polish friends Gregory, Janusz, Krzysztof and "Old Whisky" for all their help in ensuring its success. It was also our first real interaction with CPO Hanser as our professional congress organisation and the meeting set an excellent tone for the future.

The Krakow meeting already seems a long time ago and, as usual, October and November were probably the busiest months of the year. I had the pleasure of visiting Croatia and lecturing in Zagreb. It was all too short a visit, arriving at my hotel at about 1 in the morning on Saturday 23 and leaving on the morning of 23 October. However, we did manage a trip to a winery and a splendid dinner on the Saturday evening at which we were entertained by an excellent band who played wonderful Croatian folk songs

including "Vilo Moja", which I found particularly moving, even though I did not understand the words! I am grateful to Marina Kos, Luka Brčić and all their colleagues for their wonderful hospitality. We will hold a European School of Pathology on Gynaecological Pathology in Croatia in November 2011.

At the IAP Congress in São Paulo in October, I was able to have very preliminary discussions with Dietmar Schmidt about the possibility of a joint congress of the IAP and ESP in Bonn in 2016. I will do my utmost to ensure that this comes to fruition as a collaboration of equal partners.

In November, I visited Belgrade and was warmly hosted by my good friend Lole Vasiljević. I was able to visit the congress and hotel facilities in anticipation of the ESP holding its annual congress in Belgrade in 2015. A final recommendation on this will be made by the Executive Committee in February 2011 and a decision made at the General Assembly in Helsinki.

The Society continues to flourish and I am delighted to report that the Pathological Society of Great Britain and Ireland have opted for collective membership of the ESP. This is a very significant development and I hope will set an important precedent for other national societies.

A series of very successful Videomicroscopy Masterclasses have been held each month since May; these will be reviewed and a programme for 2011 developed in the near future.

In early Summer 2011, we will have a "retreat" or "time-out" to discuss the future direction of Virchows Archiv.

I am delighted to report that as from the Helsinki congress, access to all slideseminars will be included in the basic registration fee.

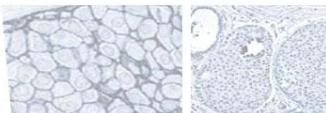
Time flies and I am already more than half way through my Presidency but it is great fun; I have the privilege of meeting and working with some delightful friends and colleagues. In the first two months of

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2011 we will have further meetings of the Advisory Council, the Working Groups and the Executive Committee. I am most grateful to the other officers, the members of the Executive Committee and Krasi Sergueva, our efficient administrator, for their ongoing enthusiasm. I know that the arrangements for the first of our annual congresses to be held in Helsinki next August/September are already well advanced and Ilmo Levi, Veli Pekka Lehto and their colleagues are working hard to ensure the success of that meeting.

May I take this opportunity as President to thank you all for your continuing support of the European Society of Pathology and to wish you all the very best for 2011.

Michael Wells



## 23<sup>rd</sup> European Congress of Pathology

27 August – 1 September 2011  
Helsinki, Finland

Helsinki Exhibition & Convention Centre

[www.esp-congress.org](http://www.esp-congress.org)

**ESP President 2009 – 2011**

Michael Wells, United Kingdom

### Local Organising Committee

Veli-Pekka Lehto,

Chair Ilmo Leivo,

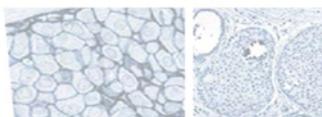
Secretary Anna Sankila

Panu Kovanen





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## Setting the standard for KRAS testing in colorectal cancer: the quality assurance program of the ESP

Prof. Han van Krieken

Selection of patients with metastasized colorectal cancer that do not benefit from treatment directed against the epidermal growth factor receptor (EGFr) is now feasible. Since the start of the new millennium the outlook for patients with metastasized colorectal cancer has improved significantly, for a main part thanks to the introduction of new, biological treatments, that target the vascular endothelial growth factor receptor (VEGFr) or the EGFr. Not all patients benefit from these treatments however, and much effort is undertaken to identify predictive markers that can be used to select patients most likely to benefit from these expensive and potentially toxic agents. The most relevant recent development in this field is the discovery that in patients with metastasised colorectal cancer EGFr targeting treatment is only effective in those patients that have wild type KRAS, a discovery that has attracted wide publicity.

KRAS mutational analysis has become part of standard care in patients treated with EGFr targeting therapy. A variety of studies have shown that in patients with metastasised colorectal cancer the addition of either cetuximab (a chimaeric IgG1 monoclonal antibody against the EGFr) or panitumumab (a fully human IgG2 EGFr antibody) as monotherapy or when added to chemotherapy increases the progression free survival. However, only patients without a mutation in the KRAS oncogene benefit from this regimen.

Testing for KRAS mutations is not standardized. Seven different mutations in codon 12 and 13 of the KRAS gene account for more than 95% of the activating KRAS mutations. There is a multitude of techniques available that can detect these KRAS mutations. Most techniques are developed and used in a limited number of laboratories, but some tests are commercial available and have been CE marked.

There is presently very little data available on which test is the most reliable. Since it is known that Her2 testing in breast cancer, another predictive biomarker, has a relatively poor reliability (about 75% according to recent data), the European Society of Pathology has initiated a quality assurance program for KRAS testing in Europe, based on experiences of and in collaboration with national programs. Quality assurance is crucial for reliable implementation of KRAS mutation testing for predicting unresponsiveness for EGFr targeted therapy. The ESP quality assurance program aims at the whole process of KRAS testing and several key issues are included ). For a reliable test, the minimum amount of invasive tumor cells needs to be determined, the quality of the DNA assessed, and the outcome the test assured and the report has to be complete and accurate. A coordinated quality assurance program is available in Europe since 2009.

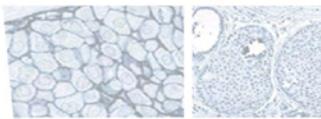
The first large assessment round included 59 laboratories from 8 different European countries. For each country, one regional scheme organizer prepared and distributed the samples for the participants of their own country. The samples included unstained sections of 10 invasive colorectal carcinomas with known KRAS mutation status. The samples were centrally validated by a reference laboratory. The laboratories could use their own preferred method for histological evaluation, DNA isolation and mutation analysis and were required to provide the results within 10 working days. The preliminary results show that 70% of laboratories correctly identified the KRAS mutational status in all samples. Both the false positive and false negative results observed negatively affect patient care. Reports of the KRAS test results often lacked essential information. Finally, it appeared that estimates of tumor cells percentage were highly variable. The laboratories that have fulfilled the criteria of the QA program are now listed at the ESP website where also further information can be found.

These findings indicate that a QA program is really needed and the ESP will continue its efforts in this area of pathology which is one the cornerstones of present day pathology.

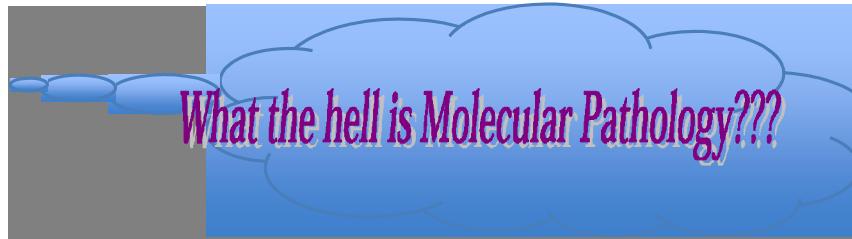




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**Prof. Generoso Bevilacqua**

Molecular Pathology is around! It is in the air! We can smell it! But many are still unable to catch it!

In front of MP some Pathologists assume an intense expression of perplexity (with a little bit of interior fear), just as the gargoyle that from the roof of Notre Dame de Paris jumped into the title!

Is it a subspecialty of Pathology? Is it something that has to be done by other specialties, such as Clinical Biochemists or Geneticists? I am too old for it, and then I am a morphologist! I am a young Resident, so first I should learn morphology, then we'll see! Have I to learn all the techniques of molecular biology? And so on.

So, what is the difference between "classic" Pathology and MP? Or, more stringent question, there is a difference?

The fact is that a very accurate descriptive analysis usually compensates (and hides) the ignorance of the essence of the process. As consequence, the books of Pathology were full of morphological details and classifications, macroscopical and microscopical, until the biomolecular revolution. Because it is a matter of revolution! When molecular biology techniques began to be available allowing scientists to understand the biological basis of physiological and pathological events. As consequence, MP does not have a precise birthday. Its birth took place along the '90s, as human tissues became object of interest for molecular biology.

Modern books of Pathology dedicate to morphology a number of pages appreciably smaller than in the past. And this reduction is directly related to the development of molecular biology. More we understand, less we have the need to describe and to classify on a morphological basis. Molecular classifications are today proposed or already adopted for many diseases, cancer included, and terms as "proteinopathies" are in the current use.

But are we sure that this scenario does not belong to Pathology? If we look carefully at the history of Pathology, we see that it was always pervaded with shapes. At the beginning was the autopsy, the study of a human body in its wholeness. Then we moved to the analysis and description of single organs. Then, the slide! With which we identified our discipline until yesterday and that is living a rejuvenation, that is "virtual", but substantial at the same time. We cannot forget the Ultrastructural Pathology, potent tool for understanding diseases, but non very useful for our diagnostic routine.

Well! Also molecules can be seen, sometimes directly, more often indirectly. So, MP is morphology at a very high magnification!

Now that we are reassured by the fact that Molecular Pathology fits well in our tradition, let's move to another concept. Everybody knows about k-ras gene status in colo-rectal cancer and Pathologists begin to know that it is possible to study k-ras gene status in formalin fixed and paraffin embedded tissues. However, if Pathologists limit themselves to pass a paraffin block or a few slices to a molecular biology lab, they abdicate. Their role becomes inferior to that of a qualified technician.

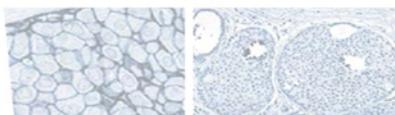
So, what have modern Pathologists to do? Which special requisite do they need to have? Answer is easy: to master the bio-molecular aspects of the etiology and pathogenesis of diseases and to use them to interpret their morphology.

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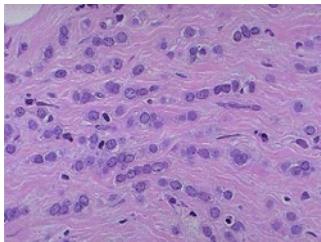


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We cannot limit to say that an infiltrative lobular carcinoma of breast is made of single rows of cancer cells, of small size, with small nuclei with homogeneously distributed fine granular chromatin. Today we need to know what intercellular junctions are, which molecular structure they have, what E-cadherin is, which gene encodes it, and that E-cadherin gene mutations are absolutely relevant in lobular carcinoma pathogenesis. These cells are born with a severe damage of their intercellular connections, so they are able to invade immediately after birth

as single cells between the collagen bands. The invasive ability of the cancer cells is caused by this very early gene mutation, and does not require a sum of numerous genetic alterations in different genes. For this reason we do not have a high grade atypia as epiphénoménon. This example of bio-molecular interpretation of the structure says that we are moving from morphology to functional morphology.

Finally, we should not forget that Pathologist with their functional morphology have a key role in biomedical research and that Pathology is still a pillar in the educational process of medical doctors.

It is time to go back to the original questions.

What is Molecular Pathology? MP is just the modern face of Pathology. To consider it as a subspecialty would mean to assassinate Pathology or to give a patrimony of centuries as a present to other Disciplines.

What can a Pathologist do for being updated? To study the bio-molecular basis of disease, that means to move from pure morphology to functional morphology.

Does he or she need a practical training in MP laboratories? Yes, but it is a secondary goal. Surely we cannot transform Pathologists in Molecular Biologists. Primary aim is the knowledge of functional morphology.

For this reason, ESP is putting a lot of effort into educational programs in Molecular Pathology and the ESP Molecular Pathology WG is very active in this frame. MPWG takes care of the organization of the MP sessions in all the ESP Congresses. The 2011 Congress in Helsinki will host three Sessions dedicated to the MP of CNS, Lung and Breast Diseases, with outstanding speakers. Then, members of the board of the WG participate often to national meetings where they illustrate MP ad its tools. Finally, MPWG is actively involved in organizing the Molecular Pathology Courses that EScop, the European School of Pathology, will start in 2011.

So, a lot of cultural and educational activities, indispensable for building up the Pathology of the Third Millennium!



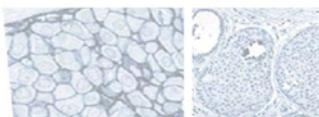
Happy New Year !!!!!!

Generoso Bevilacqua

PS: a paranoid mind could see in the red ribbon the DNA helix !!!!!!!!



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## The Pathologist



### Interview with Prof. Fred Bosman by Prof. Mia Marichal

*Professor Fred Bosman, our past-president has taken on a new challenge: the presidency of the European Association of Pathology Chairs and Program Directors a.k.a. the EAPCP. In this interview professor Bosman explains how he sees the future of this organisation and its role in pathology training in Europe.*

**MM:** A year ago, when I asked you how you intended to cope with the simultaneous retirement as Chairman in Lausanne and the handing over of the ESP presidency, you replied that for you “to retire does not mean to stop working”. And you were true to your word: not only did you continue to do research in Lausanne and setting up an undergraduate pathology course in Nepal, you took on new challenges in the Netherlands and in Belgium. This year you succeeded professor van den Tweel as president of the EAPCP. Can you explain for the reader the mission of this organization? What does it do?

**FB:** I can tell you now that the statement I made a year ago about what retirement means to me has proven to be more than true. I then had a feeling that I needed to be sufficiently involved in a variety of activities to avoid having too few things to do. Well, I think I am now busier than before. The big difference is that what I presently do is entirely the result of conscious choices I have made. I can choose what to take and what not and that makes a big difference! The EAPCP is in a crucial period of its development: one can compare it with a small family business that aspires to be a multinational enterprise. And it is a challenge to be involved in this process. When Jan van den Tweel initiated the EAPCP some five years ago, the idea was to bring together those responsible for academic pathology (the Chairs) and

for the training program (the Program Directors) as they are directly involved in shaping the future of pathology. The closely related UEMS Board of Pathology is a purely political invention composed of members representing pathology organizations in the UE countries, without necessarily having the credentials of a Chair or Program Director. As a result, its distance to what happens in the field is huge and its impact on academic development and on training has been negligible. As an example: only about 15 candidates sat the UEMS Board of Pathology examination in Krakow. The ESP might have taken on this responsibility but was heavily involved in rethinking its own role in Europe. I shared the feeling that a separate organization might achieve more. I am convinced, however, that the EAPCP should at least closely link and maybe even merge with the ESP. We need one coordinated approach for European Pathology. The EAPCP has primarily worked on defining a European training curriculum and developed a web-based progress test for pathology trainees. Both have met with acclaim and this has been a stimulus to continue.

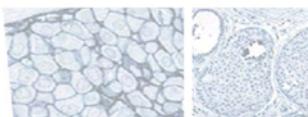
**MM:** These last 5 years the EAPCP has indeed achieved quite a lot: Pathology Chairs and Program Directors agreed on what a European pathologist should know, the organization secured an EU program and built a web based European exam with virtual slides and multiple choice questions. This is really impressive, but, to be honest, a EU Life Long Learning program funded a big part of the activities. Now that the EU program is finished, where will the EAPCP get the money from to continue its activities?

**FB:** Fortunately, the partner company in the LLL program (iPath) will continue to work for us, deploy at least two more progress tests, of which there will be two in 2011, and rebuild our website to allow for much more interaction. In the long run the progress test should become a fee for service activity: once it has reached more general recognition, departments may be willing to pay for their trainees to participate.





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In the interval, the close association with the ESP might prove vital. Living together in the ESP office in Brussels could create an administrative basis and we will request support from the ESP that has developed a vested interest in postgraduate education. As you know, I also chair the ESP education committee, which I feel as a distinct advantage in this phase of development of both.

**MM:** In Europe, several organizations are involved in pathology education. There is the ESP, the UEMS, the local IAP divisions, Path.Soc, the national societies.... Will the EAPCP be able to find its own niche?

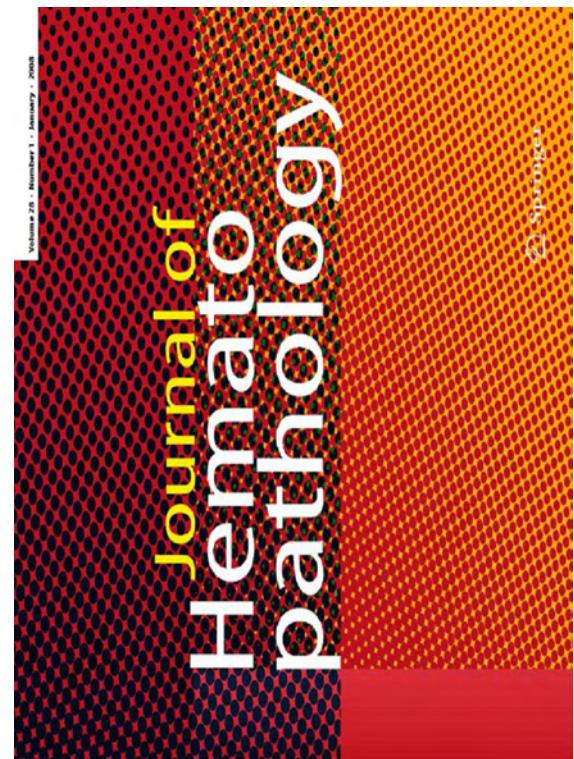
**FB:** I am convinced that a platform where Chairs of Pathology can meet regularly and set the tone for the development of our discipline, and Program Directors can strive towards common European training outcome standards, is there to stay. So the question is not whether the activities of the EAPCP will continue but rather how! As I said before, the UEMS Board of Pathology is somewhat out of sync with reality but a political necessity. EAPCP representatives participate in UEMS meetings and will strive towards close coordination and if possible some form of merger. And incorporation into ESP might be the best option to consider. These are clearly issues we will have to work on together.

**MM:** To have good post-graduates, pathology must appear more clearly as a choice for doctors when they graduate. Does the EAPCP also plan to do something about graduate training in pathology?

**FB:** We just had an EAPCP meeting in Pisa and part of the program was dedicated to graduate pathology education. For us to recruit more trainees, if possible the best of the best, we need to do two things. We need to develop convincing PR: who knows what pathology is? I admire the Path.Soc. in the UK for their efforts in the last few years. Professional approaches towards spreading the recognition that pathology is a key discipline for good medical practice, even more so in the 21st century than in the past, will need to be developed. This should start with bringing back pathology to the key position in graduate medical training it has had before. Medical students should realize that 'understanding disease' is essential to become a good practitioner and 'the science behind the cure' provides the basis for developing tomorrow's medicine. I do not doubt that you recognize both slogans: the Journal of Pathology and the Path.Soc.'s mottos.

**MM:** Thank you Fred and good luck with this new challenge. I hope that the EAPCP together with the ESP can bring Pathology graduate and post-graduate education back where it belongs: at the top.

Interested readers can consult the EAPCP web site at:  
<http://www.eapcp.org>



Dear Colleagues,

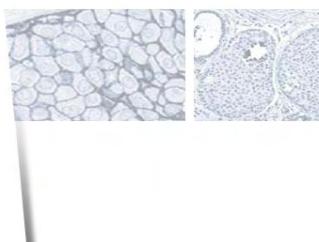
The European Society of Pathology is happy to announce you an additional benefit to the ESP membership: for 10 € members can have an annual subscription to the online version of the Journal of Hematopathology, starting with volume 4, January 2011. This Journal is the only specialized journal for pathologists with an interest in Hematopathology. For more information please click here: [www.springer.com/medicine/pathology/journal/12308](http://www.springer.com/medicine/pathology/journal/12308). The first 2 year of its existence the Journal was available only online. Now the printed version of the journal is also available. The ESP is still negotiating a reduced subscription rate for the printed version for the ESP members. We will keep you informed about this opportunity soon!

To apply for this service you can use the online membership renewal on our website or check the box on the letter you have received recently.



**Analecta Medica**

Dr. Loukas Kaklamanis



- 2)** Distant metastasis occurs late during the genetic evolution of pancreatic cancer

**Yashida S, Jones S et al**

Nature, Volume:467, 1114–1117, 28 October 2010

Metastasis, the dissemination and growth of neoplastic cells in an organ distinct from that in which they originated, is the most common cause of death in cancer patients. This is particularly true for pancreatic cancers, where most patients are diagnosed with metastatic disease and few show a sustained response to chemotherapy or radiation therapy. Whether the dismal prognosis of patients with pancreatic cancer compared to patients with other types of cancer is a result of late diagnosis or early dissemination of disease to distant organs is not known. Here we rely on data generated by sequencing the genomes of seven pancreatic cancer metastases to evaluate the clonal relationships among primary and metastatic cancers.

- 1)** The patterns and dynamics of genomic instability in metastatic pancreatic cancer  
**Campbell PJ, Yashida S et al**

Nature, Volume:467, 1109–1113, 28 October 2010

Pancreatic cancer is an aggressive malignancy with a five-year mortality of 97–98%, usually due to widespread metastatic disease. Previous studies indicate that this disease has a complex genomic landscape, with frequent copy number changes and point mutations but genomic rearrangements have not been characterized in detail. Despite the clinical importance of metastasis, there remain fundamental questions about the clonal structures of metastatic tumours, including phylogenetic relationships among metastases, the scale of ongoing parallel evolution in metastatic and primary sites, and how the tumour disseminates. Here we harness advances in DNA sequencing to annotate genomic rearrangements in 13 patients with pancreatic cancer and explore clonal relationships among metastases.

We find that pancreatic cancer acquires rearrangements indicative of telomere dysfunction and abnormal cell-cycle control, namely dysregulated G1-to-S-phase transition with intact G2-M checkpoint. These initiate amplification of cancer genes and occur predominantly in early cancer development rather than the later stages of the disease. Genomic instability frequently persists after cancer dissemination, resulting in ongoing, parallel and even convergent evolution among different metastases. We find evidence that there is genetic heterogeneity among metastasis-initiating cells, that seeding metastasis may require driver mutations beyond those required for primary tumours, and that phylogenetic trees across metastases show organ-specific branches. These data attest to the richness of genetic variation in cancer, brought about by the tandem forces of genomic instability and evolutionary selection.

We find that clonal populations that give rise to distant metastases are represented within the primary carcinoma, but these clones are genetically evolved from the original parental, non-metastatic clone. Thus, genetic heterogeneity of metastases reflects that within the primary carcinoma. A quantitative analysis of the timing of the genetic evolution of pancreatic cancer was performed, indicating at least a decade between the occurrence of the initiating mutation and the birth of the parental, non-metastatic founder cell. At least five more years are required for the acquisition of metastatic ability and patients die an average of two years thereafter. These data provide novel insights into the genetic features underlying pancreatic cancer progression and define a broad time window of opportunity for early detection to prevent deaths from metastatic disease.

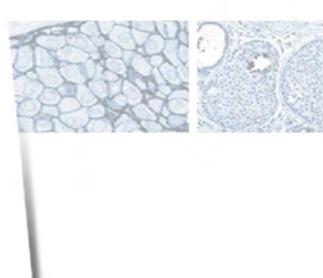
- 3)** Concealed Neuroanatomy in Michelangelo's Separation of Light From Darkness in the Sistine Chapel

**Suk, Ian BSc, BMC; Tamargo, Rafael J. MD, FACS7**

Neurosurgery 2010,66:5,851-861

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Michelangelo Buonarroti (1475–1564) was a master anatomist as well as an artistic genius. He dissected cadavers numerous times and developed a profound understanding of human anatomy. From 1508 to 1512, Michelangelo painted the ceiling of the Sistine Chapel in Rome. His Sistine Chapel frescoes are considered one of the monumental achievements of Renaissance art. In the winter of 1511, Michelangelo entered the final stages of the Sistine Chapel project and painted 4 frescoes along the longitudinal apex of the vault, which completed a series of 9 central panels depicting scenes from the Book of Genesis. It is reported that Michelangelo concealed an image of the brain in the first of these last 4 panels, namely, the *Creation of Adam*.

Here we present evidence that he concealed another neuronanatomic structure in the final panel of this series, the *Separation of Light From Darkness*, specifically a ventral view of the brainstem. The *Separation of Light From Darkness* is an important panel in the Sistine Chapel iconography because it depicts the beginning of Creation and is located directly above the altar. We propose that Michelangelo, a deeply religious man and an accomplished anatomist, intended to enhance the meaning of this iconographically critical panel and possibly document his anatomic accomplishments by concealing this sophisticated neuroanatomic rendering within the image of God.

#### 4) Endometrial Cancer in Postmenopausal Women Using Estradiol-Progestin Therapy

**Jaakkola, Susanna ; Lyytinen, Heli ; Pukkala, Eero ; Ylikorkala, Olavi**

Obstetrics & Gynecology: 2009 - Volume 114 - Issue 6 - pp 1197-1204

**OBJECTIVE:** To estimate the risk of endometrial cancer in all Finnish postmenopausal women using various forms of estradiol-progestin therapy.

**METHODS:** All Finnish women (aged more than 50 years) who had used estradiol-progestin therapy in 1994-2006 for at least 6 months ( $n=224,015$ ) were identified from the national medical Reimbursement Registry and linked to the Finnish Cancer Registry. A total of 1,364 type I and 38 type II endometrial cancers were recorded by the end of 2006. The incidence of endometrial cancer in estradiol-progestin therapy users was compared with that in the general population in this cohort study.

**RESULTS:** The use of a continuous estradiol-progestin therapy regimen for 3 years or more was associated with a 76% reduction of the risk for type 1 cancer (95% confidence interval [CI] 6-60%). In contrast, the use of a sequential estradiol-progestin therapy regimen for at least 5 years was accompanied with a 69% elevation (95% CI 43-96%) if the progestin was added monthly, and with a significantly higher, 276% risk elevation (95% CI 190-379%) if progestin was added at 3-month intervals. Sequential regimens containing norethisterone acetate, medroxyprogesterone acetate or dydrogesterone administered orally showed no significant differences in the endometrial safety. Oral and transdermal norethisterone acetate were associated with similar risk elevations. Women using a monthly sequential estradiol-progestin regimen tended to be diagnosed with endometrial cancer in an earlier stage than the background population.

**CONCLUSION:** Use of a continuous rather than a sequential estradiol-progestin regimen decreases the risk of endometrial cancer, whereas the route of administration or type of progestin does not differ in terms of endometrial cancer risk.

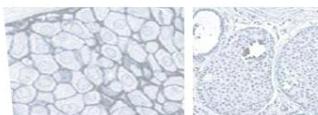
#### 5) NFKBIA Deletion in Glioblastomas

**Markus Bredel, M.D., Ph.D., Denise M. Scholtens, Ph.D., et al**

December 22, 2010 DOI: 10.1056/NEJMoa1006312

Amplification and activating mutations of the epidermal growth factor receptor (EGFR) oncogene are molecular hallmarks of glioblastomas. We hypothesized that deletion of *NFKBIA* (encoding nuclear factor of κ-light polypeptide gene enhancer in B-cells inhibitor-α), an inhibitor of the EGFR-signaling pathway, promotes tumorigenesis in glioblastomas that do not have alterations of *EGFR*.

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## Tips and tops -News in brief

Dr. Loukas Kaklamanis

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We analyzed 790 human glioblastomas for deletions, mutations, or expression of *NFKBIA* and *EGFR*. We studied the tumor-suppressor activity of *NFKBIA* in tumor-cell culture. We compared the molecular results with the outcome of glioblastoma in 570 affected persons.

*NFKBIA* is often deleted but not mutated in glioblastomas; most deletions occur in nonclassical subtypes of the disease. Deletion of *NFKBIA* and amplification of *EGFR* show a pattern of mutual exclusivity. Restoration of the expression of *NFKBIA* attenuated the malignant phenotype and increased the vulnerability to chemotherapy of cells cultured from tumors with *NFKBIA* deletion; it also reduced the viability of cells with *EGFR* amplification but not of cells with normal gene dosages of both *NFKBIA* and *EGFR*. Deletion and low expression of *NFKBIA* were associated with unfavorable outcomes. Patients who had tumors with *NFKBIA* deletion had outcomes that were similar to those in patients with tumors harboring *EGFR* amplification. These outcomes were poor as compared with the outcomes in patients with tumors that had normal gene dosages of *NFKBIA* and *EGFR*. A two-gene model that was based on expression of *NFKBIA* and O<sup>6</sup>-methylguanine DNA methyltransferase was strongly associated with the clinical course of the disease.

Deletion of *NFKBIA* has an effect that is similar to the effect of *EGFR* amplification in the pathogenesis of glioblastoma and is associated with comparatively short survival.

### 1) UK science faces facilities freeze

**Four-year budget protects grants but cuts capital spending.**

British scientists hoping for shiny new facilities this Christmas will be disappointed by their government's research-funding plans. On 20 December, the Department of Business Innovation and Skills, which oversees research and higher-education funding, unveiled a four-year budget which makes deep cuts to cash for large projects such as particle accelerators, research ships and university lab space. Meanwhile, two of the councils that support specific areas of research announced that they will put a new emphasis on the economic impact and social benefit of the work they fund. The net effect will be a squeeze on money for new projects and blue-skies research in the coming years.

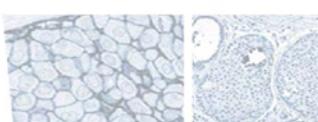
By cutting the £873-million (US\$1.3-billion) annual capital budget by roughly 40%, the government says it can maintain grant funding at the current level. Yet several key facilities will be shielded from the capital cut, including the UK Centre for Medical Research and Innovation, a new £500-million biomedical laboratory in central London. The budget also protects a handful of other planned facilities, and international subscriptions to organizations such as CERN, the European high-energy physics laboratory located near Geneva, Switzerland. But some research councils will struggle to cope with the cuts. The Natural Environment Research Council (NERC) said that it remained committed to a handful of key projects, including a replacement for its research vessel Discovery. But no new projects are likely to start in the next four years, according to Marion O'Sullivan, a NERC spokeswoman. Similarly, the Medical Research Council says the capital reductions will pose "challenges", according to a statement from John Jeans, the council's deputy chief executive. The UK government's efforts to squeeze as much value as possible from its research spending has also led two of the research councils to announce changes to their missions. The Biotechnology and Biological Sciences Research Council (BBSRC) no longer sees itself as a science 'funder', but rather as an investor of public funding in science. Matt Goode, a spokesman for the BBSRC, says this refocus is a "subtle semantic change" and that the council is not abandoning basic research. Meanwhile, the Engineering and Physical Sciences Research Council (EPSRC) announced that it would become a "sponsor" of research. "Funding is viewed as a strategic investment and not a transfer of funds without obligations," David Delpy, the EPSRC's chief, said in a video message explaining the shift. Researchers would be asked to think about impact at every stage of the research process, Delpy said.

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"Obviously this is sheer lunacy," says Paul Clarke, a chemist at the University of York, UK. "If I knew what the impact of the research would be, I wouldn't have to do the research." Research funds for English universities will also be squeezed. The Higher Education Funding Council for England (HEFCE) will have its annual £1.6 billion for research grants cut by about 3% over the next four years (universities elsewhere in Britain are overseen by other bodies). But like the research councils, the biggest cuts hit the capital budget, which will be slashed by 40% from its present level of £167 million over the same period. The HEFCE will announce how it will slice up its budget between universities in March 2011. Imran Khan, director of the Campaign for Science & Engineering in the UK, a London-based advocacy group, fears that some research councils may be forced to dip into money intended for basic research to make up for the capital shortfall. "The money will have to come from somewhere," he says.

Nature 20/12/2010      by Brumfiel G and Gilbert N

## 2) Mutation-prediction software rewarded

**California contest looks to boost software that can analyse genetic data.**

A computer program that predicts the effects of gene mutations has earned its author a doctorate, a stack of journal publications — and now named Molly.

Yana Bromberg, a bioinformatician at Rutgers University in New Brunswick, New Jersey, won the toy for her program, SNAP, in an experimental contest that culminated on 10 December in Berkeley, California. The competition, called the Critical Assessment of Genome Interpretation (CAGI), asks researchers to predict the biological effects of different mutations, and compares their results against unpublished experimental data. The contest was conceived by Steven Brenner, a computational genomicist at the University of California, Berkeley, and John Moult, a computational biologist at the University of Maryland in Rockville. Their goal is to accelerate the development of software that can quickly interpret large amounts of genetic data — for example, the whole genome sequence of a tumour from a biopsy.

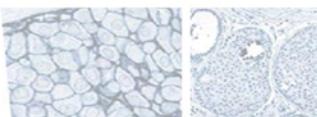
Such data is already flooding labs and will soon be hitting doctors' offices. "We've already got an enormous amount of data to contend with and we're struggling to make sense of it," says Moult. "I see CAGI as one mechanism to help with that process." He helped to start a similar competition in 1994, to improve scientists' ability to determine the shapes of proteins from their amino-acid sequences. That effort, named the Critical Assessment of protein Structure Prediction (CASP), challenges scientists to predict protein structures that have been determined experimentally, but not yet published. The results are revealed at a biannual meeting in Pacific Grove, California. CAGI works in a similar way. Instead of proteins, Brenner, Moult and coordinator Susanna Repo, a postdoc in Brenner's lab, provided several challenges that typically involved determining the biological effect of mutations in particular genes and the proteins they encode. For instance, one challenge provided entrants with different variations in the cancer-associated gene *CHEK2* that had been uncovered by a study of the gene in patients with cancer and healthy people, but not yet published. CAGI participants were asked to determine whether given mutations belonged to a patient or a control. Each team tackled these challenges differently. But their entries generally involved either predicting how a certain mutation changes the shape and function of a protein, or scouring genetic databases to determine the effects of similar mutations. "The ones that did best combined a large number of methods together," says Brenner.

Although the organizers were apprehensive about how the contest would work, "it went as well as it possibly could have", says Brenner. He and his team are still analysing the entries, and hope to reveal the official results in a peer-reviewed publication. On the basis of the success of the Berkeley workshop, they plan to hold the contest again within 2 years.

Nature 17/12/2010    by Emen Callaway

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### 3) From battlefield to bedside

**Medical research in the British military soldiers on despite defence cuts.**

Over the past ten years, British military forces have been engaged in two major conflicts, in Iraq and Afghanistan. Where the military has gone, its medical staff have gone too, and taken research with them into the field. A meeting this week at the Royal Society of Medicine in London and a raft of papers in a special issue of a Royal Society journal now highlight the importance and benefits of this research.

The UK Strategic Defence and Security Review, released by the government in October, will lead to thousands of job losses in Britain's armed forces. However, an extra £20 million (US\$31 million) per year has been earmarked for the provision of health care to men and women in the services. Some £1 million of this money will make its way to research, said Alasdair Walker, surgeon commodore in the Royal Navy and medical director of the Joint Medical Command. At the London meeting, he described the funding boost as a "quite significant enhancement". Walker points out that war and the needs of the military have always been a huge driver of medicine. Historical examples include the nineteenth-century anaesthetics pioneer Thomas Spencer Wells, who served in the army, and naval surgeon James Lind — widely regarded as having conducted the first clinical trial with his tests of citrus fruits for the treatment of scurvy in the eighteenth century. "It's in our blood. It's part of us," says Walker. "Military medicine has always been at the forefront of research."

Military medicine spans everything from disease prevention to rehabilitation. Mark Midwinter, a surgeon captain in the Royal Navy, outlined some of the research studies being carried out in war zones. For example, Midwinter is working a randomized trial for the use of nanoparticles of silver on wound dressings. Although there has been much enthusiasm for bandages containing silver — which is thought to have an antibacterial effect — solid evidence is lacking, but initial data look promising.

Modern warfare has also led to a profound change in the types of injury sustained. As detailed in several papers in the January issue of the *Philosophical Transactions of the Royal Society B*, the rise of the 'improvised explosive device' in Iraq and Afghanistan has led to a significant increase in blast injuries and severe damage to limbs.

Much attention is focused on trauma care, but many soldiers with serious injuries are now requiring long-term rehabilitation of a kind that did not exist in the past — a key issue for military medical researchers. Despite the difficulties of doing controlled clinical trials in a military setting, Evans and Lillywhite argue that important work can and is being done. They cite the Prussian military philosopher Karl von Clausewitz, who wrote during the Napoleonic Wars that, on the battlefield, "The light of reason is refracted in a manner quite different from what is normal in academic speculation."

However, they point out, "scientific reasoning can be applied in combat casualty care, to the immediate benefit of the wounded, and in the longer term to the benefit of all mankind"

Nature 17/12/2010 by Daniel Cressey

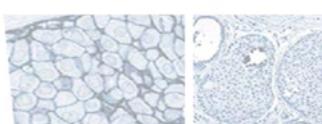
### 4) German research centre widens misconduct probe

**Investigation digs deeper after finding images were manipulated in six papers.**

Rocked by revelations of long-running scientific misconduct in its immunology department, the Research Center Borstel in Germany is to broaden its investigation into the work of a pair of former scientists suspected of systematic image manipulation in a number of research papers. An external investigation, launched in July and chaired by Werner Seeger, a biomedical researcher at the University of Giessen, Germany, found that two former

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postdocs with the centre's immunology group were guilty of using pictures of protein blots from unrelated experiments to support their findings on signalling in cells involved in allergic reactions such as asthma. The pair's supervisor, Silvia Bulfone-Paus, who chairs the centre's immunology and cell biology department, bears "substantial responsibility" for the manipulations, the committee found, but added that they found no evidence of data fabrication.

The investigation committee found manipulation of images in six papers produced between 2001 and 2009 by Elena Bulanova and Vadim Budagian. Bulfone-Paus is listed as either senior or corresponding author of the six incriminated publications. The relevant journals have been informed and the papers are likely to be retracted. But the committee has only carried out spot checks on the group's larger research output. A co-director of the centre says that a more wide-ranging investigation is needed to establish whether such manipulation took place in other papers too.

"This case threatens to harm our reputation," says Ulrich Schaible, head of molecular infection research at the centre. "It must be cleared up entirely."

Bulanova and Budagian could not be reached for comment and, according to Schaible, both have since left research. Bulfone-Paus, who also holds a position at the University of Manchester, UK, declined to comment on the committee's findings concerning her responsibility for the misconduct. A spokesperson for the University of Manchester said that the university will not comment on the preliminary findings either. Few laboratory heads have complete oversight over their group members' daily research activities, says Schaible. But as co-author of scientific publications resulting from her postdocs' experiments, Bulfone-Paus does bear partial responsibility for their misconduct, he adds. The research centre's board of curators will next month decide whether to take disciplinary action against Bulfone-Paus, says Schaible.

Meanwhile, Germany's main research funding agency, the DFG, which funded some of the group's work, has launched a separate investigation into the case. If that investigation confirms that poor oversight was partly responsible for the misconduct, Bulfone-Paus could face sanctions. The DFG has previously temporarily excluded scientists found guilty of misconduct from applying for funds or from acting as grant reviewers. Depending on the severity of such cases, the DFG can also cancel grants or demand repayment of spent funds.

Nature 13/12/2010 by Quirin Schiermeier

## 5) Human intestinal tissue grown in the lab

**The technique could be used to study disease and tailor therapies.**

By mimicking stages of embryonic development, scientists have prodded human stem cells to produce three-dimensional (3D) organ tissue that resembles the intestine and recapitulates its major cell types.

The work, reported today in *Nature*, represents the first example of human embryonic stem cells being coaxed into forming a specific 3D organ tissue in culture, says lead investigator James Wells, a developmental biologist at Cincinnati Children's Hospital Medical Center in Ohio. Scientists can use the protocol to investigate the molecular basis of human intestinal development and disease, design drugs that get absorbed better and grow tissue for transplantation therapies, he says.

Wells and his team used human embryonic stem cells, which can turn into any type of tissue, as well as human induced pluripotent stem (iPS) cells — adult cells that have been reprogrammed to behave like embryonic cells. The researchers enticed these cells to transform into intestinal cells and then into 3D structures by using a sequence of growth factors — substances that promote cell growth and specialization. The structures started to imitate the intestine once they were placed into 3D cultures filled with a mixture of different growth factors that foster growth and further development into advanced intestinal organ-like structures.

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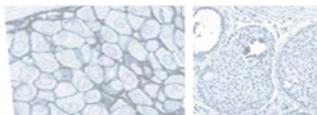
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"This is really a major advance in the field because it provides an experimental system for studying the development of the human intestine," says Steven Cohn, a gastroenterologist at the University of Virginia School of Medicine in Charlottesville. "This will allow one to study human organ development in the test tube in a way that we haven't been able to do before."

"Their ability to generate all of the cell types in the intestine was very impressive," Cohn says. "This is really the first time that I'm aware of that we've been able to recapitulate most of the development of an organ in a test tube from a human pluripotent stem cell." iPS cells are a reliable and continuous source for the creation of organ tissue, he adds.

Stephen Duncan, a stem-cell biologist at the Medical College of Wisconsin in Milwaukee, agrees that "this represents a major step forward in the gut field" because it opens the doors to examining intestinal development in humans and dissecting the mechanisms of illnesses that cause inflammation or impair nutrient absorption, such as inflammatory bowel disease and short bowel syndrome. Scientists can also use the method to screen for drugs that block cholesterol uptake, he adds. Wells and his collaborators are working on approaches to create intestinal nerve cells in the cultures and transplant the tissue in mouse models of intestinal disorders. They also plan to produce iPS cells from patients with congenital abnormalities and use the culture system to pinpoint what goes wrong during intestinal development. Then they might be able to correct the defect and restore the tissue in patients. "This is a good first step toward generating replacement tissue for people with degenerative diseases of the intestine," Wells says.

Nature 12/12 2010 by Janelle Weaver



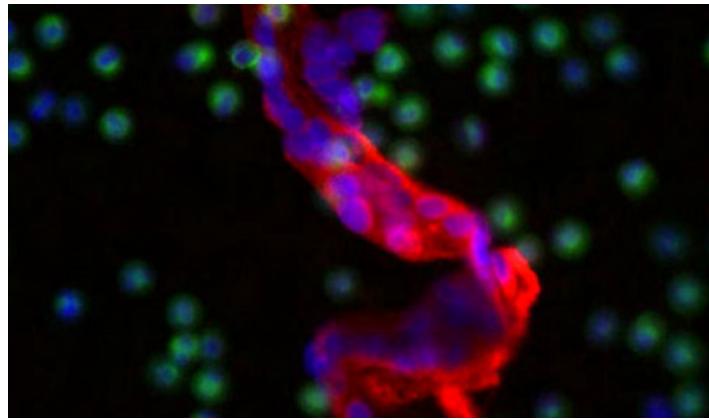
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## What's New?

### "LIQUID BIOPSY" Is it a promising tool of solid diagnostic Pathology ?

Prof. Loukas Kaklamanis

An interesting methodology is gaining more and more attention in the field of diagnostic medicine. Highly sensitive devices could capture circulating cancer cells in the blood, the so called "liquid biopsy", providing the means for a less invasive diagnostic procedure which will greatly influence the selection of therapy. Most of the research conducted so far, is taking place in academic institutions but the industrial world is apparently interested too.



Here are just a few of these companies which have made substantial investments:

"...\* Advanced Cell Diagnostics, Hayward, California, is adapting its RNAscope technology -- a system that looks for small bits of genetic material -- to search for cancer cells circulating in the blood. The company recently won a three-year, \$3 million grant from National Cancer Institute.

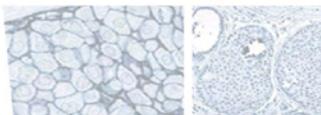
\* Biocept Inc of San Diego, California, in May got a patent for its microfluidic device to isolate circulating tumor cells from body fluids. The company's technology captures rare cells in a microfluidic device, which can be used for a variety of different tests.

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\* Epic Sciences of San Diego, California, is a start-up founded by members of Peter Kuhn's lab at the Scripps Research Institute. The company has licensed technology being developed by the lab, which has some big-name partners, including Microsoft, Pfizer and Novartis.

\* NaturalNano Inc of Rochester, New York, wants to use its nanotube technology to help capture of circulating tumor cells in the blood. A recent Cornell University study found coating the surface of a capture device with nanotubes helped cancer cells stick better.

\* OncoVista Innovative Therapies Inc of San Antonio, Texas, which owns a majority interest in German-based diagnostic company AdnaGen AG, is developing a test that detects slight changes in different cancer biomarkers found on circulating tumor cells.

\* On-Q-ity, Waltham, Massachusetts, is commercializing a microchip developed in the lab of Mehmet Toner at Massachusetts General Hospital and Harvard University. A recent study of the device showed it captured breast cancer cells in women whose cancer has spread, and tests on those cells found they were HER-2 positive, showing the test might be useful for determining what type of breast cancer a woman has.

\* Sysmex Corp of Japan is working with privately held Oncolys BioPharma to develop a technology using a virus that copies itself and emits fluorescent light in tumor cells.

\* Veridex, a unit of Johnson & Johnson based in Raritan, New Jersey, markets the CellSearch kit available through several labs including those run by Quest Diagnostics. The test was developed by former marketing partner Immunicon Corp. J&J's Dr. Bob McCormack says the company is keeping an eye on next-generation tests and sees partnerships as a possibility.

\* Vitatex of Stony Brook, New York, an affiliate of Stony Brook University and the Research Foundation of the State University of New York, claims its blood test for circulating tumor cells is 10 times more sensitive than current tests. ... ”

Researchers believe that Histopathologists could acquire a new tool to diagnose different types of cancers. They claim that it might soon be possible to determine the HER2 status of breast cancer patients from blood samples rather than tissue biopsies. If this new technology proves feasible, it would give Pathologists and medical laboratories a different, and possibly less complex, methodology to use when assessing a case of breast cancer.

“ In its report about the study, Medscape Medical News, wrote that “HER2 status derived from circulating tumor cells (CTCs) from breast cancer patients was generally concordant with that derived from tumor tissue” and that “CTCs could prove to be an alternative to biopsies for assessing tumour tissue for biomarker status. The research was conducted by scientists at Genentech. In the abstract presented at the AACR 2010 conference, the researchers pointed out that “Evaluation of cancer biomarkers from blood and other accessible tissues could significantly enable biomarker assessment by providing a relatively noninvasive source of representative tumor material. Circulating tumor cells (CTCs) isolated from blood of metastatic cancer patients hold significant promise in this regard.”

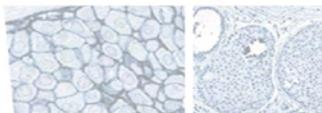
Is this a rising new technology? Should Pathologists include it in their diagnostic procedures?

I believe that it is becoming more and more convincing that the door of our laboratories should always be open to new technologies. CRCs the so called “liquid biopsy” hold significant promise as a source of neoplastic material which could provide a solid diagnostic tool.





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**Announcements:**

**European Renal Pathology Course**  
**Amsterdam, 25-27 May 2011**

It is a great pleasure to invite you to the **5th European Renal Pathology Course**, that will take place in Amsterdam from 25-27 May, 2011.

For more information, please visit this website:  
<http://www.renalpathologycourse.org/>

**The Postgraduate Course Lung, Pleural & Mediastinal Diseases**

Will be held in July 11 – 16, 2011, at the Institute of Pathology, Medical University of Graz.

For registration please fill in the registration form on our homepage:

<http://www.medunigraz.at/pathologie/postgraduate-courses>

or send your registration to:

Mrs. Edith Kleinférchner

Institute of Pathology

Medical University of Graz

Auenbruggerplatz 25, 8036 Graz, Austria

Fax 0043 / (0) 316 / 380 – 9638

E-mail: [edith.kleinférchner@medunigraz.at](mailto:edith.kleinférchner@medunigraz.at)

Kind regards  
Helmut Popper  
(Course director)

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phone: 0043 (0) 316 380 4407

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**Basel Seminars in Pathology**

Basler Fasnachts-Course 2011

Renal Transplant Pathology

March 11 - 14, 2011

To register, please write to Dr. Helmut Hopfer, Pathology, University Hospital Basel, Schönbeinstrasse 40, CH-4031 Basel, Switzerland, Email: [hhopfer@uhbs.ch](mailto:hhopfer@uhbs.ch); Telefon: +41-61-2652890;

**THEORETICO-PRACTICAL COURSE ON  
NON-GYNECOLOGIC CYTOLOGY**

**Department of Pathology, Hospital del Mar,  
Barcelona, Spain, January 19-21, 2011**

**Information :**

**F. Alameda MD.**

Dept. of Pathology, Hospital del Mar.

Passeig Marítim 25-29, 08003 Barcelona, Spain.

Phone: 34.93.248.30.31

e-mail: [86780@imas.imim.es](mailto:86780@imas.imim.es) or

**E Oliva M.D.**

Pathology Department, Massachusetts General Hospital, Boston, MA, USA

Phone: 001-617-7248272

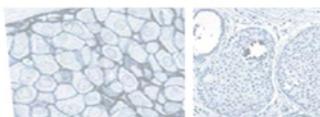
e-mail: [eoliva@partners.org](mailto:eoliva@partners.org)





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**Announcements:**

### **Workshop Soft Tissue Pathology**

9-10 June 2011, Hotel Crowne Plaza Maastricht, The Netherlands

**Registration and payment :**

Please register through the online registration for  
<http://www.unimaas.nl/congresbureau/pathology2011>.

Deadline registration: 1 June 2011.

The workshop fee includes lunches and refreshments, workshop materials, coffee and tea breaks and free bus transportation in the city centre of Maastricht during the two workshop days. Places are limited to 50. You will be registered officially once payment has been received by the conference organisation.

The workshop fees are:

**Specialists                    485 Euro**

**Research assistants\*      275 Euro**

(\* with proof of assistantship)

**Accreditation**

An accreditation request has been sent to UEMS.

### **Workshop Gastro-Intestinal Pathology**

9-10 June 2011, Hotel Crowne Plaza Maastricht, The Netherlands

**Registration and payment :**

Please register through the online registration form  
<http://www.unimaas.nl/congresbureau/pathology2011>.

Deadline registration: 1 June 2011.

The workshop fee includes lunches and refreshments, workshop materials, coffee and tea breaks and free bus transportation in the city centre of Maastricht during the two workshop days. Places are limited to 80. You will be registered officially once payment has been received by the conference organisation.

The workshop fees are:

**Specialists                    € 485,-**

**research assistants\*       € 275,-**

(\* with proof of assistantship)

**Accreditation**

An accreditation request has been sent to UEMS.

### **7th European Meeting on Molecular Diagnostics**

*Kurhaus, Scheveningen – the  
Netherlands, October 12 – 14, 2011*

[www.molecularmeeting.com](http://www.molecularmeeting.com)

