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



It is mid-August and I have almost completed one year in office as your President. It has been a very busy year. On behalf of the Society, I have visited Belgium of course, having been to the Brussels headquarters several times, but also Bulgaria, Cyprus, Germany, Greece, Poland, Romania, Spain (Granada and Seville) and London! I reported in the last newsletter that a visit to Belgrade, Serbia to participate in a course on Gynaecological Pathology was imminent. Unfortunately, I was grounded by volcanic ash, but hope to visit Belgrade next year. I am most grateful to colleagues in gynaecological pathology who gave extra lectures in my absence, particularly Sigurd Lax from Austria.

Some participants were stranded in Belgrade for several days, but I hear they made the most of their enforced vacation!

A real highlight for me was on 22nd May (10.00-16.00hrs) when I held the first "Videomicroscopy Masterclass" in the Brussels headquarters. Fourteen pathologists attended from all over Europe and I believe that the day was a great success. I certainly enjoyed the lively and intellectually stimulating interaction and several participants brought their own cases along. The installation of the videomicroscopy system in Brussels is a great asset to the Society and a series of masterclasses will be held on a monthly basis until the end of the year. We do not want the number attending each masterclass to rise above twenty; otherwise the informal, relaxed atmosphere might be lost. I am very grateful to my colleagues on the Society's Executive Committee who have agreed to give up a whole Saturday to run a masterclass and Guenter Kloeppel has already volunteered for 2011!

I have been very "hands on" insofar as the Krakow Intercongress Meeting is concerned, paying a third visit there for two days in May, and hope that I will have contributed constructively to its success; as I write we have nearly 900 registrants.

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Professor Olszewski (he has permitted me to refer to him as “Old Whisky”) and the local Krakow team (Janusz, Gregory and Krzysztof) are doing a marvellous job and, for the first time, CPO Hanser is the professional team behind the organisation.

The arrangements for Helsinki (27 August – 1 September 2011) are already advanced. I am sure that, as our first Annual Congress, it will also be a great success.

I continue to press for change in Pathology in Eastern Europe and raised the serious problems in Bulgaria and Romania at the Pathology Section of the European Union of Medical Specialists at its meeting in Berlin in June.

I also had a very constructive meeting with representatives of the Bulgarian Association of Pathologists and the Bulgarian Society of Pathology in Sofia in June. We agreed on a way forward to ensure representation of all Bulgarian pathologists in our Advisory Council and have begun to develop an educational programme for Bulgarian pathologists.

Finally, the officers of the ESP met with the officers of the Pathological Society of Great Britain and Ireland in London in April to plan for the 2014 Congress. I am delighted to report also that the Path.Soc. has agreed to introduce collective membership of the ESP for its own members. This is a very encouraging and important step for the future of European pathology and hopefully provides a model for the collective membership of other national societies, several of whom have already expressed a wish to do this.

Best wishes,

Michael Wells

**8th International Symposium on Advances in Legal Medicine (ISALM) combined with the 90th Annual Conference German Society of Legal Medicine (DGRM) which will be held from September 26 to October 1, 2011 in Frankfurt/Main (Germany).**

Scientific Board: Prof. Dr. Hansjürgen Bratzke (Institute for Forensic Medicine, University Frankfurt am Main).

Topics:

- Molecular pathology
- Molecular toxicology
- Undetected homicide
- Malpractice
- New techniques in forensic science
- Accreditation

For more information, please visit the website

[www.isalm2011.de](http://www.isalm2011.de)

## News from the Education Committee



Prof. F. Bosman

As you might remember as a long time member of the European Society of Pathology (ESP), or as a not so long time reader of our newsletters, the educational efforts of the ESP are coordinated by the Education Committee (EdCom). Our educational activities are generously supported by you all since in the annual ESP budget a substantial sum is reserved for course support and bursaries.

The EdCom covers the whole field of pathology, putting together 'General Pathology' or 'Mechanisms of Disease' if you wish (the field formerly covered by the EuroCellPath course organization) and diagnostic pathology in the form of practice oriented courses (what used to be the European School of Pathology or EScoP as founded by Gianni Busolatti). For the practice oriented courses the well established brand name EScoP has been maintained, as well as its successful format: small groups, practice oriented so lots of microscopy sessions and the high level of interactivity between participants and faculty.

What has been achieved by the committee (composed of Generoso Bevilacqua, Helmut Popper, Teresa Ribalta, Josep Lorreta Trull, Jovan Vasiljevic and myself with Gianni Busolatti as advisor)?

First of all, EScoP courses continue to thrive. With an 'on the shelf' approach – we dispose of a series of well developed course programs and dedicated faculty that can be deployed on request – course organization is relatively straightforward with a local organizer taking care of the local facilities and the EdCom as the responsible for the course program, faculty and EU wide accreditation. As the ESP executive committee has two members on the EdCom, close coordination with the ESP organization is guaranteed. Courses have run in 2009 in Ankara (GI pathology) and in Kraiova (Gynecopathology). Courses in the fall of 2010 will be in Zagreb (GI pathology) and in Kraiova (Urological Pathology).

Course proposals have been under development in most of the working groups – allowing us to develop a full menu of these 'update' courses. The term 'update' is important here as the courses cater to senior trainees or practicing pathologists, parting on the principle that basic training is taken care of in the local postgraduate pathology educational programs.

Secondly, quite a bit of attention has been paid to conceiving of a European training program in Molecular Pathology. What is under development is a program providing basic education in molecular biology as it applies to pathology, both in terms of concepts and of laboratory methods. This will be followed by specialty courses dedicated to the application of molecular methods to diagnostic pathology, as for the EScoP courses using a mixture of lectures and case based learning.

Eventually, completion of the full courses might be confirmed in the form of a certificate of proficiency. In close interaction with the working group Molecular Pathology this program is detailed and around the Krakow congress we will be able to provide much more detail.

What about 'mechanisms of disease' teaching? The EdCom feels that this needs to be optimally integrated into basic pathology training, as a fixed element in training courses rather than in the form of optional courses 'for the happy few'. EScoP courses as a rule will therefore also have some lectures focusing on (molecular) mechanisms of disease, rather than on diagnostic practice.

An element of reflection is the enormous potential of e-learning and the considerable amount of educational material ESP activities annually generate. We are in the process of putting this in a format for the ESP website – allowing those looking for web-based course material to learn or to test operational knowledge, all from your favourite desk in the office or at home.

A lot is still under construction. Much of that will appear in a tangible form in the near future. For us this should pretty much be an interactive effort. Catering to the needs of our members can only be more than a pious wish if members express themselves. Tell us what you liked and what not. Tell us what you need. Do not hide your creative impulses. We are open for new ideas!

Fred T Bosman

Chair Education Committee



Prof.A.Ensari

## News from the Digestive Diseases Working Group

Dear All,

I am Arzu Ensari from Ankara, Turkey. I was graduated from Ankara University Medical School many many years ago! I finished my training in Pathology in the same University and went to UK to do my PhD, which was again many many years ago!! I have been working on Gastrointestinal Pathology for nearly 20 years and am willing to do so for another 20, perhaps??!! Just kidding...My other interest is the "heart-shaped" microscopic structures. They make the ever lasting GI microscopy sessions much more exciting and amusing.

It is a pleasure for me to introduce the Digestive Diseases Working Group to you. Our working group is one of the largest in terms of the number of its member pathologists. I share the pleasure of being the chairperson of the working group with our secretary, Prof. Dina Tiniakos from Athens. It would not be wrong to say that Digestive Diseases Working Group is one of the most active amongst other working groups of the ESP. We have been organizing courses, workshops as well as fruitful sessions at the ESP Congresses. In the past two years, Prof. Fred Bosman has been running EScOP courses on Digestive Diseases; so far we had Kraiova and Ankara courses which will be followed by this year's Zagreb course. All of these events are being announced on the ESP webpage with the great help from Krasi.

As a working group, we have started a European Initiative on Serrated Polyps of the Colorectum with an aim to set the minimum set of diagnostic criteria. This initiative was performed in a two-step manner first of which was discussed in Florence. We have a session again in Krakow where the results of the final part of the project will be discussed. A survey regarding the criteria used for the diagnosis of serrated polyps was also displayed on our website.

You must all be aware of the collaborative programme designed by our working group and the working group of molecular pathology: the KRAS EQA programme. The details are also on the web. We are grateful to our former chairperson Prof. Han van Krieken for starting this initiative and are proud to be part of it.

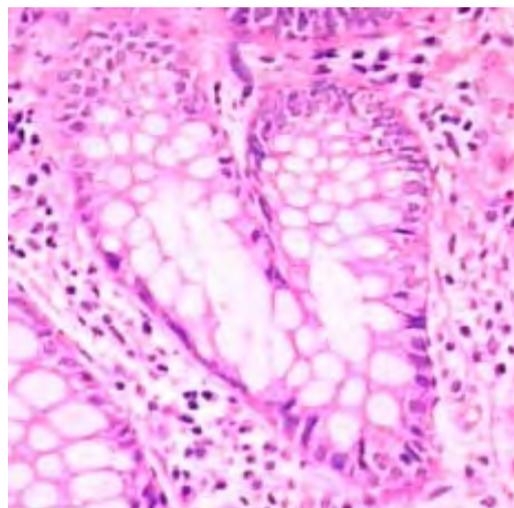
We are (though we meant to do it in the beginning of 2010) going to have monthly case discussions on our webpage, very soon.

Well, folks, I guess that's all from my side. I would be very happy to welcome you all to our working group activities.

Hope to see you all, soon, in Krakow.

Best wishes to all,

Arzu.



Prof. Arzu Ensari

## **EuroClonality WORKSHOP: “Clonality assessment in Pathology” February 14-16, 2011**

### Introduction

Clonality testing is at present an established tool in the diagnosis of malignant lymphomas. Between 5-15% of samples submitted to pathology laboratories which are suspected to be malignant lymphomas can benefit from clonality testing, provided that this is performed in laboratories with sufficient expertise. With the introduction of a new and complete set of primer sets for the full program of clonality testing by the Biomed-2 group in 2003, a major step in standardization and quality improvement was set. At the moment many laboratories throughout the world are introducing the technology, resulting in questions on pitfalls in technique and the interpretation of the results.

### EuroClonality/BIOMED2 workshops

Therefore, the EuroClonality/Biomed-2 consortium decided to organize annual workshops for laboratories that have introduced clonality testing using the new Biomed-2 primers sets in order to further improve the quality and reliability of the technique in routine practice. Since the vision of the EuroClonality/Biomed-2 consortium is that clonality testing can be performed only reliably when there is close interaction between the molecular biologist and the (hemato)pathologist these workshops are organized for such partners.

The workshops are for a maximum number of 16 persons and uses cases from the Nijmegen group as well as cases from the participants on a hands-on basis, using multiheaded microscopy for pathology evaluation and raw data from clonality tests for interpretation.

We therefore invite persons to the workshop:

- who have started to use the Biomed-2 PCR technique
- who are able to bring cases for evaluation during the workshop
- who participate as combination of pathology and molecular biology: 2 persons per institute will be accepted for the workshop.

### Participation

The registration fee for participation in the workshop is €200. The registration form, including personal details and description of the cases to be presented, should be received by the Workshop Secretariat ([workshop@euroclonality.org](mailto:workshop@euroclonality.org)) no later than December 1, 2010. The registrants will be informed about the acceptance for the workshop no later than December 17, 2010. Information on the program, travel to Nijmegen and accommodation fees will be provided upon acceptance of the registrants. With this background, we are convinced that the workshops are a very fruitful experience that will lead to improved diagnosis of malignant lymphomas and thereby better care for our patients.

On behalf of the EuroClonality/Biomed-2 consortium on Clonality testing,

Patricia Groenen, Han van Krieken, Ton Langerak and Jacques van Dongen

contact: [workshop@euroclonality.org](mailto:workshop@euroclonality.org)

[www.EuroClonality.org](http://www.EuroClonality.org)



## Views on News.

Prof. L. Kaklamanis

### The “Pile of Ps”: Pandemia, panic, profits, priorities, prevention



On 10 August 2010 WHO's director general, Margaret Chan, announced that the H1N1 influenza virus has moved into the post-pandemic period, almost one year after the official declaration of the “swine flu” world pandemic. The total number of deaths worldwide reached 18.499 , a figure so much lower compared to the official estimates of hundreds of thousand human losses. The WHO's estimate for 2 billion likely H1N1 cases was a huge failure of prediction, even after the winter season in Australia and New Zealand showed that only 1-2 out of 1000 people were infected.

The panic created worldwide led to an unprecedented race of governments to stockpile drugs and vaccines. Huge piles of unused antiviral drugs and vaccines are now stocked showing the scale of enormous public cost. At the same time drug companies have banked vast profits (\$ 9-10 billions for vaccines alone) according to JP Morgan bank.

WHO's handling of the pandemic has led to a vast number of reviews and investigations by the authorities including the Council of Europe, European Parliament and WHO itself, following allegations of industry influence.

An investigation by the *BMJ* and the Bureau of Investigative Journalism, published on 12 June 2010, showed that this was not far from the case. Deborah Cohen and Philip Carter reported that some of the experts advising WHO on the pandemic had declarable financial ties with drug companies with pipeline products including antivirals and influenza vaccines.

Fiona Godlee, (editor in chief, *BMJ*) points out in her editorial: *“As an example, WHO's guidance on the use of antivirals in a pandemic was authored by an influenza expert who at the same time was receiving payments from Roche, the manufacturer of oseltamivir (Tamiflu), for consultancy work and lecturing.*

*Although most of the experts consulted by WHO made no secret of their industry ties in other settings, WHO itself has so far declined to explain to what extent it knew about these conflicts of interest or how it managed them.*

*This lack of transparency is compounded by the existence of a secret “emergency committee,” which advised the director general Margaret Chan on when to declare the pandemic—a decision that triggered costly pre-established vaccine contracts around the world. Curiously, the names of the 16 committee members are known only to people within WHO.”*

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An inquiry by British MP Paul Flynn for the Council of Europe Parliamentary Assembly—published in mid-June—was critical. He showed that decision making around the A/H1N1 crisis has been lacking in transparency. He also pointed to distortion of priorities of public health services, a waste of huge sums of public money, provocation of unjustified fear, and the creation of health risks through vaccines and medications which might not have been sufficiently tested before being authorised in fast-track procedures. “These results need to be critically examined by public health authorities at all levels with a view to rebuilding public confidence in their decisions,” it said.

There is no doubt that

- the world should be grateful that the H1N1 2009 pandemic proved a flash in the pan compared to what was predicted to be
- had there been a huge death roll, nobody could have been able to blame WHO and ask decision making processes to be a subject of scrutiny
- planning for the worst, preventing and hoping for the best remains a reasonable approach.

However it is more than evident that

- the panic created was not only because of the fear of an epidemic threat and its uncertainty of mutational behaviour
- close working relationships existed between disease experts and drugs industry at the time of major decision processes
- waste of public money in unjustified stockpiled drugs could equally harm the public itself
- H1N1 might have claimed fewer victims than ordinary common influenza virus epidemics. But its biggest victims might be WHO’s credibility and governments’ managerial capability.

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[http://assembly.coe.int/CommitteeDocs/2010/20100329\\_MemorandumPandemie\\_E.pdf](http://assembly.coe.int/CommitteeDocs/2010/20100329_MemorandumPandemie_E.pdf).

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Loukas Kaklamanis MD, D.Phil

## Analecta Medica

1)



Effects of *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis

Wendy De Roock MD, Bart Claes MSc, David Bernasconi MSc, Jef De Schutter MSc, Bart Biesmans MSc et al.

*Lancet Oncol* 2010;11 753-763

Following the discovery that mutant *KRAS* is associated with resistance to anti-epidermal growth factor receptor (EGFR) antibodies, the tumours of patients with metastatic colorectal cancer are now profiled for seven *KRAS* mutations before receiving cetuximab or panitumumab. However, most patients with *KRAS* wild-type tumours still do not respond. We studied the effect of other downstream mutations on the efficacy of cetuximab in, to our knowledge, the largest cohort to date of patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab plus chemotherapy in the pre-*KRAS* selection era.

1022 tumour DNA samples (73 from fresh-frozen and 949 from formalin-fixed, paraffin-embedded tissue) from patients treated with cetuximab between 2001 and 2008 were gathered from 11 centres in seven European countries. 773 primary tumour samples had sufficient quality DNA and were included in mutation frequency analyses; mass spectrometry genotyping of tumour samples for *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* was done centrally. We analysed objective response, progression-free survival (PFS), and overall survival in molecularly defined subgroups of the 649 chemotherapy-refractory patients treated with cetuximab plus chemotherapy.

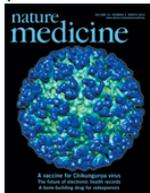
40.0% (299/747) of the tumours harboured a *KRAS* mutation, 14.5% (108/743) harboured a *PIK3CA* mutation (of which 68.5% [74/108] were located in exon 9 and 20.4% [22/108] in exon 20), 4.7% (36/761) harboured a *BRAF* mutation, and 2.6% (17/644) harboured an *NRAS* mutation. *KRAS* mutants did not derive benefit compared with wild types, with a response rate of 6.7% (17/253) versus 35.8% (126/352; odds ratio [OR] 0.13, 95% CI 0.07–0.22;  $p < 0.0001$ ), a median PFS of 12 weeks versus 24 weeks (hazard ratio [HR] 1.98, 1.66–2.36;  $p < 0.0001$ ), and a median overall survival of 32 weeks versus 50 weeks (1.75, 1.47–2.09;  $p < 0.0001$ ). In *KRAS* wild types, carriers of *BRAF* and *NRAS* mutations had a significantly lower response rate than did *BRAF* and *NRAS* wild types, with a response rate of 8.3% (2/24) in carriers of *BRAF* mutations versus 38.0% in *BRAF* wild types (124/326; OR 0.15, 95% CI 0.02–0.51;  $p = 0.0012$ ); and 7.7% (1/13) in carriers of *NRAS* mutations versus 38.1% in *NRAS* wild types (110/289; OR 0.14, 0.007–0.70;  $p = 0.013$ ). *PIK3CA* exon 9 mutations had no effect, whereas exon 20 mutations were associated with a worse outcome compared with wild types, with a response rate of 0.0% (0/9) versus 36.8% (121/329; OR 0.00, 0.00–0.89;  $p = 0.029$ ), a median PFS of 11.5 weeks versus 24 weeks (HR 2.52, 1.33–4.78;  $p = 0.013$ ), and a median overall survival of 34 weeks versus 51 weeks (3.29, 1.60–6.74;  $p = 0.0057$ ). Multivariate analysis and conditional inference trees confirmed that, if *KRAS* is not mutated, assessing *BRAF*, *NRAS*, and *PIK3CA* exon 20 mutations (in that order) gives additional information about outcome. Objective response rates in our series were 24.4% in the unselected population, 36.3% in the *KRAS* wild-type selected population, and 41.2% in the *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* exon 20 wild-type population.

While confirming the negative effect of *KRAS* mutations on outcome after cetuximab, we show that *BRAF*, *NRAS*, and *PIK3CA* exon 20 mutations are significantly associated with a low response rate. Objective response rates could be improved by additional genotyping of *BRAF*, *NRAS*, and *PIK3CA* exon 20 mutations in a *KRAS* wild-type population.

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2)



**An oncogene–tumor suppressor cascade drives metastatic prostate cancer by coordinately activating Ras and nuclear factor- $\kappa$ B**

*Junxia Min, Alexander Zaslavsky, Giuseppe Fedele, Sara K McLaughlin, Elizabeth E Reczek, Thomas De Raedt, Isil Guney, David E Storchlic, Laura E MacConaill, Rameen Beroukhim, Roderick T Bronson, Sandra Ryeom, William C Hahn, Massimo Loda & Karen Cichowski*

Nature Medicine Volume: 16, Pages: 286–294 (2010)

Metastasis is responsible for the majority of prostate cancer–related deaths; however, little is known about the molecular mechanisms that underlie this process. Here we identify an oncogene–tumor suppressor cascade that promotes prostate cancer growth and metastasis by coordinately activating the small GTPase Ras and nuclear factor- $\kappa$ B (NF- $\kappa$ B). Specifically, we show that loss of the Ras GTPase-activating protein (RasGAP) gene *DAB2IP* induces metastatic prostate cancer in an orthotopic mouse tumor model. Notably, *DAB2IP* functions as a signaling scaffold that coordinately regulates Ras and NF- $\kappa$ B through distinct domains to promote tumor growth and metastasis, respectively. *DAB2IP* is suppressed in human prostate cancer, where its expression inversely correlates with tumor grade and predicts prognosis. Moreover, we report that epigenetic silencing of *DAB2IP* is a key mechanism by which the polycomb-group protein histone-lysine *N*-methyltransferase *EZH2* activates Ras and NF- $\kappa$ B and triggers metastasis. These studies define the mechanism by which two major pathways can be simultaneously activated in metastatic prostate cancer and establish *EZH2* as a driver of metastasis.

3)



**Somatic mutations and losses of expression of microRNA regulation-related genes *AGO2* and *TNRC6A* in gastric and colorectal cancers**

*Min S Kim<sup>1</sup>, Ji E Oh<sup>1</sup>, Yoo R Kim<sup>1</sup>, Sang W Park<sup>1</sup>, Mi R Kang<sup>1</sup>, Sung S Kim<sup>2</sup>, Chang H Ahn<sup>3</sup>, Nam J Yoo<sup>1</sup>, Sug H Lee<sup>1,\*</sup>*

*The Journal of Pathology* Volume 221, Issue 2, pages 139–146, June 2010

Mounting evidence indicates that deregulation of microRNAs (miRNAs) are involved in development of many human diseases, including cancers. Regulation of miRNA is a complicated process and some components in the regulation are known to be altered in human cancers. Among the miRNA regulation-related genes, we found that *AGO1*, *AGO2*, *TNRC6A*, *TNRC6C*, *TARBP2* and *EXPORTIN5* genes have mononucleotide repeats in their coding sequences.

To see whether these genes are mutated in cancers with microsatellite instability (MSI), we analysed the mononucleotide repeats in 27 gastric cancers (GCs) with high MSI (MSI-H), 18 GC with low MSI (MSI-L), 45 GC with stable MSI (MSS), 41 colorectal cancers (CRCs) with MSI-H, 14 CRCs with MSI-L and 45 CRCs with stable MSI (MSS) by single-strand conformation polymorphism (SSCP) analysis and DNA sequencing. We found *AGO2*, *TNRC6A*, *TARBP2*, *TNRC6C* and *EXPORTIN5* mutations in 10, six, one, one and one cancer(s), respectively. They were detected in MSI-H but not in MSI-L or MSS cancers. The GCs and CRCs with MSI-H harboured one or more mutations of the genes in 22% and 27%, respectively. We also analysed Ago2 and TNRC6A protein expressions in GCs and CRCs with MSI-H. In cancers with MSI-H, loss of Ago2 expression was observed in 40% of GCs and 35% of CRCs, while loss of TNRC6A was observed in 52% of the GCs and 54% of the CRCs.

Our data indicate that frameshift mutations in *AGO2* and *TNRC6A* and their losses of expression are common in GCs and CRCs with MSI-H, and suggest that these alterations may contribute to the cancer development by deregulating miRNA regulation

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4)

#### ***Myocardial Fibrosis as an Early Manifestation of Hypertrophic Cardiomyopathy***

Carolyn Y. Ho, M.D., Begoña López, Ph.D., Otavio R. Coelho-Filho, M.D., Neal K. Lakdawala, M.D., Allison L. Cirino, M.S., C.G.C., Petr Jarolim, M.D., Ph.D., Raymond Kwong, M.D., Arantxa González, Ph.D., Steven D. Colan, M.D., J.G. Seidman, Ph.D., Javier Díez, M.D., Ph.D. and Christine E. Seidman, M.D.

NEJM 2010; 363:552-563, August 5, 2010

Myocardial fibrosis is a hallmark of hypertrophic cardiomyopathy and a proposed substrate for arrhythmias and heart failure. In animal models, profibrotic genetic pathways are activated early, before hypertrophic remodeling. Data showing early profibrotic responses to sarcomere-gene mutations in patients with hypertrophic cardiomyopathy are lacking.

We used echocardiography, cardiac magnetic resonance imaging (MRI), and serum biomarkers of collagen metabolism, hemodynamic stress, and myocardial injury to evaluate subjects with hypertrophic cardiomyopathy and a confirmed genotype.

The study involved 38 subjects with pathogenic sarcomere mutations and overt hypertrophic cardiomyopathy, 39 subjects with mutations but no left ventricular hypertrophy, and 30 controls who did not have mutations. Levels of serum C-terminal propeptide of type I procollagen (PICP) were significantly higher in mutation carriers without left ventricular hypertrophy and in subjects with overt hypertrophic cardiomyopathy than in controls (31% and 69% higher, respectively;  $P < 0.001$ ).

The ratio of PICP to C-terminal telopeptide of type I collagen was increased only in subjects with overt hypertrophic cardiomyopathy, suggesting that collagen synthesis exceeds degradation. Cardiac MRI studies showed late gadolinium enhancement, indicating myocardial fibrosis, in 71% of subjects with overt hypertrophic cardiomyopathy but in none of the mutation carriers without left ventricular hypertrophy.

5)



#### ***HPV-associated head and neck cancer: a virus-related cancer epidemic***

Dr [Shanthi Marur](#) MD [Gypsyamber D'Souza](#) PhD

Prof [William H Westra](#) MD, Prof [Arlene A Forastiere](#) MD

*Lancet Oncol* 2010;11 781-790

A rise in incidence of oropharyngeal squamous cell cancer—specifically of the lingual and palatine tonsils—in white men younger than age 50 years who have no history of alcohol or tobacco use has been recorded over the past decade. This malignant disease is associated with human papillomavirus (HPV) 16 infection. The biology of HPV-positive oropharyngeal cancer is distinct with P53 degradation, retinoblastoma RB pathway inactivation, and P16 upregulation. By contrast, tobacco-related oropharyngeal cancer is characterised by TP53 mutation and downregulation of CDKN2A (encoding P16). The best method to detect virus in tumour is controversial, and both in-situ hybridisation and PCR are commonly used; P16 immunohistochemistry could serve as a potential surrogate marker. HPV-positive oropharyngeal cancer seems to be more responsive to chemotherapy and radiation than HPV-negative disease. HPV 16 is a prognostic marker for enhanced overall and disease-free survival, but its use as a predictive marker has not yet been proven.

Many questions about the natural history of oral HPV infection remain under investigation. For example, why does the increase in HPV-related oropharyngeal cancer dominate in men? What is the potential of HPV vaccines for primary prevention? Could an accurate method to detect HPV in tumour be developed? Which treatment strategies reduce toxic effects without compromising survival? Our aim with this review is to highlight current understanding of the epidemiology, biology, detection, and management of HPV-related oropharyngeal head and neck squamous cell carcinoma, and to describe unresolved issues.

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6) **Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome**

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We report the design, synthesis, and assembly of the 1.08-mega-base pair *Mycoplasma mycoides* JCVI-syn1.0 genome starting from digitized genome sequence information and its transplantation into a *M. capricolum* recipient cell to create new *M. mycoides* cells that are controlled only by the synthetic chromosome. The only DNA in the cells is the designed synthetic DNA sequence, including "watermark" sequences and other designed gene deletions and polymorphisms, and mutations acquired during the building process. The new cells have expected phenotypic properties and are capable of continuous self-replication.

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In 1977, Sanger and colleagues determined the complete genetic sequence of phage  $\phi$ X174, the first DNA genome to be completely sequenced. Eighteen years later, in 1995, our team was able to read the first complete genetic sequence of a self-replicating bacterium, *Haemophilus influenzae*. Reading the genetic sequence of a wide range of species has increased exponentially from these early studies. The ability to rapidly digitize genomic information has increased by more than eight orders of magnitude over

Efforts to understand all this new genomic information have spawned numerous new computational and experimental paradigms, yet our genomic knowledge remains very limited. No single cellular system has all of its genes understood in terms of their biological roles. Even in simple bacterial cells, do the chromosomes contain the entire genetic repertoire? If so, can a complete genetic system be reproduced by chemical synthesis starting with only the digitized DNA sequence contained in a computer?

Our interest in synthesis of large DNA molecules and chromosomes grew out of our efforts over the past 15 years to build a minimal cell that contains only essential genes. This work was inaugurated in 1995 when we sequenced the genome of *Mycoplasma genitalium*, a bacterium with the smallest complement of genes of any known organism capable of independent growth in the laboratory. More than 100 of the 485 protein-coding genes of *M. genitalium* are dispensable when disrupted one at a time.

We developed a strategy for assembling viral-sized pieces to produce large DNA molecules that enabled us to assemble a synthetic *M. genitalium* genome in four stages from chemically synthesized DNA cassettes averaging about 6 kb in size. This was accomplished through a combination of in vitro enzymatic methods and in vivo recombination in *Saccharomyces cerevisiae*. The whole synthetic genome [582,970 base pairs (bp)] was stably grown as a yeast centromeric plasmid (YCp).

Several hurdles were overcome in transplanting and expressing a chemically synthesized chromosome in a recipient cell. We needed to improve methods for extracting intact chromosomes from yeast. We also needed to learn how to transplant these genomes into a recipient bacterial cell to establish a cell controlled only by a synthetic genome. Because *M. genitalium* has an extremely slow growth rate, we turned to two faster-growing mycoplasma species, *M. mycoides* subspecies *capri* (GM12) as donor, and *M. capricolum* subspecies *capricolum* (CK) as recipient.

To establish conditions and procedures for transplanting the synthetic genome out of yeast, we developed methods for cloning entire bacterial chromosomes as centromeric plasmids in yeast, including a native *M. mycoides* genome. However, initial attempts to extract the *M. mycoides* genome from yeast and transplant it into *M. capricolum* failed. We discovered that the donor and recipient mycoplasmas share a common restriction system. The donor genome was methylated in the native *M. mycoides* cells and was therefore protected against restriction during the transplantation from a native donor cell. However, the bacterial genomes grown in yeast are unmethylated and so are not protected from the single restriction system of the recipient cell. We overcame this restriction barrier by methylating the donor DNA with purified methylases or crude *M. mycoides* or *M. capricolum* extracts, or by simply disrupting the recipient cell's restriction system.

We now have combined all of our previously established procedures and report the synthesis, assembly, cloning, and successful transplantation of the 1.08-Mbp *M. mycoides* JCVI-syn1.0 genome, to create a new cell controlled by this synthetic genome.

Loukas Kaklamanis MD, D.Phil

## Masterclass Gastrointestinal Pathology

Sept. 17, 2010

### Masterclass venue

Office of the European Society of Pathology

Rue Bara 6

Brussels

### Time

10.00-16.00 with a lunch break

### Format

- Small group (max. 25 participants)
- Videomicroscopy, slide based
- Interactive approach: the 'master' is more moderator of the discussion than oracle with the final answers
- Case based: the faculty has selected didactic cases but participants are strongly encouraged to bring their own cases along

### Faculty

- Prof. Fred T Bosman (Lausanne/Maastricht)
- Prof. Johan G Offerhaus (Utrecht)

### Registration fee

- €20,-.
- Registration is on a first come first serve basis, registration is confirmed when the registration fee has been paid.

### Course content

The course will focus on problems encountered in daily practice in the field of Gastrointestinal pathology. Significant attention will be paid to the diagnosis of premalignant lesions in the GI tract, including new entities (notably sessile serrated adenomas/polyps). We will review neuroendocrine neoplasms in the tubal gut. New developments in gastric and colorectal cancer will also be addressed.

As inflammatory pathology of the GI tract regularly poses problems in daily practice the afternoon session will focus mostly on this area. Key features of relevant infectious conditions will be reviewed but also problematic issues in the pathology of inflammatory bowel disease.

## Tips and Tops- News in Brief

### 1) Drugs designed to combat age-related diseases work as claimed,

according to research published last week in the *Journal of Biological Chemistry*. The authors, most of whom work for the GlaxoSmithKline (GSK) subsidiary Sirtris Pharmaceuticals, hope that the findings will quell debates over whether the drugs activate a key anti-ageing protein called SIRT1. Sirtris, based in Cambridge, Massachusetts had been working on compounds that activate SIRT1 and showed promising effects, prompting London-based drug giant GSK to buy the company for US\$720 million in 2008. The drugs are thought to mimic the effects of the red wine component resveratrol. Critique resurfaced this year when scientists at Pfizer in Groton, Connecticut, raised questions over SIRT1-activating compounds being developed by GSK. GSK says that these compounds are more potent than resveratrol at activating SIRT1 and therefore more useful as drugs. *Nature June 2010*

### 2) European countries seek to cut drug costs:

*In May 2010, the Greek Government announced cuts averaging 25% in the price they pay wholesalers for patented drugs. Pharmaceutical companies, already among those to whom Greece owes some €6.5 billion in unpaid hospital debts, were dismayed. Two groups—Novartis and Leo Pharma—said they would prefer to withdraw from the Greek market. But the country is not alone in seeking to reduce its drugs bill. Spain plans similar cuts of 10–16%; Germany proposes raising its mandatory rebate on patented medicines by 10%, which amounts to much the same thing; and Ireland intends to cut the costs of generic drugs by up to 40%. In the UK, the new coalition government talks of instituting a “value-based” approach to drug-pricing when the Pharmaceutical Price Regulation Scheme—a compact with the industry that limits the profits a company can make—expires at the end of 2013.*

*France has one of the highest per-head expenditures on pharmaceuticals in Europe—US\$554—Spain spends \$517 per head, Italy \$509, and Germany \$498. And costs are growing. In France, sales of expensive new drugs in the country are increasing by 20% per year. This burden, in France and elsewhere, falls overwhelming on the state. Responsibility for assessing the quality, efficacy, and safety of drug products lies with the European Medicines Agency (EMA). Should they approve a medicine, a request is despatched to the European Commission for market authorisation; once granted, this authorisation is valid across the EU. But the EMA's bailiwick extends no further than this. Member states have sole responsibility for drugs pricing and reimbursement; though, of course, they might choose to consult with EMA or WHO. Talha Burki /Lancet Oncology July 2010*

### 3) Since mid-June, 2010, the UK's National Institute for Clinical Excellence (NICE) has issued statements indicating that it will not support licensing applications for eight cancer drugs—

erlotinib for maintenance treatment of NSCLC, trabectedin for relapsed ovarian cancer, imatinib for GIST (both in the adjuvant setting and for higher doses for patients with relapsed unresectable or metastatic disease), ofatumumab for chronic lymphocytic leukaemia, bevacizumab for metastatic breast cancer, mifamurtide for osteosarcoma, trastuzumab for HER2-positive gastric cancer, and everolimus for renal-cell cancer. In the same period, only pemetrexed for maintenance therapy of NSCLC was approved. NICE's position on some of these drugs was typically reached on the grounds of cost. For instance, erlotinib for maintenance therapy of NSCLC was turned down because “the overall cost of erlotinib had been underestimated” in the economic models submitted by the drug's manufacturer. Other decisions were reached on clinical grounds—eg, adjuvant imatinib for GIST only delayed relapse rather than lengthening survival, among other factors considered.

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*But prolonged freedom from relapse is often the best outcome a patient can expect with some diseases and, rightly or wrongly, progression-free survival is becoming the standard measure in many settings in oncology, rather than overall survival. The Lancet August 2010*

4) US District Court Judge for New York, Robert Sweet, ruled in favour of the American Civil Liberties Union and College of American Pathologists on March 29, **invalidating seven gene patents on BRCA1 and BRCA2** held by Myriad Genetics and the University of Utah (*New York Times*, March 30, 2010). BRCA1 and BRCA2 mutations are associated with breast and ovarian cancer risk. With at least a fifth of human genes under patent, the decision sent shockwaves through the multibillion-dollar biotechnology industry. But restrictions on individual gene patents could hasten innovation in genome-wide diagnostic cancer testing and research, said experts contacted by *The Lancet Oncology*. Myriad argued that isolated genes are “markedly different” from genomic DNA in structure and function to justify patenting their use as diagnostic and prognostic tools. But Sweet dismissed Myriad’s argument as “lawyer’s tricks”, and ruled that simply isolating and purifying a product of nature is not, alone, a sufficient innovation for patent protection in the case of genes, because of DNA’s unique quality of carrying information. Myriad’s 20-year patents on BRCA1 and BRCA2 will expire in 2014 and 2015, respectively. *Bryant Furlow /Lancet Oncology May 2010*

5) ***The US Food and Drug Administration approved the first-ever vaccine to treat cancer on 29 April.*** *After a three-year battle with the regulatory agency and three phase 3 trials, the treatment—called Provenge, by Seattle-based Dendreon—extended median survival time in men with advanced prostate cancer by more than four months.*

*The success of Provenge could herald many more therapeutic vaccine treatments for everything from brain tumors to renal cancer, says Joseph Pantginis, a biotech analyst with Roth Capital Partners in New York. “It finally breaks the glass ceiling after years of skepticism and many failures in the cancer immunotherapy space.”*

Here are ten promising cancer vaccines currently in mid- to late-stage development.

Company	Product	Type of cancer	Phase <sup>a</sup>
CellDex Therapeutics & Pfizer	CDX-110	Glioblastoma (brain)	2
GlaxoSmithKline	MAGE-A3 ASCI	Lung, melanoma	3
Geron	GRNVAC1	Acute myelogenous leukemia	2
Vical	Allovectin-7	Melanoma	3
Biovest International	BiovaxID	Non-Hodgkin’s lymphoma	3
Oncothyreon & Merck	Stimuvax	Breast & lung	3
Oxford BioMedica	TroVax	Kidney	3
Argos	AGS-003	Kidney	2
New Link Genetics	HyperAcute	Lung, pancreas	2
TVAX Biomedical	TVAX immunotherapy	Astrocytoma (brain) & kidney	2

<sup>a</sup>Ongoing or completed trial phase.

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**Agenda for the General Assembly, European Society of Pathology,  
Krakow, 1<sup>st</sup> September 2010, 18.30h. until 19.30h.**

1. Welcome.
2. Approval of the Minutes of the General Assembly in Florence, September 2009.
3. Report of the President.
4. Report of the Treasurer.
5. Presentation of Honorary membership: Prof. Niki Agnantis.
6. Working Group items: Approval of new WG History of Pathology.
7. ESP Congress, Helsinki, 2011. Report of the Chairman of the Organising Committee.
8. ESP Congress, Prague, 2012. Report of the Chairman of the Organising Committee.
9. Approval of the sites of future ESP congresses:
  - a). ESP Congress, Lisbon 2013.
  - b). ESP Congress/Joint meeting with the Pathological Society of Great Britain and Ireland 2014.
10. Date and place of next meetings.
  - a). General Assembly, Helsinki, September 2011.
  - b). General Assembly, Prague, September 2012.

## The Pathologist



Interview with Christian Garbar, the new head of the department of pathology at the "Institut Jean Godinot", Reims, France, Europe....

**MM:** Christian, I wanted to interview you because you are actually doing what European pathologists should do more: moving around, working in different departments and even countries. Many European pathologists remain in their own country and even in the same university or private lab during their whole career, but you changed quite frequently. What makes you different from those other European pathologists?

**CG:** To change places is probably the hereditary aspect of my career! My grandparents came from old Czechoslovakia in 1935 to work in Belgium. My grandfather's brother also immigrated and went to France. One of his grand children is now a Law Professor at the University of Tours.

**MM:** So your ancestors have probably planted the seed. What about yourself? Can you describe your career in terms of "changing places"?

**CG:** It is true that I practised in several laboratories. After my training at the UCL, I initially wanted to extend my training and apply what I learned, by working in another environment. Later I took the opportunities whenever they presented themselves and this gave me the possibility to do research, to see interesting cases and particularly to train residents in two Belgian Universities, the UCL and the VUB. I also spent some years in a private lab in the Walloon region of Belgium. With my latest move, the task became somewhat different and certainly more demanding: I am now head of pathology and cytology at the "Institut Jean Godinot", an oncology centre in Reims (France).

**MM:** While Belgians will appreciate that changing from an ultra catholic university, the UCL, to the VUB, a university that rejects dogmas and places freedom of thought at the forefront, may have been a challenge, everybody will probably understand that going from a French speaking environment to a Flemish one, may have been even more difficult?

**CG:** Philosophically, I feel closer now to the VUB than to the UCL. Surely, when I started working at the VUB, ethical questions such as abortion and especially euthanasia were, at first, unsettling; but you are right, changing languages was by far the bigger challenge. For me, discussing with colleagues, especially during interdisciplinary meetings, when everybody seemed to speak at the same time, was very difficult; writing reports, on the other hand, was easy; the fact that I prefer short texts, followed by a diagnosis, instead of using long descriptions, is an advantage, and helps a lot when one has to use a foreign language.

**MM:** Would you support the introduction of one language for communication between medical professionals in Europe?

**CG:** Yes, surely. To date, English is "the" language for international medical publications and lectures; for routine work, however, I think that reports should be made in the patient's and physician's language, because both the patient and the physician should understand every detail of the diagnosis. In my view, it would be unwise and very difficult to impose one language, probably English, to be used by all pathologists in Europe for routine work. Cultural heterogeneity does not permit this. Nevertheless, within Europe, patients should be able to consult or get a treatment in specialist centres in other countries than their own, especially for unusual cancers and other rare diseases. In those cases, a résumé of the chart should be available in a universal language, preferably English.

**MM:** It seems indeed that before Europe can think of becoming a Union with one language, we have still a long way to go! The big challenge will be for the different countries to keep their identity, while at the same time being able to communicate in a practical way. I see this as a big problem for residents who want to have part of their training outside their own country. Training directors are in favour, students like it, but there are language barriers that will remain difficult to overcome. Do you have a solution for this?

**CG:** Maybe a mandatory course in medical and scientific English should be introduced in the European medical curriculum? The solution is not simple; as a general rule, I would encourage everybody to dare to speak or write in a foreign language, even when one does not master it as well as one would like. I am a real role model for this!

**MM:** Lets stop dreaming about a unified European language for the time being. How are you adapting to the French medical culture? I am sure that there must be many differences between the way things are run in the Champagne region, as compared to the Flemish/Brussels way of doing things?

**CG:** Curiously, there is little difference between the Belgian or Flemish approach and the French way of doing things, at least where pathology is concerned. Modern pathology tends to apply more en more checklist reporting, based for instance on the checklists of the College of American Pathologist. In France we use the protocols of INCa (Institut National du Cancer), which are quite similar. For the classification of diseases we use the WHO. For cytology, we tend to use more and more universal standards, such as Bethesda for GYN and this tendency extends to other organs, such as the thyroid. The oncologists follow the ASCO guidelines. Immunohistochemistry, molecular biology, liquid-based cytology, automatic staining... are commercialised by the same international manufacturers as everywhere else. The quality system for laboratories is ISO 15189, which is also used in many other European countries.

A unified medical/pathological Europe exists already in the Western European countries. I expect the "newer" European countries will soon follow. Administratively, immigration is also made easier by new European laws. In my case, the biggest difficulties I encountered are related to changes in our personal lives: organising our new life with the kids, our parents, home and friends. It has also been difficult to leave my colleagues and a laboratory where I felt at home. Nevertheless, moving to another country permits me to achieve my professional dream by creating a modern laboratory of cytology and pathology and I have my wife, who is a cytotechnician, to help me. Yes...I already feel like a real European and I am sure many other European pathologists will soon follow.

**MM:** thank you, Christian. I hope what you learned in the different places you have frequented, will help you to become a great head of your new department. Good Luck!!

Prof. Mia Marichal