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Is immunotherapy a potential game changer in managing human papillomavirus (HPV) infection and intraepithelial neoplasia?

A B S T R A C T

The International Papillomavirus Conference was held in Washington DC in April 2023 and encompassed wide ranging basic, clinical and public health research relating to animal and human papillomaviruses. This editorial is a personal reflection, it does not attempt to be comprehensive and reports on some key aspects centred on the prospects for immune interventions in prevention and treatment of HPV infections and early precancers with a focus on cervical neoplasia. There is optimism for the future impact of immunotherapy in treating early HPV associated disease. This will depend on developing an appropriate design of vaccines and delivery vehicles which then need to be properly tested in clinical trials that are able to measure a useful clinical endpoint. Thereafter vaccines (prophylactic or therapeutic) still need global access and sufficient uptake to deliver impact and a key and necessary driver is education.

Prophylactic vaccination and cervical screening with widespread coverage from 2020 onwards was modelled and shown to have the potential to avert up to 12·5–13·4 million cervical cancer cases by 2069 and, by the end of this century, achieve an average cervical cancer incidence of around at least four per 100 000 women per year for all country human development index categories [1]. Delivering this outcome, while achievable in high income countries, was always going to be more challenging for low-middle income countries (LMIC). A WHO global strategy to accelerate the elimination of cervical cancer as a public health problem was presented and unanimously endorsed by the World Health Assembly in August 2020. The targets are focused on a societal based elimination with 90% of girls to be fully vaccinated with a HPV prophylactic vaccine by 15 years of age; 70% of women to be screened with a high-precision test at 35 and 45 years of age, and 90% of women identified with the cervical disease to receive treatment and care by 2030.

A presentation by *Dillner (Sweden)* reported that 125 countries had some sort of prophylactic vaccination programme and one vendor alone had provided 525 million doses. Unfortunately, the impact of the Covid 19 pandemic and vaccine shortages has significantly undermined the already ambitious vaccination targets set. This is encouraging the inclusion of gender-neutral vaccination [2] as well as the concept of immunizing the transmitting age cohort [3] to boost impacts. Importantly, *Bruni (Spain)* highlighted the deficit in access to adequate screening in LMIC where 90% of cases occur [4] plus of the challenges in implementing treatment strategies linked to available screening [5]. The good news is that with high coverage vaccination, the licenced VLP vaccines continue to show long term and herd protection with excellent safety data. There is now persuasive evidence for the efficacy of one dose regimes of the VLP vaccines in preventing HPV associated neoplasia [6–9]. Indeed, the WHO has sanctioned the latter [10] which has been adopted by the UK and Australia with 2 dose variations for the immunocompromised. This will undoubtedly simplify the logistics of vaccination programmes in LMIC and is predicted to deliver cost effective protection even with assumptions of waning immunity providing there is sufficient coverage plus a catch-up vaccination strategy [11]. The imminent availability of biosimilar vaccines from new manufacturers will overcome issues of supply as well as impact price. Further technical improvements that reduce cold chain requirements will also help logistical issues and deliver improved cost effectiveness [12]. Even so, it is apparent that an additional approach will be required particularly for LMIC in order to deliver timely equitable cervical cancer prevention.

Therapeutic HPV vaccines (TxV), which could clear persistent high-risk HPV infection and/or cause regression of pre-cancerous lesions, are in early clinical development and might offer one such approach [13]. The precise vaccine specifications, including required efficacy, to optimize the impact and add value are likely to be pivotal in TxV development. *Stanley (UK)* outlined the likely key elements based on our knowledge from both animal and human immunological research. The goal should be to generate specific T cells versus E6/E7 oncogenes but also including E1/E2 targets, with a diversity of T-cell receptor (TCR) affinity and producing an appropriate range of polyfunctional cytokines to be able to optimally target HPV infection or associated intraepithelial neoplasia. It is probable that such T cells may be best produced with a prime/boost vaccination regime but there is an absolute necessity to provide the necessary signals (possibly using selective adjuvants) to enable the programming of such effectors for targeting the mucosal infection/lesion sites. Modelling studies were reported by *Canfell (Australia)* on the potential impact of TxV mass vaccination for eliminating a productive infection or inducing regression of a primary lesion with differing scenarios for delivery and follow up testing. Obviously, there are plethora of assumptions required (which may not be correct) but the results predicted, for example in sub-Saharan Africa, a significant impact over a hundred years, particularly important if 90-70-90 approach does not deliver. There are a number of issues that will need to be addressed in plotting a successful pathway to implementing this type of strategy.

Immune ignorance, deviation and escape. The natural history of viral infection and early carcinogenesis is characterised by viral stealth and immune deviation in the lesion microenvironment. High-risk HPV is

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an obligate intracellular parasite with its lifecycle driven by deregulation of the differentiation of its target epithelium. In the cervix, infection is favoured at the transformation zone (TMZ) of the squamous columnar junction where reserve cells are targeted and generate a metaplasia [14]. A productive viral infection can yield infectious viral particles in terminally differentiated cells without necessarily alerting the immune system. For clearance of a pathogenic infection, induction of a local inflammatory response dovetailed to recruit the best immune effectors to resolve the threat is needed. This requires a nonspecific innate immune response where local damage and/or specific pathogen associated molecular patterns engage with pattern recognition receptors on antigen presenting cells (APCs) for activation and sampling of the local antigen environment. These APCs then migrate to local lymph nodes in a chemokine-dependent manner, where relevant antigen-specific T cells are activated and subsequently become recruited to the inflammatory site. In some people, for unknown reasons, this does not happen and the HPV infection helps to subvert this process. In addition to the stealth tactic (immune ignorance), the viral gene expression leads to early compromise of the innate immune system (e. g. loss of APCs) facilitating viral persistence and increased risk of cancer. Over time, a series of interactive and self-reinforcing events accumulate an immune suppressive microenvironment through the actions of multiple immune receptors, chemokines or cytokines (immune deviation) promoting chronic infection [15]. Viral persistence gives opportunity for viral oncogene sabotaged cellular DNA repair to promote genomic instability, with selection of genetic changes with advantage (including for immune escape) driving lesion neoplastic progression.

Novel factors regulating immune recognition in PV infection are still being discovered. *Lambert (USA)* described the use of the mouse PV (MmuPV1) infection model to investigate virus-host interactions. RNA seq data from virus induced ear papillomas compared to normal tissue in nude mice identified the upregulation of stress keratins [16] These had previously been reported as relevant to tumourgenesis in HPV 16 transgenic mice [17]. Over expression of stress keratin K17 was confirmed at the protein level in MmuPV1 induced papillomas in immunocompetent FVB/N mice. Using knockout (KO) mice for K17 established its requirement for papilloma growth in immunocompetent mice. It was shown that there was rapid regression of the papillomas with the reduced proliferation of the cells and downregulation of viral transcription in the KO mice dependent on T cell surveillance. It is apparent that K17 regulates global gene expression and specifically host genes associated with the immune response and cell cycle/division. This dysregulation in the K17KO mice correlates with increased numbers of infiltrating $CD8^+$ T cells and upregulation of interferon (IFN)γ-related genes, including CXCL9 and CXCL10, prior to complete regression. Blocking the receptor for these chemokines prevented early regression. More recent work has investigated the role of oestrogen in MmuPV1 infection and associated disease in the female reproductive tract [18]. Oestrogen-treatment facilitated MmuPV1 infection and/or establishment in wild type (WT) mice and viral clearance was not seen in either WT or K17KO mice. While neoplastic disease progression was promoted by the presence of K17 the latter was exacerbated by oestrogen. It appears that the steroid induces a systemic immune-suppressive state in MmuPV1-infected animals while oestrogen and K17 modulate the local immune microenvironment of the MmuPV1-induced neoplastic lesions. The results support a role for oestrogen and K17 at multiple stages of papillomavirus induced disease at least in part through immunomodulation. Cervix infection by MmuPv1 in oestrogen treated K17 null mice increases the number of sustained lesions. The severity of the latter is proportional to the degree of neutrophil infiltration but depletion exacerbates the disease state implying an anti-tumour neutrophil component. This is consistent with recent studies which have highlighted the role of recruitment of neutrophils by activated T cells to attack cancers [19]. Myeloid cells are most often associated with an immunosuppressive environment where cytotoxic T cells become exhausted by chronic stimulation and fail to kill tumour cells [20]. In a mouse tumour model, in attempts to boost endogenous anti-tumour CD8 T cells, activating antibodies to CD40 (TNF receptor superfamily; stimulation boosts T cell activation) and *anti*-PD1 (unblocks a checkpoint control to boost T cell anti-tumour responses) were used [21]. Successful immunotherapy was critically dependent on the preferential recruitment to the tumour of a subset of neutrophils with an immature phenotype expressing high L-selectin and a type-1 IFN signalling signature. It was also shown that the efficacy of these neutrophils depends on the ability of a particular subset of dendritic cells to cross present antigen to CD8 T cells. This recent work highlights the central role of the innate immune system in coordinating and optimising anti-tumour immune responses. As mentioned above, an early consequence of HPV infection can be the loss of antigen presenting cells. In a second example, antibodies to OX40 (CD134, a TNF receptor) and to CTLA4 (CD152, an immune checkpoint receptor), to respectively stimulate T cells and unblock checkpoint control, are used to boost T cell anti-tumour responses together with CD4 T helper cells expressing a cancer specific TCR. In this scenario, the recruitment and activation of the non-specific anti-tumour neutrophils is critically dependent on the CD4 T cells. In this study, mature neutrophils were active, inducing nitic oxide synthase to effect killing [22]. Clearly more research is required to better understand and control the spectrum of neutrophil activities ranging from toxic to protective of tumours.

Yet another level of complication is illustrated by the recognition that the ability of CD8 T cells to gain access to the lesional epithelium can be dependent on factors like the vascular endothelial expression of mucosal addressin cell adhesion molecule-1, the ligand that supports entry of α4β7 T cells into tissue. In persistent dysplastic epithelium there is a dysregulation in expression of vascular adhesion molecules which plays a role in immune evasion very early in the course of HPV disease [23]. These various examples reinforce the need to devise vaccines and immunisation regimes which can facilitate the efficient entry to the target tissue of antigen specific T cells able to overcome any local immune suppression but also cooperate with other anti-tumour effectors.

The above examples identify novel but insufficiently understood mechanisms by which papillomavirus-infected cells evade or can be controlled by host immunity. These types of observations emphasize the need to better understand host (tissue specific)-virus interactions from relevant animal models as these aspects are virtually impossible to study in real time in e.g. human anogenital disease. Usefully, MmuPv-1 infection can develop lesions in cutaneous and mucosal sites including the base of the tongue although development of invasive cancers in immunocompetent mice is relatively rare. A presentation from *Bilger (USA)* asked the question how long does it take to form a cancer with a surprising answer. When MmuPV1 is presented at a skin wound site in K14E5 mice, lesions appear with an earlier onset, higher incidence and reduced frequency of spontaneous regression than in non-transgenic mice [24]. However, the E5 transgene alone can promote skin tumours upon wounding, albeit with reduced efficiency. The E5 is acting like a co-carcinogen in papillomavirus-induced pathogenesis in the context of a natural papillomavirus infection model. As expected, there was reduced T cell infiltration with clear differences apparent with the E5 transgenic compared to WT mice by 4 weeks. At two weeks, there is clear evidence of virus production, at 4 weeks dose dependent persistence and such lesions can display the histopathological features of a cancer although only a minority will fully progress. In human cervical neoplasia, it is generally believed that the only cancers that screening can prevent are those that have not developed yet and that tumours rarely arise and grow to diagnostic size within less than 5 years. Is the potential for progression seeded, albeit relatively infrequently, at the very start of infection and more importantly is this already immune compromised?

HPV detection, clearance and latency. Clearance usually occurs rapidly among infections that are destined to clear, regardless of type [25]. It is persistent infection with high-risk HPV types which is associated with the development of cervical intraepithelial neoplasia (CIN3)+ with an 8 year % risk of 55, 33, 32, 31 for HPV types 16, 33, 18,

and 31 respectively [26]. In contemplating therapeutic immune intervention for such circumstances, it will be vital to establish exactly what is meant by endpoints like viral or lesion clearance and the best methods and timings to monitor any efficacy. *Doorbar (UK)* showed an example of a productive HPV 16 infection (no neoplastic changes apparent) and a HPV45 high grade cervical intraepithelial neoplastic lesion at another site in the same cervix. In this type of patient, the HPV16 could resolve spontaneously, or be "cleared" by natural or vaccine induced (cell mediated) immunity but it is also possible that HPV 16 episomes could still persist in some undifferentiated stem cell as an undetectable latent infection. The threat from such latency and the role of any immune memory in controlling future infections and/or reactivations is really not known. By contrast, the HPV45 associated high grade cervical intraepithelial lesion (unproductive of virions with likely virus/host genome integration disabling E2 expression) might not be susceptible to immunity raised against HPV 16/18 oncogene targeted vaccine and/or the local immune deviation may well have compromised the ability to deliver cure. To what extent these hurdles can be efficiently surmounted is unknown but recent advances in vaccine design and delivery may provide a suitable platform for effective immunotherapy.

Tx vaccines for treating CIN. At this point, the reality is that although many different TxV vaccines have been tested, the evidence so far available is that they may not work well enough [27]. Most of such vaccines target the HPV 16 or HPV 16 and 18, E6 and E7 oncoproteins using a variety of delivery vehicles based on nucleic acids (DNA/RNA) peptides, proteins or bacterial and viral vectors. A presentation by *Kawana (Japan)* reviewed the results from phase IIB clinical trials with a double-blind, placebo controlled, randomized design, of three vaccines in tests of regression rates of cervical intraepithelial neoplasia (CIN) 2/3. These were VGX3100 (DNA-based vaccine targeting the E6 and E7 proteins of HPV-16 and -18), Tipapkinogen Sovacivec (TS; a modified vaccinia virus Ankara (MVA), a highly attenuated replication-deficient strain of vaccinia virus, with inserted genes for human cytokine IL-2, and modified forms of HPV 16 E6 and E7 proteins) and IGMKK16E7 (Bacterial vector lactobacilli-based vaccine encoding HPV 16 E7). In the per protocol sets, the respective complete regression rates in vaccine treated CIN2/3 patients were around 40, 24 and 31% but this represented only 23, 14 or 19% greater than the spontaneous regression rates. These differences are more evident for TS and IGMKK vaccines if only HPV16 and/or CIN3 patients are considered.

The results from the VGX-3100 vaccine trials, 49% histopathological regression from CIN2/3 to CIN 1 at six months with no recurrence of high grade squamous intraepithelial lesion (HSIL) and 91% with no detectable HPV-16/18 infection at 18 months [28,29], provided the platform for the vaccine to enter prospective, randomized, double blind, placebo-controlled phase 3 clinical trials in patients with HPV 16 and/or 18 CIN 2/3. The primary endpoint was the proportion of participants with no HSIL or HPV16 and/or HPV 18 at week 36 (NCT03185013; NCT03721978). The first (REVEAL 1) indicated that this vaccine met its primary endpoint in a modified intent-to-treat (mITT) analysis (i.e., excluding eight patients without sufficient results). 23.7% of 131 patients in the vaccinated group responded (with HSIL regression and HPV clearance), while 11.3% of 62 patients in the placebo group did so at week 36. There was a modest but statistically significant vaccination efficacy (12.4%) [30,31]. Following the results of the first of the trials and talks with the FDA, the primary endpoint for the second study (REVEAL 2) was changed. This narrowed the analysis to a biomarker-based subpopulation of women that the sponsor believed were more likely to respond to therapy, rather than all comers. Unfortunately, VGX-3100 was no better than placebo at improving lesion regression and viral clearance in the biomarker-based subpopulation of women with high-grade squamous intraepithelial lesions, However, VGX-3100 did significantly improve lesion regression and viral clearance in the original all-participants primary endpoint population. This attempt to make a phase 3 trial better resulted in making it worse as it subsequently failed against the new measure but delivered on the original endpoint. This is a hard and expensive lesson since the FDA no longer rate REVEAL 2 as pivotal for potential licensure and one or two additional trials will be required in the biomarker population, further compounded by the possibility that it might not have been a good choice of subpopulation in the first place [32].

There are many other Tx vaccines in development and/or in clinical trial [12,31,33] and future novelties in formulation, adjuvantation and immunisation regimes may be able to help surpass the bar which is set so high in respect of overcoming immune barriers or clinical trial requirements. The key question is what level of efficacy would be of value (and licensable). The answer will vary depending on the efficacy of existing treatment which in a screened population for cervical cancer is extremely high. With more efficacious vaccines the prevention of precancer as an endpoint might be proven but would still require large and very long duration clinical trials. When considering other anogenital sites (vulvar, anus) where treatment options based on excision are less attractive it is possible that a lower efficacy could still be of clinical value. Not to be discussed here, is the fact that some treatments of HPV associated cancers using checkpoint inhibitor immunotherapy are already licenced for some conditions but there is still need for massive improvements. This is likely to come from a better understanding of the tumour microenvironment and its dynamic influence on the immune response. More importantly it will require the means to influence multivarious immune, tissue related and viral factors by the rationale deployment of immunotherapeutic interventions and their optimal sequencing in the context of conventional treatment approaches for particular conditions.

Tx Vaccines for treating HPV infection. There is of course no treatment option for HPV infection per se so this might be a more tractable goal but designing trials to test such vaccine approaches will need to account a natural clearance rate of between 6 months and 2 years of acquisition and the fact a minority progress to precancer. One possible design of trial could test individuals with incident HPV infection (no CIN) for impact of the vaccine compared to placebo, on the time to clearance and duration of subsequent HPV negativity. There is little doubt that if sufficiently efficacious this would prove a useful incentive in the uptake of screening since it provides a treatment option for the management of women who receive a positive HPV test and clearing infections will also reduce transmission. Since the precise events that lead to persistence and the potential sequelae are unknown it is not clear whether all infections will be equally responsive to a TxV. More importantly, utilising additional vaccine antigens including E1 and E2 might be a recipe for broader vaccine specificity relevant to early gene expression in infection and with more potential for cross reaction to multiple HPV types than with the more type specific E6 and E7 proteins. To address this TxVs using different viral vectors, chimpanzee adenovirus (ChadOx1) and MVA, have been developed which target E1, E2, E4 and E5 as well as E6 and E7 antigens from five high-risk HPV subtypes [34]. This additional targeting and opportunity for a prime boost vaccination schedule is aimed at achieving higher clinical efficacy than other TxV. NCT04607850 is a phase 1b/2, randomised, placebo-controlled, dose-ranging study to evaluate safety, tolerability and immunogenicity of a chimpanzee adenovirus (ChAdOx1)- and MVA-vectored multi-genotype high-risk HPV vaccines in women with low-grade HPV-related cervical lesions.

Other cancer sites and gender issues. Our knowledge of the natural history of HPV associated carcinogenesis at the cervix is generally believed to be relevant to other genital sites [14] as well as the anus [35] but for the oropharynx HPV associated cancers, there is no definitive information about precursor lesions [36]. There were several studies presented on the investigation of blood (HPV specific antibodies or DNA) or saliva to detect (screen) and monitor HPV associated OPSCC. This will be the topic of a coming review for TVR (Punyadeera in preparation). If TxV can be successful deployed to treat infection and dysplasia of the cervix then there is expectation that this would also influence disease at other sites where there is HPV driven

carcinogenesis, including in men. A potential complication is that there are differences in HPV acquisition both by gender and site of infection. For example, a high prevalence of genital HPV is found in men across their lifespan and with a constant acquisition rate with age whereas that rate of new infections decreases in women [37,38]. Similarly, anal HPV prevalence in men appears constant across the lifespan [39,40]. There is a lack of understanding of such differences but these may be influenced by distinctions in lifetime sexual practices, reactivation of latent infections or fluctuations in the level of viral replication in individuals with persistent infections or differential protection conferred from naturally acquired immunity. Consistent with the latter, the proportion of seroconversion (neutralising antibodies) following natural HPV infection in men is lower than women, with a low level of response not usually protective against infection [41] possibly making men more susceptible to recurrent infections. All this points to the benefit of gender-neutral prophylactic HPV vaccination to directly benefit men as well as to more rapidly achieve population level declines in HPV infection and related diseases among both men and women.

There is a significant female and male anal cancer disease burden with the global age-standardized incidence rate of HIV-negative squamous cell carcinoma higher in women (0.55 cases per 100 000) than men (0.28) but when considering HIV-positivity, it is higher in men (0.07) than women (0.02) [42]. HIV + people show a high prevalence and incidence of anal HPV infection and anal HSIL correlated with an elevated risk of anal cancer [43]. Efforts to prevent anal cancer in at-risk groups, based on the secondary prevention of cervical cancer, have been developed using high-resolution anoscopy and cytology where those screened as positive, have HSIL removal through ablation, surgical excision, or other treatments [44,45].

Anal cancer prevention is highly desirable since the cancer is associated with poor survival at later stages. Intensity-modulated radiotherapy followed by chemotherapy (mitomycin-C and 5-fluorouracil) is considered the standard of care, albeit with associated acute and chronic side effects, with surgery only used for the lowest risk, early-stage tumours or for recurrent/persistent disease [46]. Data on the success of screening and early treatment of anal precancers was presented by *Palefsky (USA)*. A phase 3 clinical trial (ANCHOR study) was conducted in HIV + persons 35yrs or older who had biopsy proven anal HSIL, randomly assigned to receive treatment (ablation or excision or topical treatment with fluorouracil or imiquimod). The primary endpoint was progression to anal cancer in a time event analysis. For participants with biopsy proven HSIL, the risk of anal cancer was significantly reduced with treatment compared to active monitoring [47]. At 48 months progression was 0.9% in the treatment compared to 1.8% in the monitored group. The progression rate from HSIL appears to be high and obviously biomarkers that can improve the sensitivity and specificity of precancer detection will be of great value. It is interesting to speculate as to whether TxV intervention might be of significant value in treatment of anal dysplasia.

Final comments. Plenary speaker, *Barney Graham (USA)* reflected on the world's response in developing vaccines against to COVID19. In these exceptional circumstances, from over 350 vaccine projects, some 150 had some clinical evaluation with only about 6.5 months to reach a phase 3 evaluation for some of the best candidates. Existing knowledge of the virus life cycle informing antigen design [48], the use of the mRNA technology allowing for chemical synthesis [49] as well as other vectors [50,51] were critical in vaccine development. Testing was facilitated by the frequency of population-based cases allowing for timely success in preventing many deaths [52]. Unfortunately, there has been much less impact in LMIC, which emphasises the need for justice, equity, cooperation and coordination in delivering vaccines. This apparently rapid development was in fact a major beneficiary of more than 40 years of experience in trying to produce HIV vaccines. Likewise flagging mRNA vaccines as a panacea for use in other conditions is unwarranted. In spite of some of the riders to therapeutic HPV vaccine development mentioned above, I am optimistic about their eventual impact in HPV associated disease providing the appropriate design of vaccines and delivery vehicles are properly tested in clinical trials that are able to measure a useful clinical endpoint. Thereafter vaccines (prophylactic or therapeutic) still need global access and sufficient uptake to deliver impact and a key and necessary driver is education.

Author statement

I thank all the participants of the IPVC for their contributions, and make apology to those whose name has not been specifically acknowledged or where their topics have not been covered. This article has not been published or submitted to any other journal.

Declaration of competing interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] K.T. Simms, J. Steinberg, M. Caruana, M.A. Smith, J.B. Lew, et al., Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study, Lancet Oncol. 20 (3) (2019 Mar) 394–407, https://doi.org/10.1016/S1470-2045(18)30836-2.

[2] M. Lehtinen, I. Baussano, J. Paavonen, S. Vänskä, J. Dillner, Eradication of human papillomavirus and elimination of HPV-related diseases - scientific basis for global public health policies, Expert Rev. Vaccines 18 (2) (2019 Feb) 153–160, https://doi.org/10.1080/14760584.2019.1568876.

[3] F.X. Bosch, C. Robles, M. Díaz, M. Arbyn, I. Baussano, et al., HPV-FASTER: broadening the scope for prevention of HPV-related cancer, Nat. Rev. Clin. Oncol. 13 (2) (2016 Feb) 119–132, https://doi.org/10.1038/nrclinonc.2015.146.

[4] L. Bruni, B. Serrano, E. Roura, L. Alemany, M. Cowan, et al., Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis, Lancet Global Health 10 (8) (2022 Aug) e1115–e1127, https://doi.org/10.1016/S2214-109X(22)00241-8.

[5] A. Baena, D. Mesher, Y. Salgado, S. Martínez, G.R. Villalba, et al., ESTAMPA study group. Performance of visual inspection of the cervix with acetic acid (VIA) for triage of HPV screen-positive women: results from the ESTAMPA study, Int. J. Cancer 152 (8) (2023 Apr 15) 1581–1592, https://doi.org/10.1002/ijc.34384.

[6] A.R. Kreimer, J.N. Sampson, C. Porras, J.T. Schiller, T. Kemp, et al., Costa Rica HPV vaccine trial (CVT) group. Evaluation of durability of a single dose of the bivalent HPV vaccine: the CVT trial, J. Natl. Cancer Inst. 112 (10) (2020 Oct 1) 1038–1046, https://doi.org/10.1093/jnci/djaa011.

[7] R.V. Barnabas, E.R. Brown, M.A. Onono, E.A. Bukusi, B. Njoroge, et al., Efficacy of single-dose HPV vaccination among young African women, NEJM Evid 1 (5) (2022 Jun), EVIDoa2100056, https://doi.org/10.1056/EVIDoa2100056.

[8] R.V. Barnabas, E.R. Brown, M. Onono, E.A. Bukusi, B. Njoroge, et al., KEN SHE Study Team, Single-dose HPV vaccination efficacy among adolescent girls and young women in Kenya (the KEN SHE Study): study protocol for a randomized controlled trial, Trials 22 (1) (2021 Sep 27) 661, https://doi.org/10.1186/s13063-021-05608-8.

[9] K. Baisley, T.J. Kemp, A.R. Kreimer, P. Basu, J. Changalucha, et al., Comparing one dose of HPV vaccine in girls aged 9-14 years in Tanzania (DoRIS) with one dose of HPV vaccine in historical cohorts: an immunobridging analysis of a randomised controlled trial, Lancet Global Health 10 (10) (2022 Oct) e1485–e1493, https://doi.org/10.1016/S2214-109X(22)00306-0.

[10] https://www.who.int/news/item/20-12-2022-WHO-updates-recommendations-on-HPV-vaccination-schedule.

[11] A.R. Kreimer, T. Cernuschi, H. Rees, J.M.L. Brotherton, C. Porras, J. Schiller, Public health opportunities resulting from sufficient HPV vaccine supply and a single-dose vaccination schedule, J. Natl. Cancer Inst. 115 (3) (2023 Mar 9) 246–249, https://doi.org/10.1093/jnci/djac189.

[12] O. Illah, A. Olaitan, Updates on HPV vaccination, Diagnostics 13 (2) (2023 Jan 9) 243, https://doi.org/10.3390/diagnostics13020243.

[13] H.J. Prudden, S.L. Achilles, C. Schocken, N. Broutet, K. Canfell, et al., Therapeutic HPV Vaccine PPC Expert Consultation Group. Understanding the public health value and defining preferred product characteristics for therapeutic human papillomavirus (HPV) vaccines: world Health Organization consultations, Vaccine 40 (41) (2022 Sep 29) 5843–5855, https://doi.org/10.1016/j.vaccine.2022.08.020. October 2021-March 2022.

[14] J. Doorbar, K. Zheng, A. Aiyenuro, W. Yin, C.M. Walker, et al., Principles of epithelial homeostasis control during persistent human papillomavirus infection

and its deregulation at the cervical transformation zone, Curr Opin Virol 51 (2021 Dec) 96–105, https://doi.org/10.1016/j.coviro.2021.09.014.
[15] S. Smola, C. Trimble, P.L. Stern, Human papillomavirus-driven immune deviation: challenge and novel opportunity for immunotherapy, Ther Adv Vaccines 5 (3) (2017 Jun) 69–82, https://doi.org/10.1177/2051013617717914.
[16] W. Wang, A. Uberoi, M. Spurgeon, E. Gronski, V. Majerciak, et al., Stress keratin 17 enhances papillomavirus infection-induced disease by downregulating T cell recruitment, PLoS Pathog. 16 (1) (2020 Jan 22), e1008206, https://doi.org/10.1371/journal.ppat.1008206.
[17] R.P. Hobbs, A.S. Batazzi, M.C. Han, P.A. Coulombe, Loss of Keratin 17 induces tissue-specific cytokine polarization and cellular differentiation in HPV16-driven cervical tumorigenesis in vivo, Oncogene 35 (43) (2016 Oct 27) 5653–5662, https://doi.org/10.1038/onc.2016.102.
[18] W. Wang, M.E. Spurgeon, A. Pope, S. McGregor, E. Ward-Shaw, et al., Stress keratin 17 and estrogen support viral persistence and modulate the immune environment during cervicovaginal murine papillomavirus infection, Proc. Natl. Acad. Sci. U. S. A. 120 (12) (2023 Mar 21), e2214225120, https://doi.org/10.1073/pnas.2214225120.
[19] A. Ager, Cancer immunotherapy: T cells and neutrophils working together to attack cancers, Cell 186 (7) (2023 Mar 30) 1304–1306, https://doi.org/10.1016/j.cell.2023.03.005.
[20] L.M. McLane, M.S. Abdel-Hakeem, E.J. Wherry, CD8 T cell exhaustion during chronic viral infection and cancer, Annu. Rev. Immunol. 37 (2019 Apr 26) 457–495, https://doi.org/10.1146/annurev-immunol-041015-055318.
[21] J. Gungabeesoon, N.A. Gort-Freitas, M. Kiss, E. Bolli, M. Messemaker, et al., A neutrophil response linked to tumor control in immunotherapy, Cell 186 (7) (2023 Mar 30) 1448–1464.e20, https://doi.org/10.1016/j.cell.2023.02.032.
[22] D. Hirschhorn, S. Budhu, L. Kraehenbuehl, M. Gigoux, D. Schröder, et al., T cell immunotherapies engage neutrophils to eliminate tumor antigen escape variants, Cell 186 (7) (2023 Mar 30) 1432–1447.e17, https://doi.org/10.1016/j.cell.2023.03.007.
[23] C.L. Trimble, R.A. Clark, C. Thoburn, N.C. Hanson, J. Tassello, et al., Human papillomavirus 16-associated cervical intraepithelial neoplasia in humans excludes CD8 T cells from dysplastic epithelium, J. Immunol. 185 (11) (2010 Dec 1) 7107–7114, https://doi.org/10.4049/jimmunol.1002756.
[24] A.D. Torres, M.E. Spurgeon, A. Bilger, S. Blaine-Sauer, A. Uberoi, et al., The human papillomavirus 16 E5 gene potentiates MmuPV1-Dependent pathogenesis, Virology 541 (2020 Feb) 1–12, https://doi.org/10.1016/j.virol.2019.12.002.
[25] S.N. Adebamowo, B. Befano, L.C. Cheung, A.C. Rodriguez, M. Demarco, et al., Different human papillomavirus types share early natural history transitions in immunocompetent women, Int. J. Cancer 151 (6) (2022 Sep 15) 920–929, https://doi.org/10.1002/ijc.34128.
[26] F.L. Sand, C. Munk, K. Frederiksen, J. Junge, T. Iftner, et al., Risk of CIN3 or worse with persistence of 13 individual oncogenic HPV types, Int. J. Cancer 144 (8) (2019 Apr 15) 1975–1982, https://doi.org/10.1002/ijc.31883.
[27] C. Ventura, Luís Â, C.P. Soares, A. Venuti, F. Paolini, et al., The effectiveness of therapeutic vaccines for the treatment of cervical intraepithelial neoplasia 3: a systematic review and meta-analysis, Vaccines 10 (9) (2022 Sep 19) 1560, https://doi.org/10.3390/vaccines10091560.
[28] C.L. Trimble, M.P. Morrow, K.A. Kraynyak, X. Shen, M. Dallas, et al., Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial, Lancet 386 (10008) (2015 Nov 21) 2078–2088, https://doi.org/10.1016/S0140-6736(15)00239-1.
[29] P.K. Bhuyan, M. Dallas, K. Kraynyak, T. Herring, M. Morrow, et al., Durability of response to VGX-3100 treatment of HPV16/18 positive cervical HSIL, Hum. Vaccines Immunother. 17 (5) (2021 May 4) 1288–1293, https://doi.org/10.1080/21645515.2020.1823778.
[30] https://www.prnewswire.com/news-releases/inovio-announces-positive-results-from-reveal-1-a-phase-3-pivotal-trial-evaluating-vgx-3100-its-dna-based-hpv-immunotherapy-for-the-treatment-of-high-grade-precancerous-cervical-dysplasia-caused-by-hpv-16-andor-hpv-18-301237793.html.
[31] J. Tang, M. Li, C. Zhao, D. Shen, L. Liu, et al., Therapeutic DNA vaccines against HPV-related malignancies: promising leads from clinical trials, Viruses 14 (2) (2022 Jan 25) 239, https://doi.org/10.3390/v14020239.
[32] https://www.fiercebiotech.com/biotech/inovios-endpoint-switcheroo-backfires-phase-3-misses-new-measure-hits-old.
[33] A. Gohar, A.A. Ali, W.F. Elkhatib, G.S. El-Sayyad, D. Elfadil, A.M. Noreddin, Combination therapy between prophylactic and therapeutic human papillomavirus (HPV) vaccines with special emphasis on implementation of nanotechnology, Microb. Pathog. 171 (2022 Oct), 105747, https://doi.org/10.1016/j.micpath.2022.105747.
[34] G. Hancock, J. Blight, C. Lopez-Camacho, J. Kopycinski, M. Pocock, et al., A multigenotype therapeutic human papillomavirus vaccine elicits potent T cell responses to conserved regions of early proteins, Sci. Rep. 9 (1) (2019 Dec 10), 18713, https://doi.org/10.1038/s41598-019-55014-z.
[35] L. Sichero, A.R. Giuliano, L.L. Villa, Human papillomavirus and genital disease in men: what we have learned from the HIM study, Acta Cytol. 63 (2) (2019) 109–117, https://doi.org/10.1159/000493737.
[36] M. Lechner, J. Liu, L. Masterson, T.R. Fenton, HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management, Nat. Rev. Clin. Oncol. 19 (5) (2022 May) 306–327, https://doi.org/10.1038/s41571-022-00603-7.
[37] J.S. Smith, P.A. Gilbert, A. Melendy, R.K. Rana, J.M. Pimenta, Age-specific prevalence of human papillomavirus infection in males: a global review, J. Adolesc. Health 48 (6) (2011 Jun) 540–552, https://doi.org/10.1016/j.jadohealth.2011.03.010.
[38] K. Vahle, J.W. Gargano, R.M. Lewis, T.D. Querec, E.R. Unger, et al., Prevalence of human papillomavirus among women older than recommended age for vaccination by birth cohort, United States 2003–2016, J. Infect. Dis. 225 (1) (2022 Jan 5) 94–104, https://doi.org/10.1093/infdis/jiab334.PMID:34161559.
[39] A.A. Deshmukh, H. Damgacioglu, D. Georges, K. Sonawane, J. Ferlay, et al., Global burden of HPV-attributable squamous cell carcinoma of the anus in 2020, according to sex and HIV status: a worldwide analysis, Int. J. Cancer 152 (3) (2023 Feb 1) 417–428, https://doi.org/10.1002/ijc.34269.
[40] G.M. Clifford, D. Georges, M.S. Shiels, E.A. Engels, A. Albuquerque, et al., A meta-analysis of anal cancer incidence by risk group: toward a unified anal cancer risk scale, Int. J. Cancer 148 (1) (2021 Jan 1) 38–47, https://doi.org/10.1002/ijc.33185.
[41] A.R. Giuliano, R. Viscidi, B.N. Torres, D.J. Ingles, S.L. Sudenga, et al., Seroconversion following anal and genital HPV infection in men: *the HIM study*, Papillomavirus Res 1 (2015 Dec 1) 109–115, https://doi.org/10.1016/j.pvr.2015.06.007.
[42] B. Serrano, M. Brotons, F.X. Bosch, L. Bruni, Epidemiology and burden of HPV-related disease, Best Pract. Res. Clin. Obstet. Gynaecol. 47 (2018 Feb) 14–26, https://doi.org/10.1016/j.bpobgyn.2017.08.006.
[43] F. Wei, M.M. Gaisa, G. D'Souza, N. Xia, A.R. Giuliano, et al., Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies, Lancet HIV 8 (9) (2021 Sep) e531–e543, https://doi.org/10.1016/S2352-3018(21)00108-9.
[44] D.B. Stewart, W.B. Gaertner, S.C. Glasgow, D.O. Herzig, D. Feingold, S.R. Steele, Prepared on behalf of the clinical practice guidelines committee of the American society of colon and rectal surgeons. The American society of colon and rectal surgeons clinical practice guidelines for anal squamous cell cancers (revised 2018), Dis. Colon Rectum 61 (7) (2018 Jul) 755–774, https://doi.org/10.1097/DCR.0000000000001114.
[45] M.A. Thompson, M.A. Horberg, A.L. Agwu, J.A. Colasanti, M.K. Jain, et al., Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV medicine association of the infectious diseases society of America, Clin. Infect. Dis. 73 (11) (2021 Dec 6) e3572–e3605, https://doi.org/10.1093/cid/ciaa1391. Erratum in: Clin Infect Dis. 2021 Dec 08;: Erratum in: Clin Infect Dis. 2022 Nov 30;75(11):2052.
[46] L.T. Tchelebi, C. Eng, C.A. Messick, T.S. Hong, E.B. Ludmir, et al., Current treatment and future directions in the management of anal cancer, Ca - Cancer J. Clin. 72 (2) (2022 Mar) 183–195, https://doi.org/10.3322/caac.21712.
[47] J.M. Palefsky, J.Y. Lee, N. Jay, S.E. Goldstone, T.M. Darragh, et al., ANCHOR investigators group. Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer, N. Engl. J. Med. 386 (24) (2022 Jun 16) 2273–2282, https://doi.org/10.1056/NEJMoa2201048.
[48] B. Hu, H. Guo, P. Zhou, Z.L. Shi, Characteristics of SARS-CoV-2 and COVID-19, Nat. Rev. Microbiol. 19 (3) (2021 Mar) 141–154, https://doi.org/10.1038/s41579-020-00459-7. Epub 2020 Oct 6. Erratum in: Nat Rev Microbiol. 2022 May;20(5):315.
[49] J. Nelson, E.W. Sorensen, S. Mintri, A.E. Rabideau, W. Zheng, et al., Impact of mRNA chemistry and manufacturing process on innate immune activation, Sci. Adv. 6 (26) (2020 Jun 24), eaaz6893, https://doi.org/10.1126/sciadv.aaz6893.
[50] Z. Zhang, J. Mateus, C.H. Coelho, J.M. Dan, C.R. Moderbacher, et al., Humoral and cellular immune memory to four COVID-19 vaccines, Cell 185 (14) (2022 Jul 7) 2434–2451.e17, https://doi.org/10.1016/j.cell.2022.05.022.
[51] S. Soleimanpour, A. Yaghoubi, COVID-19 vaccine: where are we now and where should we go? Expert Rev. Vaccines 20 (1) (2021 Jan) 23–44, https://doi.org/10.1080/14760584.2021.1875824.
[52] O.J. Watson, G. Barnsley, J. Toor, A.B. Hogan, P. Winskill, A.C. Ghani, Global impact of the first year of COVID-19 vaccination: a mathematical modelling study, Lancet Infect. Dis. 22 (9) (2022 Sep) 1293–1302, https://doi.org/10.1016/S1473-3099(22)00320-6.

Peter L. Stern
Division of Molecular & Clinical Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, UK
E-mail address: peter.stern@manchester.ac.uk.