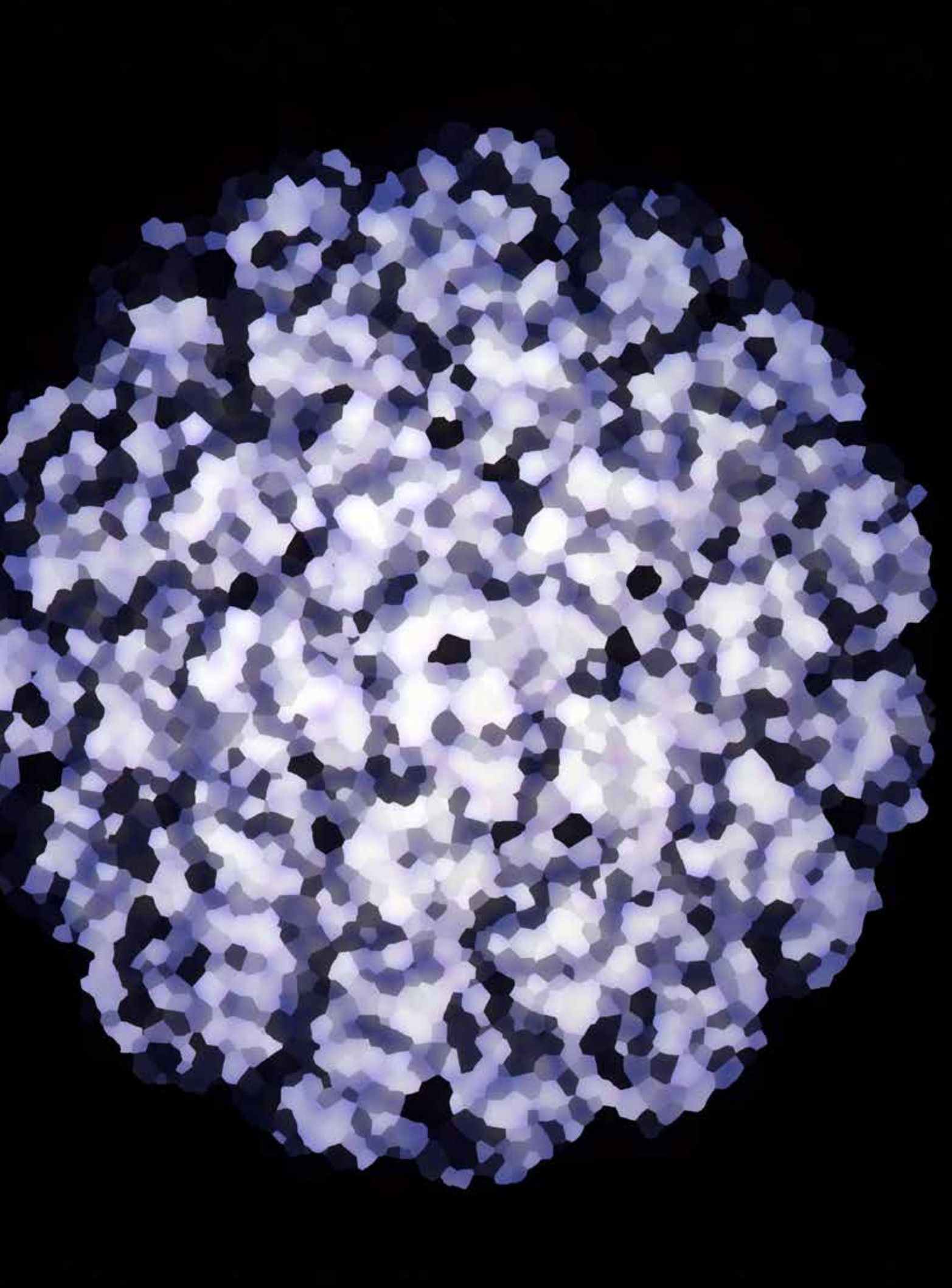

Section of Infections (INF)

Section head
Dr Massimo Tommasino

The Section of Infections (INF) consists of two groups: the Infections and Cancer Biology Group (ICB) and the Infections and Cancer Epidemiology Group (ICE). The groups have similar goals in evaluating the role of infectious agents in human carcinogenesis using complementary strategies. ICB is mainly focused on the characterization of the molecular mechanisms of different infectious agents in altering fundamental cellular events, as well as on the development of laboratory assays that can be used in epidemiological research. The work in ICE centres on performing worldwide epidemiological studies to evaluate the role of infections in human cancers.

In the past two years, ICB has characterized several novel mechanisms of oncogenic viruses, such as human papillomaviruses (HPV), Epstein–Barr virus (EBV), and Merkel cell polyomavirus (MCPyV). ICB has found that different oncogenic viruses have the ability to target the same events in cellular cancer pathways (i.e. evasion of the immune surveillance and induction of cellular transformation). For example, several HPV types, EBV, and MCPyV are able to downregulate the expression of Toll-like receptor 9, which plays a fundamental role in pathogen recognition and activation of innate immunity. In addition, cutaneous HPV type 38 and EBV induce the accumulation of a strong antagonist of the tumour suppressor p53, ΔNp73α.

Recent research efforts in ICE include the estimation of the global burden of cancer attributable to infectious agents and, in particular, the variation in the frequency of HPV infection and HPV-related malignancies. Special efforts have gone into establishing multiyear studies on the effectiveness of HPV vaccination and HPV-based screening in the two low-resource countries, Bhutan and Rwanda, which have been the first to successfully adopt HPV vaccination practices. Finally, ICE has strengthened its efforts to evaluate the determinants of cancer and possible prevention strategies in HIV-positive individuals at a time when their survival is improving even in sub-Saharan Africa.

In addition, ICB and ICE have performed several collaborative studies that led to the characterization of the relationship between mucosal HPV type 16 polymorphisms, geographical distribution, and severity of the cervical disease (Cornet *et al*., 2012a, 2013a, 2013b). The two groups have also joined forces to better define the role of HPV infection in the etiology of cancer of the head and neck in Europe and Asia.

In the 2012–2013 biennium, INF has published articles in high-ranking journals, covering a wide range of topics related to infections and cancer (ICB: 27 publications and 6 articles in press; ICE: 75 publications and 12 articles in press).

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The main goal of the Infections and Cancer Biology Group (ICB) is to elucidate molecular mechanisms of both well-established and potential oncogenic viruses. In the past two years, studies have focused on cutaneous and mucosal HPV types, several members of the polyomavirus family, and EBV. The studies used several in vitro experimental models, including cells that are the natural host of the studied viruses (e.g. primary human keratinocytes for HPVs and primary B-cells for EBV). In particular, functional studies were focused on characterizing the impact of viral proteins on key cellular events in carcinogenesis, such as regulation and inactivation of tumour suppressors and evasion of immune surveillance (Accardi *et al.*, 2013; Chiantore *et al.*, 2012; Cornet *et al.*, 2012a; Hasan *et al.*, 2013; Saidj *et al.*, 2013; Saulnier *et al.*, 2012; Siouda *et al.*, 2012; Thomas *et al.*, 2013; Viarisio *et al.*, 2013). As a complementary strategy to functional studies, laboratory assays have been established for the detection of the DNA or RNA of approximately 120 infectious agents in human specimens. These assays have a high throughput, sensitivity, and specificity, allowing the use of a broad spectrum of human specimens, including skin swabs, saliva, urine, and formalin-fixed, paraffin-embedded tissues. The features of the assays have enabled initiation and completion of several collaborative epidemiological studies that evaluate the role of HPV types and other viruses in different types of cancers; for example, oropharyngeal cancer and non-melanoma skin cancer (NMSC) (Anantharaman *et al.*, 2013; Comar *et al.*, 2012; Halec *et al.*, 2013; Iannacone *et al.*, 2012, 2013a; Polesel *et al.*, 2012a; Rollison *et al.*, 2012). Examples of functional studies completed in the biennium are highlighted in the following paragraphs.

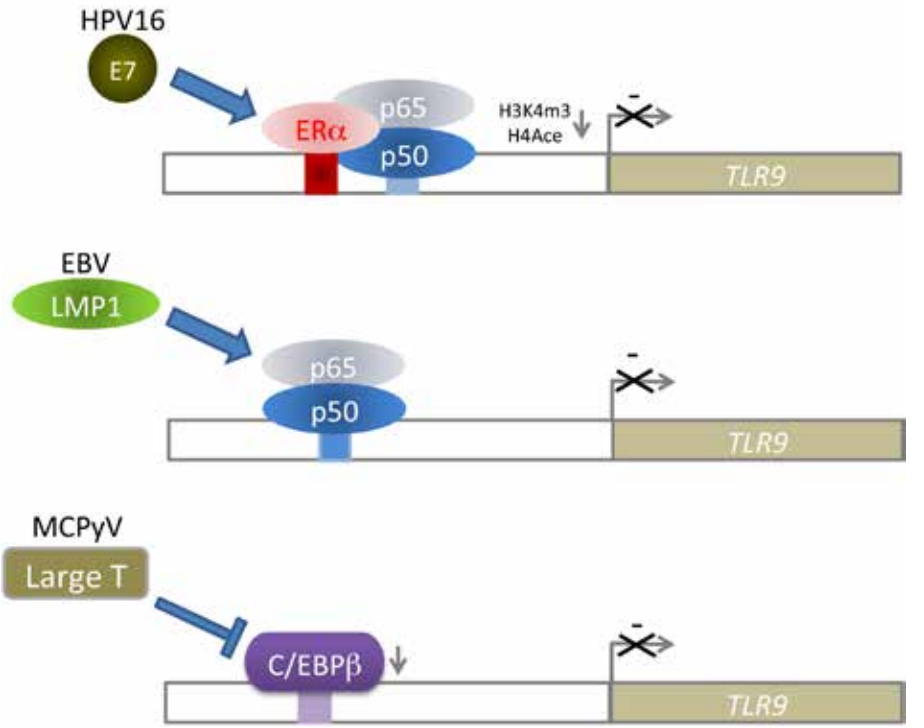
Several oncogenic viruses target the innate immune response by downregulating TLR9 expression

It has previously been shown that HPV16 and EBV deregulate immunity by suppressing the function of the double-stranded DNA (dsDNA) innate sensor Toll-like receptor 9 (TLR9) (Figure 1). In a recent study, the mechanism of these HPV-induced events was partially dissected. Using in vitro and ex-in vivo models, it was shown that the HPV16 E7 oncoprotein promotes the formation of an inhibitory transcriptional complex containing NF-κB, p50/p65, and ERα (Figure 1). The E7-mediated transcriptional complex also recruited the histone demethylase JARID1B and histone deacetylase HDAC1. The entire complex bound to a specific region on the TLR9 promoter, which resulted in decreased methylation and acetylation of histones upstream of the TLR9 transcription start site. The findings also indicate that the HPV16-induced TLR9 downregulation affects the interferon response, which negatively regulates viral infection (Hasan *et al.*, 2013). The transcription factor ERα is a member of the nuclear receptor family that translocates into the nucleus upon binding to the sex hormone estradiol. Epidemiological studies showed that high levels of circulating estrogens are a risk factor for both breast and HPV-mediated cervical carcinogenesis. Based on data that highlight the inhibitory role of ERα in TLR9 expression, it is hypothesized that ERα signalling favours cervical cancer development in part by promoting an efficient and permanent downregulation of TLR9 messenger RNA (mRNA) levels.

In an independent study, it was demonstrated that the recently isolated oncogenic virus, MCPyV, which is associated with the majority of Merkel cell carcinomas (MCCs), is also able to inhibit the expression of TLR9 by a distinct mechanism (Shahzad *et al.*, 2013). These findings showed that MCPyV large T antigen (LT) expression downregulates TLR9 expression in epithelial and MCC-derived cells. Accordingly, silencing of LT expression results in upregulation of TLR9 mRNA levels. LT inhibits TLR9 expression by decreasing mRNA levels of the C/EBPβ transactivator, a positive regulator of the TLR9 promoter (Figure 1).

In summary, these studies showed that downregulation of TLR9 expression is a

Figure 1. Oncogenic viruses downregulate TLR9 expression by different mechanisms. HPV16 E7 and EBV LMP1 activate the NF-κB signalling pathway, inducing the translocation of NF-κB complexes (p50/p65), which together with the estrogen receptor alpha (ERα) and epigenetic enzymes are recruited to the TLR9 promoter. The binding of these complexes to TLR9 promoter correlated with a decrease of histone 4 acetylation (H4Ace) and trimethylation of histone H3 at lysine 4 (H3K4m3) and inhibition of TLR9 expression. Large T antigen from MCPyV downregulates the TLR9 mRNA levels by inhibiting the expression of a positive regulator of TLR9 promoter, C/EBPβ. EBV, Epstein–Barr virus; MCPyV, Merkel cell polyomavirus.



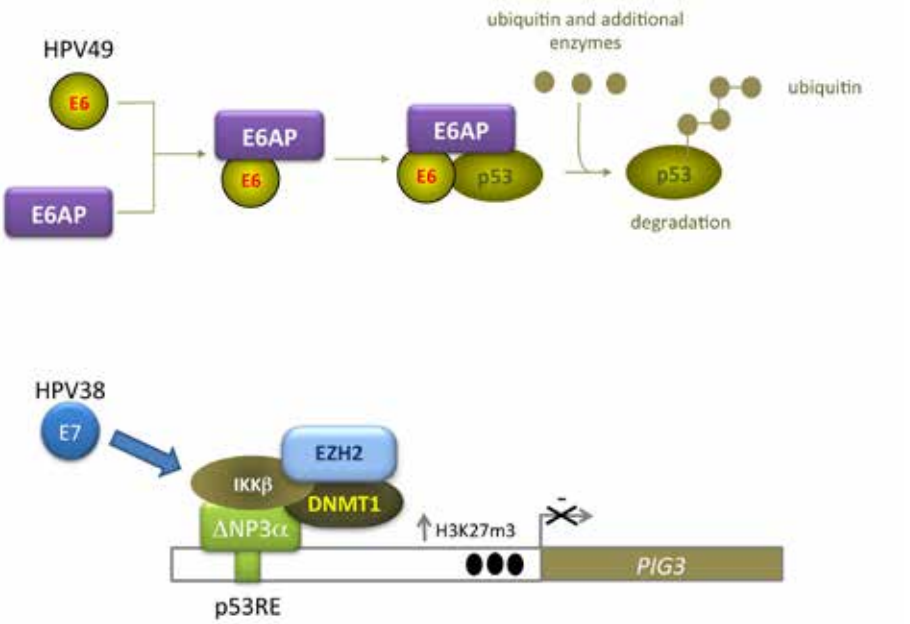
highly conserved phenomenon among the oncogenic viruses, underscoring the importance of this event in virus-mediated carcinogenesis.

Identification of a novel viral mechanism of inactivation of the p53 tumour suppressor

In the past decade, several epidemiological and biological studies have been performed to evaluate the possible role of cutaneous β HPV types in the development of NMSC. In particular, the biological properties of the oncoproteins E6 and E7 from many β HPV types have been characterized, and it has been observed that certain β HPV types (i.e. HPV38 and 49) display transforming properties (Cornet *et al.*, 2012a). A key event in HPV-mediated cellular transformation is the inactivation of p53 tumour suppressor. The mucosal high-risk HPV types associated with cervical cancer are able to inactivate p53, promoting its degradation via the proteasome pathway, a phenomenon mediated by the viral E6 oncoproteins. It has been observed that β HPV49 E6 is also able to induce p53 degradation, showing for the first time that this property is conserved in E6 from mucosal and cutaneous HPV types (Figure 2). In addition, a novel mechanism of p53 activation of β HPV38 E7 has been characterized. This viral oncoprotein is able to induce accumulation of a strong p53 antagonist, ΔNp73α, that in turn forms a transcriptionally inhibitory complex together with IKKβ and two epigenetic enzymes, namely DNA methyltransferase 1 (DNMT1) and enhancer of zeste homolog 2 (EZH2). HPV38 E7 favours the recruitment of this complex to the p53-regulated promoter, preventing its activation (Saidj *et al.*, 2013) (Figure 2).

Interestingly, it was recently demonstrated that the oncogenic virus EBV is also able to induce accumulation of ΔNp73α via the oncoprotein LMP-1. This phenomenon is mediated by the LMP-1-dependent activation of c-Jun NH2-terminal kinase 1 (JNK-1), which in turn favours the recruitment of p73 to the ΔNp73 promoter. A specific chemical inhibitor of JNK-1 or silencing JNK-1 expression strongly downregulated ΔNp73α mRNA levels in LMP-1-containing cells.

Figure 2. Beta cutaneous HPV types use different mechanisms to inhibit the transcriptional functions of p53. As high-risk mucosal HPV types, HPV16 E6 targets p53 for degradation via the ubiquitin/proteasome pathway. The E6 oncoprotein from beta cutaneous HPV type 49 associates with the ubiquitin-protein ligase E6AP. The dimeric complex then binds p53 and E6AP catalyses multi-ubiquitination of p53 in the presence of ubiquitin and additional enzymes of the ubiquitin pathway. E6 oncoprotein from beta cutaneous HPV38 induces the accumulation of a p53 antagonist ΔNp73α. The latter binds the p53 responsive elements of p53-regulated promoters and favours the recruitment of additional cellular proteins, i.e. IκBα kinase β (IKKβ), the Polycomb-group 2 member EZH2, and DNA methyltransferase DNMT1. The two epigenetic enzymes, EZH2 and DNMT1, promote the trimethylation of histone H3 at lysine 27 (H3K27me3) and DNA methylation (M), respectively preventing the activation of p53-regulated promoters.



Accordingly, LMP-1 mutants deficient in activating JNK-1 did not induce ΔNp73α accumulation. Inhibition of ΔNp73α expression in EBV immortalized B cells led to the stimulation of apoptosis and the upregulation of a large number of cellular genes as determined by whole-transcriptome shotgun sequencing (RNA-seq). In particular, the expression of genes encoding products known to have anti-proliferative/pro-apoptotic functions, as well as genes known to be deregulated in different B-cell malignancies, was altered by ΔNp73α downregulation (Accardi *et al.*, 2013).

Together, these findings show that β HPV types share properties with well-established oncogenic viruses. HPV49, similarly to the mucosal high-risk HPV16, promotes p53 degradation via the proteasome pathway. In addition, β HPV38 and EBV are able to antagonize p53 functions, inducing the accumulation of ΔNp73α.

Role of the DOK1 tumour suppressor in carcinogenesis

Downstream of tyrosine kinase 1 (DOK1) is a newly identified tumour suppressor that downregulates several cellular signalling pathways. DOK1 inhibits cell proliferation and constitutes a negative regulator of the human immune system. These studies have identified a mutated DOK1 in chronic lymphocytic leukaemia exclusively confined in the nucleus, and subsequently shown that the suppressive activity of DOK1 is regulated by its subcellular localization. The role of DOK1 in human neoplasia was further supported by the findings that the expression of the gene was constitutively repressed through promoter hypermethylation in several human cancers, including head and neck, lung, gastric, and liver cancer and Burkitt lymphoma (Saulnier *et al.*, 2012). Additional studies have recently shown that the transcription factor E2F1 regulates the expression of DOK1. DNA

methylation of the DOK1 core promoter region found in head and neck cancer cells hampered the recruitment of E2F1 to the DOK1 promoter and compromised its expression. Interestingly, and similarly to p53 and other established tumour suppressors, E2F1-induced DOK1 transcription occurred in the presence of cellular stresses, such as accumulation of DNA damage induced by etoposide. DOK1 silencing promoted cell proliferation and protected against etoposide-induced apoptosis, indicating that DOK1 acts as a key mediator of cellular stress-induced cell death (Siouda *et al*., 2012).

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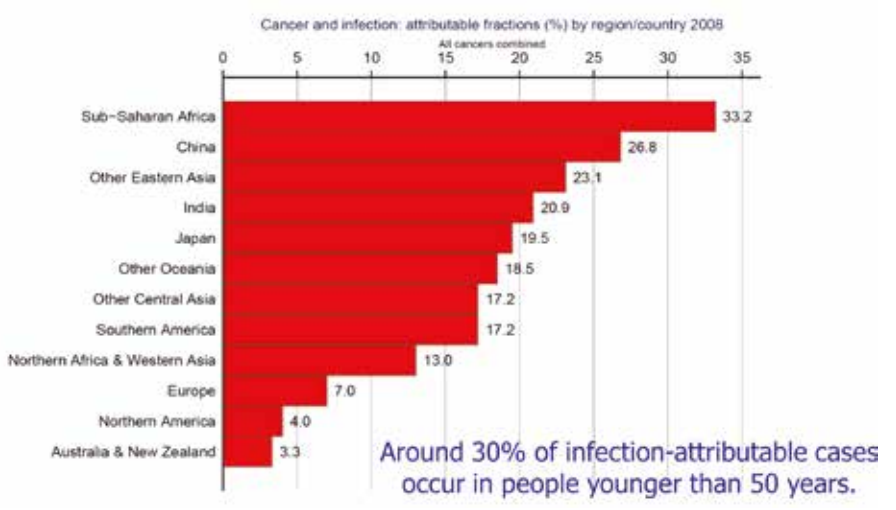
The main goal of the Infections and Cancer Epidemiology Group (ICE) is to elucidate the contribution of infectious agents, such as human papillomavirus (HPV), human immunodeficiency virus (HIV), hepatitis B and C virus (HBV/HCV), and *Helicobacter* species, to the etiology of cancer. For a substantial number of current ICE projects, ICB lends expertise for viral testing or other biological aspects.

In the past two years, exciting new opportunities have emerged to use the knowledge of the infection–cancer link to prevent malignancies associated with HPV and HIV cancer (Chen CJ *et al.*, 2013; Clifford *et al.*, 2013; Crosbie *et al.*, 2013; de Martel *et al.*, 2013; Franceschi and Wild, 2013; Plummer, 2013; Tsu *et al.*, 2012), and these opportunities have allowed ICE to move increasingly into translational research. In addition, ICE is engaged in many inter-Section collaborations, notably with the Section of Cancer Information (CIN) on age-period cohort analyses of selected cancers (Vaccarella *et al.*, 2013a), the Section of Nutrition and Metabolism (NME) on thyroid cancer, the Section of Genetics (GEN) on interaction between HPV and susceptibility genes, and the Section of Early Detection and Prevention (EDP) on the prevention of cancer of the stomach and cervix.

Global burden of cancer attributable to infections

In collaboration with CIN, ICE used data from Globocan and a variety of literature sources to calculate the fraction of cancer attributable to infection worldwide and in eight geographical regions (de Martel *et al.*, 2012). Overall, 2 million (16.1%) of the total 12.7 million new cancer cases that occurred in 2008 are attributable to infections. This fraction is higher in less developed countries (22.9%) than in more developed countries (7.4%) and varies 10-fold by region, from < 4% in Australia/New Zealand and the USA to 33.2% in sub-Saharan Africa (Figure 1). The most important infectious agents are *Helicobacter pylori*, HBV/HCV, and HPV, which together are responsible for 1.9 million cases of gastric, liver, and cervix uteri cancers, respectively. Application of existing public health methods for infection prevention, such as vaccination, safe injection practices, or antimicrobial treatments, could have a major impact on the future burden of cancer worldwide.

Figure 1. Variation in infection-attributable cancers (at least 2 million per year, 16% of total cancer cases worldwide). Figure compiled from de Martel *et al.* (2012).



HPV and cervical cancer prevention

In the 2012–2013 biennium, ICE's main focus was HPV (Crosbie *et al.*, 2013). For HPV vaccines and HPV-based screening to be successful, accurate knowledge of the infection burden and type-specific distribution of HPV types in different parts of the world is needed. ICE carried out new population-based HPV prevalence surveys on exfoliated cervical cells in Vanuatu (Aruhuri *et al.*, 2012), in the Islamic Republic of Iran (Khodakarami *et al.*, 2012), in China (Zhao *et al.*, 2012), and in Bhutan and Rwanda. Work in Bhutan and Rwanda was the first step of a multiyear project meant to demonstrate the early impact of successful implementation of vaccination against HPV in two low- and middle-income countries (LMICs) (Table 1). Bhutan and Rwanda have achieved the highest HPV vaccine coverage in the developing world (> 90% of adolescent girls in 2010 and 2011), and are also committed to improving their screening programmes through the introduction of HPV test-based screening. The impact of vaccination and screening will therefore be evaluated jointly by ICE. To evaluate the impact of HPV vaccination among adolescent girls in the two countries, a novel type of HPV survey has been conceived based on the collection of urine samples in female

Table 1. Early impact of the HPV vaccination programme in Rwanda and Bhutan

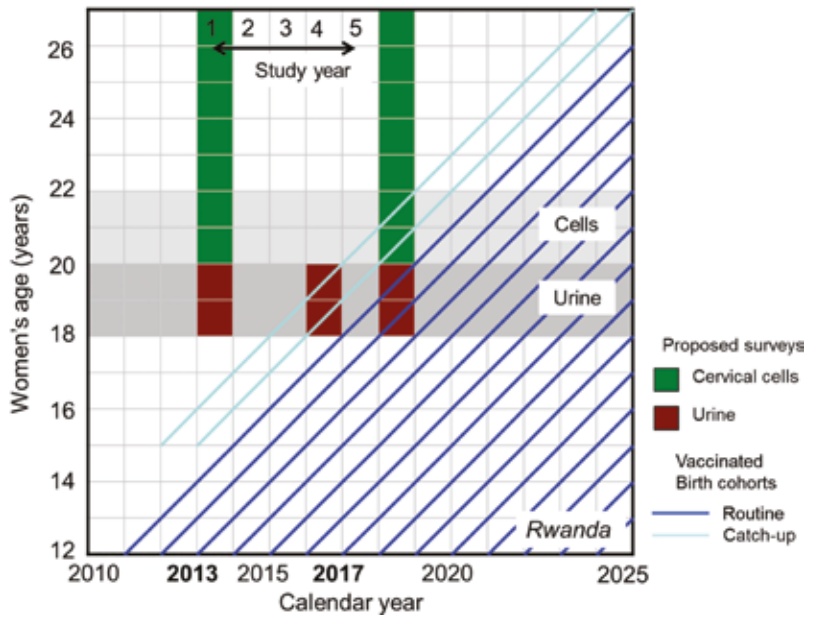
Baseline HPV prevalence survey across a broad age range of unvaccinated women (Year 1)
A cross-sectional survey of ~2500 women, stratified by age, will establish the prevalence of HPV in cervical cytology samples from unvaccinated women in Rwanda.
Invasive cervical cancer (ICC) case series (Year 1)
HPV genotype distribution in tumour biopsies from 100+ ICC cases.
Repeat HPV survey in young, sexually active women (Year 5)
A second cross-sectional survey of 1500 sexually active women aged < 25 years, using the same recruitment and identical HPV testing protocol as the baseline survey. The 5-year impact of the vaccine will be measured by reduction in the prevalence of HPV16/18 DNA infections.
Monitoring type-specific HPV prevalence in urine samples from adolescents (Years 1, 3, and 5)
Avoiding the need for a gynaecological examination has potential to greatly facilitate HPV vaccine impact monitoring. A pilot study of HPV detection in urine from repeat surveys of 1000 18–19-year-olds will be performed.

students aged 18–19 years. Newly-conceived media and devices for self-collection will avoid DNA degradation in urine samples and allow the shipment to IARC without the need for additional, potentially detrimental, manipulations. The Lexis diagram in Figure 2 shows that in Rwanda, for instance, we will be able to compare the first generation of HPV vaccine recipients with previously unvaccinated women of the same age by 2017 in female students and by 2019 in young women participating in the cervical cell survey. Timely high-quality data on the effectiveness of HPV vaccination and HPV-based screening in the two LMICs that have been the first to successfully adopt HPV vaccination will hopefully encourage and facilitate the introduction of these successful programmes into other LMICs.

In addition, ICE released the first systematic comparison of the distribution of individual HPV types in 115 789 HPV-positive women with and without cervical cancer or pre-neoplastic lesions (Guan *et al.*, 2012, 2013). Figure 3 shows the unique behaviour of HPV16 and 18 among high-risk HPV (hrHPV) types, i.e. their relative rarity in cytologically normal women and a steep increase in their prevalence as cervical lesions become more severe. The global HPV database is kept up-to-date and provides insight into differences in the carcinogenic potential of HPV types in the general female population (Bzhalava *et al.*, 2013; Halec *et al.*, 2013) and in HIV-infected women (De Vuyst *et al.*, 2012b). To further expand the study of factors that influence the geographical variability and different scope for progression into cervical cancer of HPV infections, we also evaluated HPV16 variants in collaboration with ICB (Cornet *et al.*, 2012b, 2013a, 2013b).

Finally, better statistical methods were devised to evaluate and project the benefits of HPV vaccination and screening in HIV-negative and HIV-positive women. HPV vaccination of a single birth cohort of girls aged 9–13 years is recommended as a priority by WHO and supported by the GAVI Alliance. However, ICE showed that according to an ad hoc dynamic model, the addition of a catch-up round of girls aged 12–15 years can bring forward by

Figure 2. Rwanda: Cervical cell- and urine-based surveys by age, calendar year, cohort, and vaccination status.



5 years the 50% reduction in HPV16/18 prevalence due to vaccination compared with targeting 11-year-old girls only (Figure 4) (Baussano *et al.*, 2013a). Assuming an affordable vaccine cost, the addition of a catch-up vaccination round is, therefore, worth considering in LMICs to make economies of scale in vaccine delivery and extend vaccine benefits to older adolescents whose future access to cervical screening is uncertain. With respect to screening, concerns were expressed about the lack of specificity of HPV testing in African women, most notably HIV-positive women, due to a very high prevalence of hrHPV types. We showed that the positive predictive value (PPV) for cervical intraepithelial neoplasia (CIN) 2/3 of HPV testing in high-risk populations was very high, particularly in women aged ≥ 45 years because of the accumulation of CIN2/3

Figure 3. Positivity (± 1.96 SE) for human papillomavirus (HPV) types 16, 18, and 45 as a proportion of HPV-positive samples, by cervical disease grade. ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia grade; ICC, invasive cervical cancer; SE, standard error. Source: Guan *et al.* (2012); reproduced with permission from John Wiley & Sons.

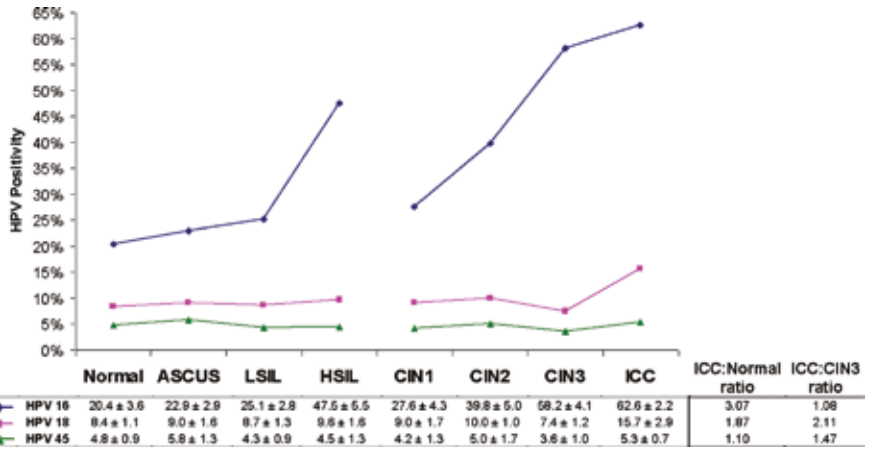
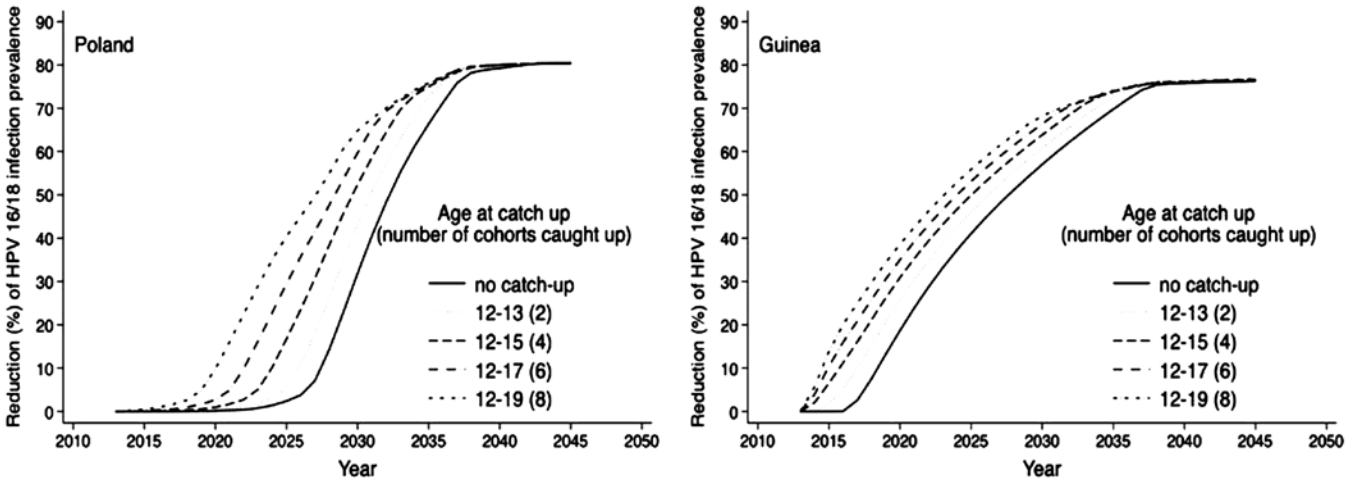


Figure 4. Reduction (%) of HPV16/18 infection prevalence among women aged ≥35 years by catch-up strategy (best case scenario). Left panel: Poland. Right panel: Guinea. HPV, human papillomavirus. Source: Baussano *et al.* (2013a); reproduced with permission from John Wiley & Sons.



over time and the lack of adequate cervical screening (Giorgi-Rossi *et al.*, 2012). High PPV demonstrates the efficacy and potential cost-effectiveness of HPV testing in high-risk women despite low test specificity.

HPV and cancer of the head and neck

The contribution of HPV infection to head and neck cancer (HNC) is still ill-defined, varies greatly by cancer site and world region, and depends on competing causal factors such as tobacco smoking and chewing (Chaturvedi *et al.*, 2013; Gillison *et al.*, 2013). ICE continued evaluating the contribution of lifestyle factors to these malignancies (Chuang *et al.*, 2012a; Garavello *et al.*, 2012; Li *et al.*, 2012; Wyss *et al.*, 2013) and also carried out a meta-analysis of studies in which the prevalence of molecular and serological HPV markers was compared across different HNC cases and cancer-free controls (Combes and Franceschi, 2013). Data on HPV DNA detection by polymerase chain reaction (PCR) and p16 expression in HNC biopsies suggested that the probability of a cancer of the oral cavity or larynx/hypopharynx being attributable to HPV is at least 5-fold lower than that for oropharyngeal cancer. Seropositivity for HPV16 E6 or E7 shows larger differences across sites, but findings vary between studies. Because HPV DNA and p16 detection lack specificity, and E6 and E7 antibody detection lacks sensitivity and reproducibility, these tests are not completely satisfactory. Limited data on markers of HPV-driven carcinogenesis (i.e. in situ hybridization or HPV E6/E7 mRNA), mainly from the USA, suggest that HPV-attributable HNC is rare in the oral cavity (~3%), larynx (~7%), and hypopharynx (~0%). We also showed that HPV positivity was associated with better survival exclusively in oropharyngeal sites and tobacco smoking was a strong prognostic factor (Sethi *et al.*, 2012). Finally, SPLIT (Study on HPV and Precancerous Lesions in the Tonsil), a multicentre study coordinated by ICE, elucidates the prevalence and features of pre-cancerous lesions in cancer-free tonsils according to the presence of HPV markers or tobacco smoking.

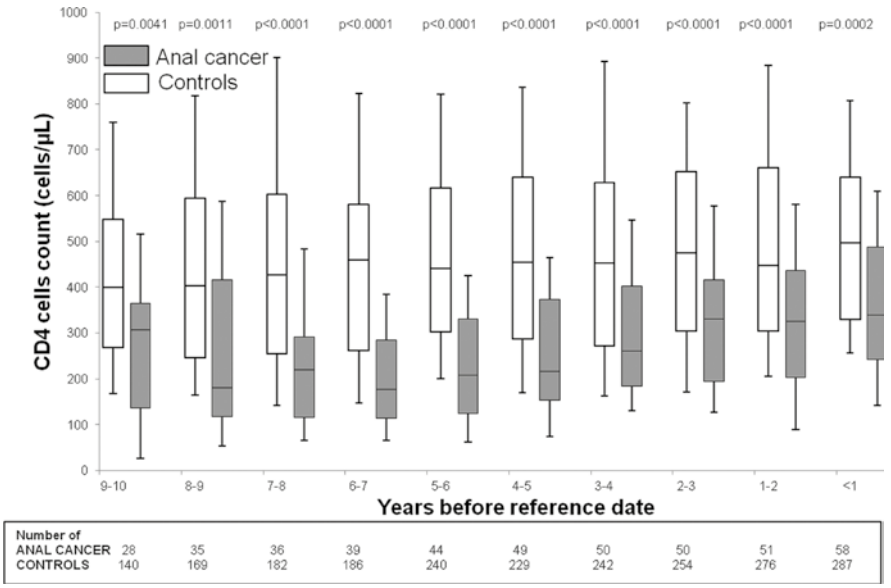
HIV/AIDS

An issue of current importance to ICE is cancer risk in people with HIV/AIDS (PWHA), now that combined antiretroviral therapy (cART) has improved survival in PWHA and the cancer burden is set to increase as PWHA age. A new record-linkage study from the Swiss HIV Cohort suggested that the approximately 3-fold excess of lung cancer in people with HIV compared with the general population was not clearly associated with the severity of immunosuppression and was mainly attributable to heavy smoking (Clifford *et al.*, 2012). Although HIV-positive people, particularly men who have sex with men, are at excess risk for anal cancer, it has been difficult to disentangle the influences of very high HPV prevalence, immunodeficiency, and cART use. According to a case–control study nested in the Swiss HIV Cohort Study (Bertisch *et al.*, 2013), current smoking was significantly associated with anal cancer (odds ratio [OR], 2.59; 95% confidence interval [CI], 1.25–5.34), as well as low CD4+ cell counts, whether measured at nadir or at cancer diagnosis. ICE's study was the first to show that the influence of CD4+ cell counts appeared to be stronger 6–7 years before (OR for < 200 versus ≥ 500 cells/μL, 14.0; 95% CI, 3.85–50.9) than in proximity to anal cancer diagnosis (Figure 5). Smoking cessation and avoidance of even moderate levels of immunosuppression appear to be important in reducing long-term anal cancer risks.

An ICE study in Kenya suggested that avoidance of even moderate levels of immunosuppression may also be essential to prevent cervical cancer, a disease that was difficult to study in populations in developed countries because of the preventive influence of cervical screening (De Vuyst *et al.*, 2012b). A study of 498 HIV-positive women in Nairobi, Kenya, showed that the burden of hrHPV and CIN2/3 was high and was related to immunosuppression level. However, cART use had a favourable effect on hrHPV prevalence but not on CIN2/3. This may be explained by the fact that cART use in Kenyan women may have been started too late to prevent CIN2/3 (De Vuyst *et al.*, 2012a).

To further explore this issue, ICE is engaged in evaluating the potential impact of cART on cervical cancer prevention (Clifford *et al.*, 2013). Indeed, access to cART is improving in sub-Saharan Africa and other LMICs far more rapidly than is access to high-quality cervical screening. Prolonged survival because of cART use will probably lead to a similar increase in cervical cancer incidence in HIV-infected women as was seen for anal cancer incidence in high-income countries in the first years after cART introduction. If, as for anal cancer, cervical cancer risk is increased at even moderately decreased levels of CD4+ cell counts, then immediate access to and regular use of cART would be key to the prevention of cervical cancer in HIV-positive women in sub-Saharan Africa, in combination with future HPV vaccination and cervical screening (Clifford *et al.*, 2013).

Figure 5. CD4+ cell counts before reference date among anal cancer cases and controls in Swiss HIV-positive individuals. Source: Bertisch *et al.* (2013); reproduced with permission from Oxford University Press.



Innovative statistical methods for epidemiology

Statistical models in cancer research often deal with sources of complexity such as repeated measurements, interval censoring, and hierarchical structure. For example, in the study of multiple HPV infections of the cervix, one needs to separate the sources of variation that make different HPV types cluster together (Carozzi *et al.*, 2012; Vaccarella *et al.*, 2013b). We address the most challenging problems using Bayesian hierarchical models. To support this, ICE has developed the statistical software package JAGS (http://mcmc-jags.sourceforge.net/), which is free and is distributed worldwide. This allows the user to define complex models using the probabilistic programming language BUGS, which are then analysed using Markov chain Monte Carlo simulation. Version 3.3.0 has beAen downloaded > 18 000 times since its release in October 2012.

In collaboration with the Education and Training Group (ETR), ICE offers the course Statistical Practice in Epidemiology with R, an introduction to the R language and environment for statistical analysis and graphics for cancer epidemiologists (http://www.r-project.org) (see also the ETR Report).

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