Therapies and vaccines against the virus

- (Therapeutic) HPV Vaccine

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The BCN HPV Course
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IrsiCaixa
Institut de Recerca de la Sida

Conflict of Interest / Disclosure

- Co-founder, shareholder and CSO of AELIX Therapeutics

- Consultancy agreements with Astrivax, Omniscope, Gritstone, Virometix, Alta Mar Capital

- **I am NO expert on HPV !**

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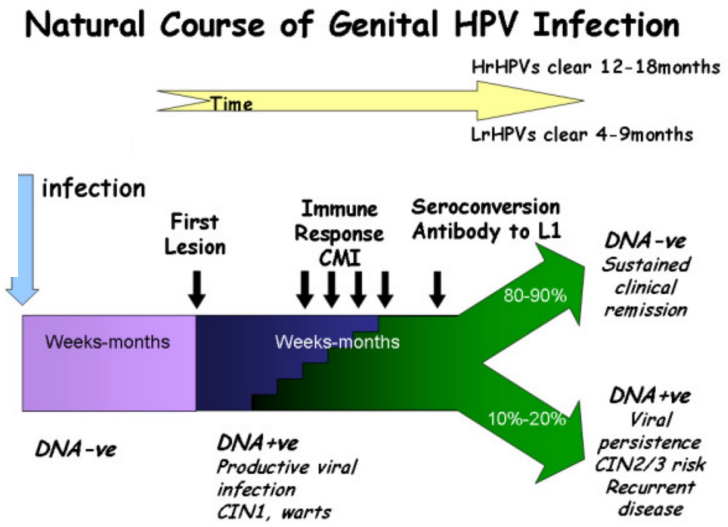
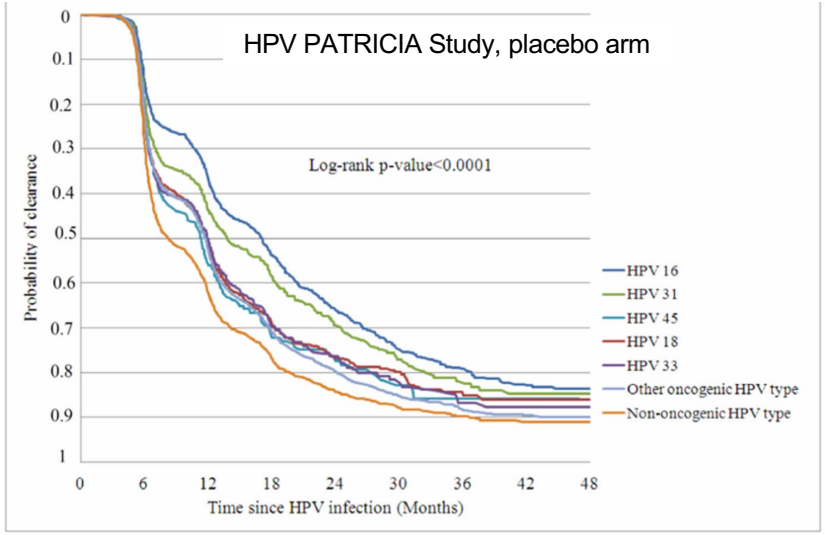
Therapies and vaccines against the virus

- (Therapeutic) HPV Vaccine

- Concepts of prophylactic vs therapeutic vaccination
- Potential hurdles for a therapeutic HPV vaccine
- Some insights from therapeutic vaccination for HIV

Natural course of HPV infection and virus clearance

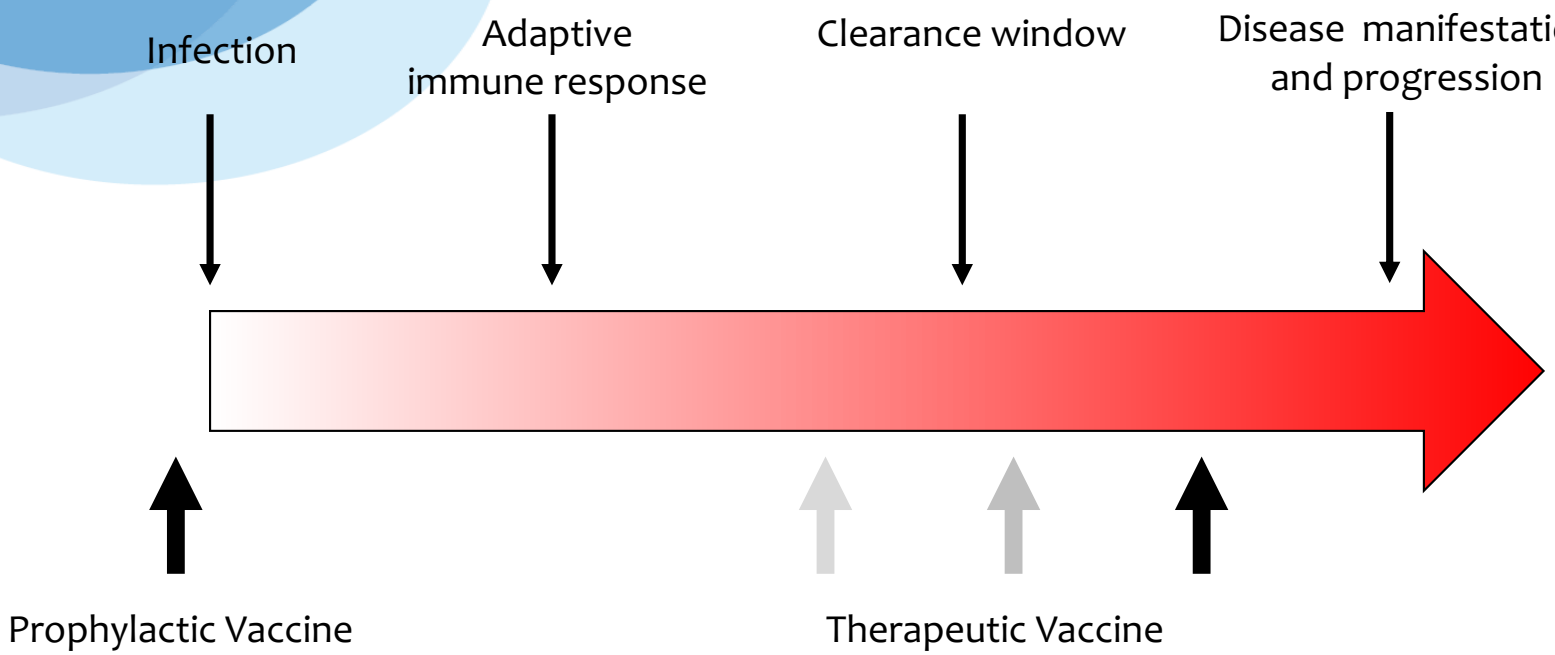




- 90% of infections are being considered cleared spontaneously after a couple of years
- Differences exist between HPV genotypes, with the more oncogenic types being less well cleared and associated with highest risk for disease progression
- For all practical purposes for therapeutic vaccine development, it can - and possibly should - be assumed that HPV can also persist, despite negative (i.e. undetectable) viral DNA tests. Clinical relevance ?

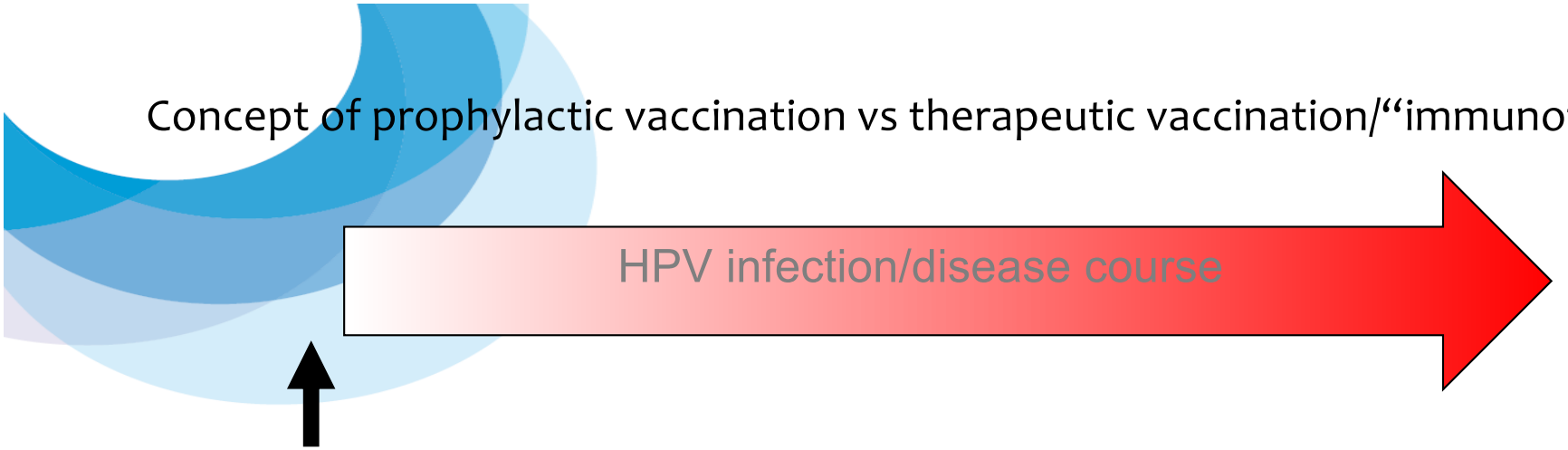
Stanley, M. Infect. Agent Cancer 2010
Jaisamrarn, PLOS One 2013

Concept of prophylactic vaccination vs therapeutic vaccination/“immunotherapy”



Questions on timing, immunogen, route, vector, dosing, induction and longevity of adequate vaccine response

Concept of prophylactic vaccination vs therapeutic vaccination/“immunotherapy”



- Induction of a protective, ideally sterile immunity prior to first exposure
- Target population is young, healthy and immune competent
- Immune naive to HPV, i.e. no pre-existing immunity to virus (different to the therapeutic setting)
- HPV L1-targeting vaccines of different valency highly effective
- Protective immune mechanism thought to be antibodies, although no specific immune marker defined for efficacy
- Role of adaptive T cell immunity unclear, aside from assumed Th for B cell maturation

Concept of prophylactic vaccination vs therapeutic vaccination/“immunotherapy”

Therapeutic Vaccine

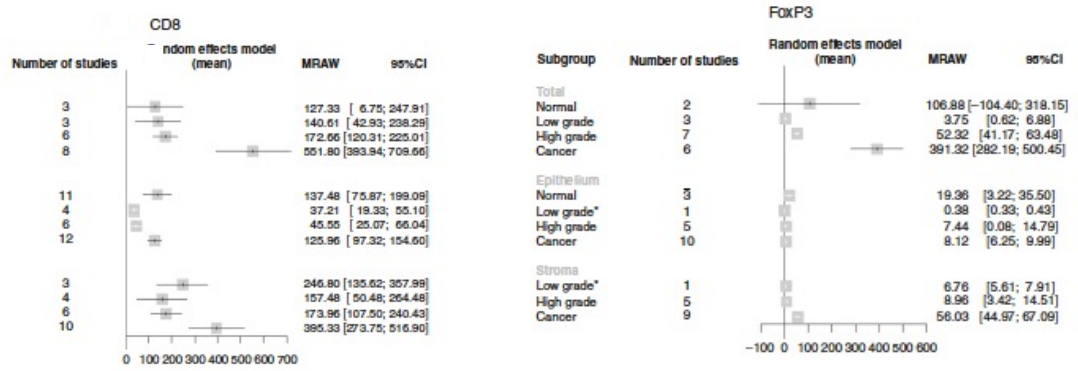
- Induction of a virus-specific immunity able to control and/or clear infection, possibly mediated by CD8 T- cells able to eliminate infected cells
- Target population is still relatively young but co-infections (for instance HIV) can have negative implications
- Vaccine-induced response needs to control a fully established viral infection in specific microenvironments and at different clinical stages with disseminated disease: optimal timing ?
- Questions on the type and effector cells that mediate effective adaptive immunity in this setting
- Pre-existing, at least partly ineffective immunity to virus that may influence vaccination outcome

What data support the feasibility of a HPV therapeutic vaccination/"immunotherapy"

- While systemic immune responses can be weak, regressing lesions have been found to harbor strong T-cell infiltrates which may mediate lesion regression.
  - need to look in lesions when defining effective immunity ?!
- Even in patients with advanced disease, not all (30-50%) progress to invasive carcinoma, suggesting that some immune mechanisms are controlling progressive disease and that therapeutic vaccination may be feasible.

BUT:

- Some infiltrating T-regulatory cell populations in precancerous lesions may be detrimental to further disease control



Litwin, Br J Cancer 2021

What data support the feasibility of a HPV therapeutic vaccination/"immunotherapy"

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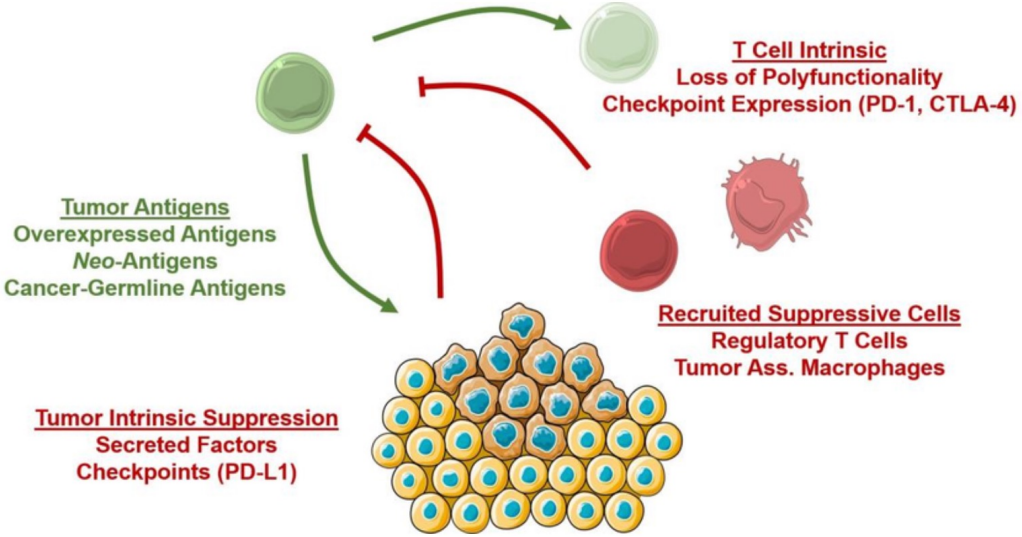
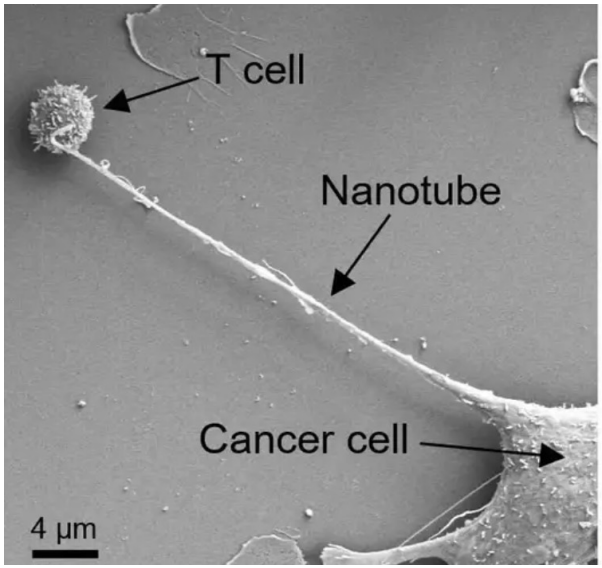
BUT:

- Some infiltrating T-regulatory cell populations in precancerous lesions may be detrimental to further disease control
- Therapeutic vaccination using VLP-based L1 vaccines is i) poorly immunogenic compared to prophylactic setting, ii) may not induce cellular immunity and iii) does not cover viral genes expressed in cancerous lesions
- HPV exerts strong immunosuppressive effects on the mucosal environment, including down-regulation of HLA molecules and modulation of the cytokine milieu

Determinants of an "effective" immunity induced by therapeutic vaccination

- A Th1-biased cell-mediated immune response appears critical for regression of HPV-induced disease
- The presence of Granzyme B expressing CD8 T cells has been linked to regression of CIN1 (Woo et al, BJOG 2008)
- Effector T cell infiltration into intraepithelial neoplasia needs to be possible but may require to counteract the immune modulation exerted by the virus (Trimble JI 2010)





Perica, 2015
Saha 2022

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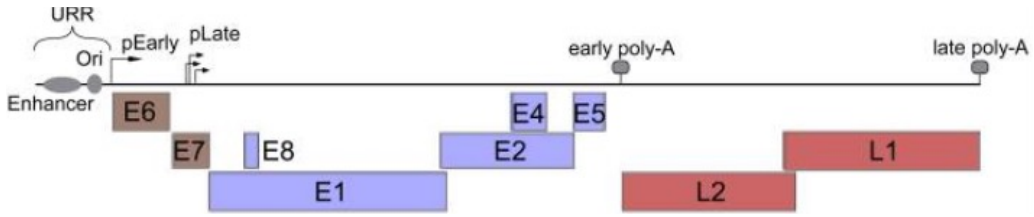
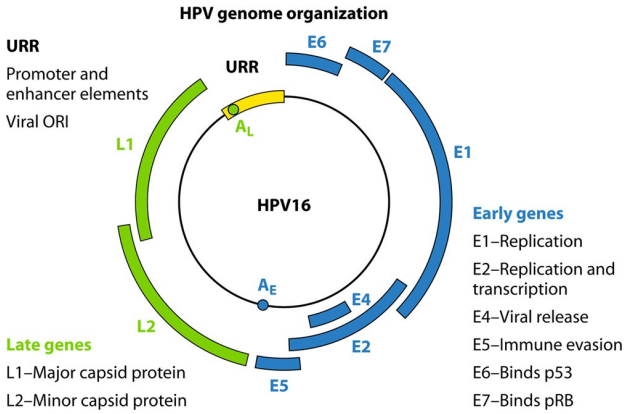
- Timing of intervention may be critical and depends on virus gene expression profiles:



Bodily et al Trend Microbiol 2021. Stanley Clin Med Rev 2012



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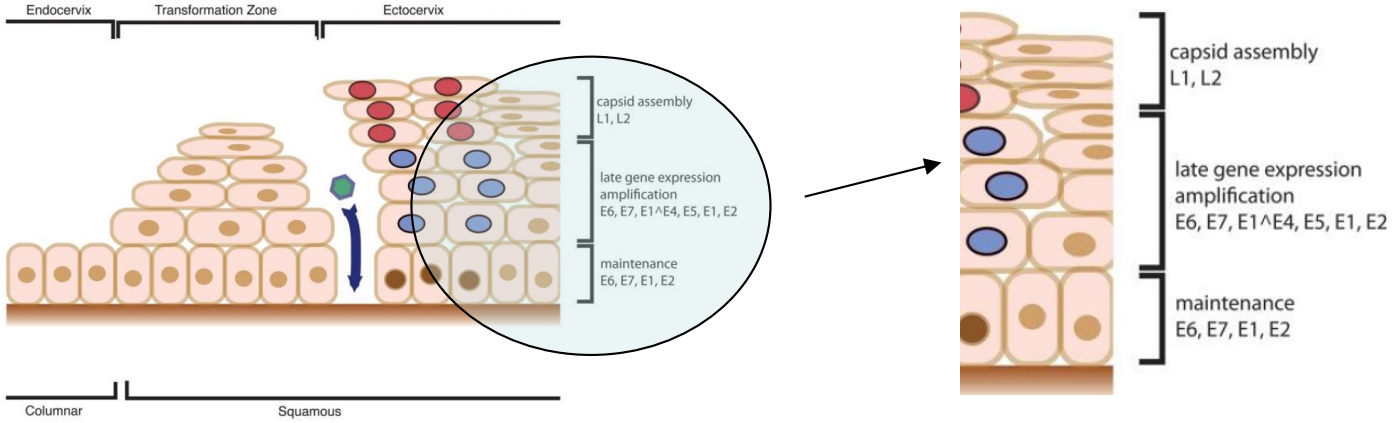
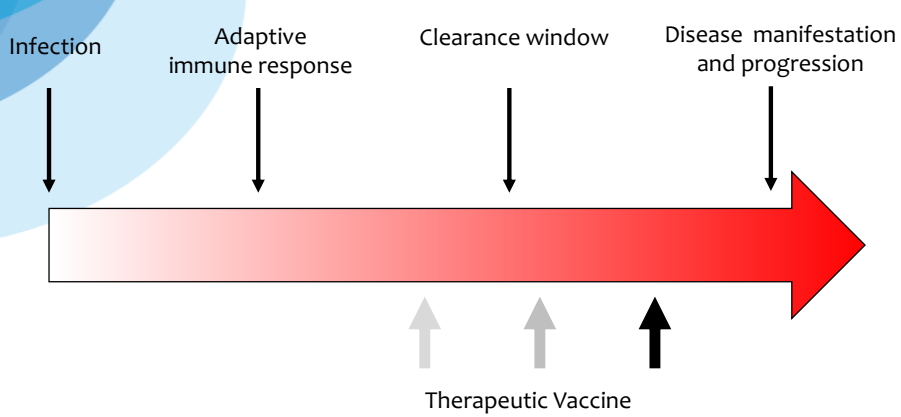


Bodily et al Trend Microbiol 2011

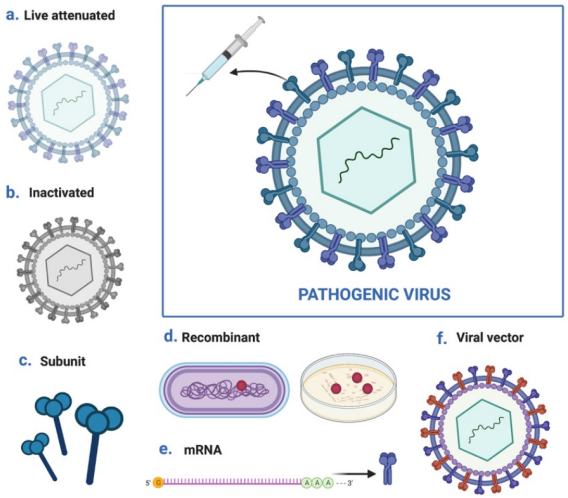
Timing and Immunogen considerations for therapeutic HPV vaccination



- HPV gene expression becomes heavily dysregulated as disease progresses
- Early(ier) interventions may take advantage of HPV E1 and E2 gene expression, while later on, only E6 and E7 are targetable with L2 being present when new viral particles are built
- However, later stages will have evolved more immune evasive environments and exhausted the virus-specific T cell responses
- Need for clinical trials with a broader range of viral antigens tested in individuals with less evolved disease

Vector Choices for therapeutic HPV vaccination

- Suitable to induce robust CD8 T cell responses
  - Life attenuated, MVA, Adeno vectors, DNA, RNA
- Prime-boost regimen to boost responses, expand effector function repertoire and to locate them to the site of action though *Prime-Pull* strategies
  - May require local immunization, intra lesions



Matelski et al 2021

Pipeline of therapeutic HPV vaccination

Vaccine Platform	Vaccine	Antigen	Conditions	Phase/NCT Number	Study Start	Status
Bacterial vector vaccine	ADXS11-001	HPV16 E7	EAs,UCC	Phase II/NCT01266460	May 23,2011	Completed
			OC	Phase I/NCT01598792	February 2012	Terminated
			AC,RC	Phase II/NCT02399813	September 2015	Completed
			UCC,SCCHN	Phase I/Phase II NCT02291055	April 2015	Active, not recruiting
			SCCHN	Phase II/NCT02002182	December 2013	Active, not recruiting
Viral vector vaccine	Ad/MG1-E6E7	HPV16/18 E6/E7	HPV-Associated Cancers	Phase I/NCT03618953	June 21,2018	Active, not recruiting
	TG4001	HPV16 E6/E7	UCC,ASCC	Phase I/Phase II NCT03260023	September 11,2017	Recruiting
	TA-HPV	HPV16/18 E6/E7	UCC	Phase II/NCT00002916	November 1996	Completed
	PRGN-2009	HPV16/18 E6/E7	UCC,OC,RC,AC	Phase I/Phase II NCT04432597	August 11,2020	Recruiting
Peptide based vaccine	TVGV-1	HPV16 E7	HSIL	Phase II/NCT02576561	November 2015	Unknown status
	TA-CIN	HPV16 L2/E6/E7	UCC	Phase I/NCT02405221	April 4,2019	Recruiting
	ProCervix	HPV16/18 E7	Genital Infection Viral	Phase II/NCT01957878	December 2013	Completed
	PepCan	HPV16 E6	SCCHN	Phase I/Phase II NCT03821272	November 13,2019	Recruiting
			HSIL	Phase II/NCT02481414	November 30,2015	Active, not recruiting
	ISA101b	HPV16 E6/E7	UCC	Phase I/Phase II NCT02128126	September 2013	Completed
			SCC,SCCHN	Phase II/NCT04369937	July 6,2020	Recruiting
			UCC	Phase II/NCT04646005	June 28,2021	Recruiting
	ISA 101	HPV16 E6/E7	Malignant Neoplasms of Lip Oral Cavity and Pharynx	Phase II/NCT03258008	April 4,2018	Active, not recruiting
			Solid Tumors	Phase II/NCT02426892	December 23,2015	Active, not recruiting
	Human papillomavirus 16 E7 peptide	HPV16 E7	UCC	Phase I/NCT00003977	November 1999	Completed
	human papillomavirus 16 E6/E7 peptide	HPV16 E6/E7	AC,UCC,EC	Phase I/NCT00019110	November 1995	Completed
	SGN-00101	HPV16 E7	RRP	Phase II/NCT00038714	November 2001	Completed
			UCC,CIN III	Phase II/NCT00075569	March 2004	Completed
			UCC,CIN III	Phase II/NCT00054041	June 2004	Completed
	Hespecta	HPV16 E6	Tumors or Premalignant Lesions	Phase I/NCT02821494	March 2015	Completed

Mo et al, Front Cell Inf Microbiol 2022

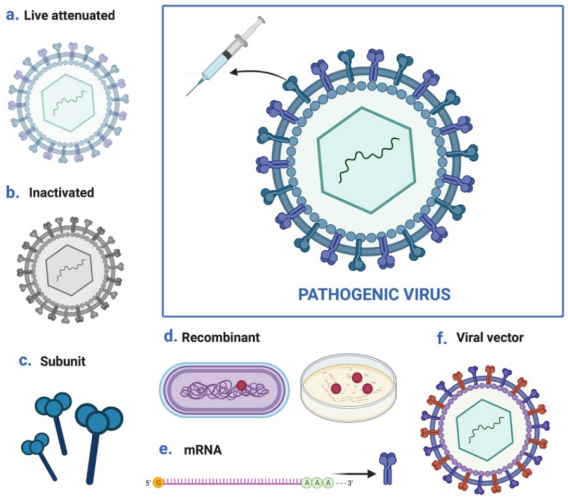
Pipeline of therapeutic HPV vaccination

Liposome-based Vaccine	PDS0101	HPV16 E6/E7	SCCHN,OPSCC	Phase II/NCT04260126	March 29,2021	Recruiting
			UCC IB3/II	Phase II/NCT04580771	October 14,2020	Recruiting
			CIN I	Phase I/NCT02065973	February 2014	Completed
	DPX-E7	HPV16 E7	SCCHN,UCC,AC	Phase I/Phase II NCT02865135	December 2016	Active, not recruiting
DNA-based Vaccine/Viral vector Vaccine	pNGVL4a-Sig/E7(detox)/HSP70 with TA-HPV	HPV16/18 E6/E7	UCC,CIN III	Phase I/NCT00788164	November 2008	Recruiting
DNA-based Vaccine/ Peptide and protein-based Vaccine	pNGVL4a-Sig/E7(detox)/HSP70 with TA-CIN	HPV16 L2/E6/E7	ASC-US,ASC-H,LSIL	Phase II/NCT03911076	May 22,2019	Recruiting
	pNGVL4aCRTE6E7L2 with TA-CIN	HPV16 L2/E6/E7	ASC-US,LSIL	Phase I/NCT03913117	December 31,2021	Not yet recruiting
DNA-based Vaccine	VGX-3100	HPV16/18 E6/E7	CIN II/III	Phase I/NCT01304524	April 2011	Completed
	pNGVL4a-Sig/E7(detox)/HSP70	HPV16 E7	UCC,CIN II/III	Phase I/Phase II NCT00121173	November 2003	Completed
	pNGVL4aCRTE6E7L2	HPV16 L2/E6/E7	CIN II/III	Phase I/NCT04131413	September 14,2020	Recruiting
	pNGVL4a-CRT/E7(Detox)	HPV16 E7	SCCHN	Phase I/NCT01493154	April 2012	Terminated
			CIN II/III	Phase I/NCT00988559	September 2009	Completed
	INO-3112	HPV16/18 E6/E7	SCCHN	Phase I/Phase II NCT02163057	August 13,2014	Completed
			UCC	Phase I/Phase II NCT02172911	June 6,2014	Completed
			UCC	Phase II/NCT02501278	May 2016	Withdrawn
	GX-188E	HPV16/18 E6/E7	UCC	Phase I/Phase II NCT03444376	May 23,2018	Recruiting
			CIN I	Phase II/NCT02596243	August 2015	Unknown status
			CIN I	Phase II/NCT02139267	July 2014	Completed
DC-based Vaccine	DC Vaccines Targeting HPV E6/E7 Protein	HPV16/18 E6/E7	CIN I/II	Phase I/NCT03870113	April 1,2019	Not yet recruiting

Mo et al, Front Cell Inf Microbiol 2022

Vector Choices for therapeutic HPV vaccination

- Suitable to induce robust CD8 T cell responses
  - Life attenuated, MVA, Adeno vectors, DNA, RNA
- Prime-boost regimen to boost responses, expand effector function repertoire and to locate them to the site of action though *Prime-Pull* strategies
  - May require local immunization, intra lesions
- Adjuvating through the use of viral and bacterial vectors

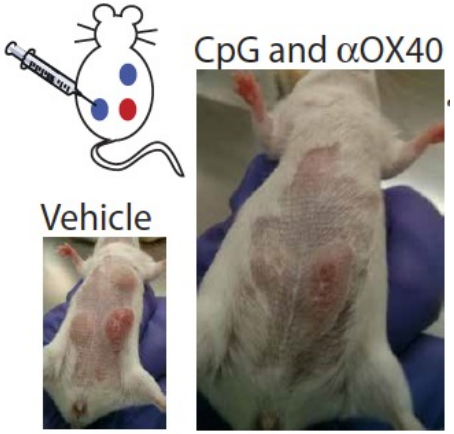


Matelski et al 2021

- Modulation of the immune milieu and restoration of exhausted immunity by Immune checkpoint inhibitors (PD1, CTLA4) and TLR agonists beyond Imiquimod and Resiquimod (Toll-like receptor (TLR)-7 and TLR-8 agonists)

Role of microenvironment: Restoration of effector functions for HPV vaccination

- Local tumour treatment with CpG (TLR9 agonist) and anti-OX40 (secondary co-stimulatory immune checkpoint molecule), leads to systemic elimination of the same, but not of unrelated tumours

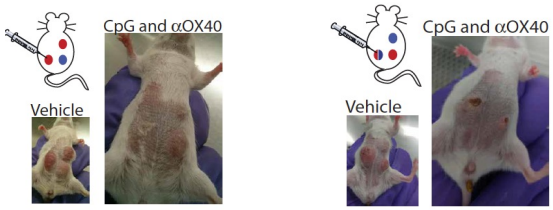


SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Eradication of spontaneous malignancy by local immunotherapy

Idit Sagiv-Barfi,[1] Debra K. Czerwinski,[1] Shoshana Levy,[1] Israt S. Alam,[2] Aaron T. Mayer,[2] Sanjiv S. Gambhir,[2] Ronald Levy[1]*

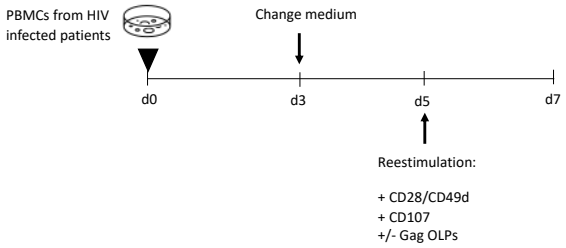


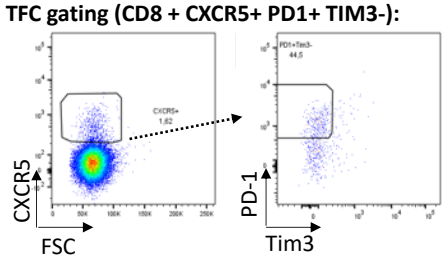
- X40 is expressed on both intratumoral FoxP3+ Tregs and activated T-effs. Anti-OX40 antibody could therefore act by inhibition/depletion of T-regs, by stimulation of T-effs, or by a combination of both.

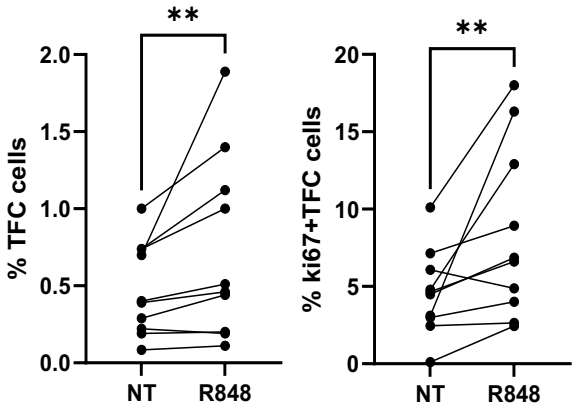
- Presence of T-reg in HPV lesions has been associated with progressive disease. Could such local treatment therefore induce and/or reactivate an effective systemic responses ? (ANCHOR, etc)

Restoration of effector functions for therapeutic HPV vaccination

- Translation to HPV infection in ChronVirVac (Caixa Health, *HR17 – 00199,* PI Andreas Meyerhans UPF)
- 1st stage in ex-vivo stimulation of HPV, EBV and HIV specific T cells from individuals with progressive viral diseases with a-OX40, CpG



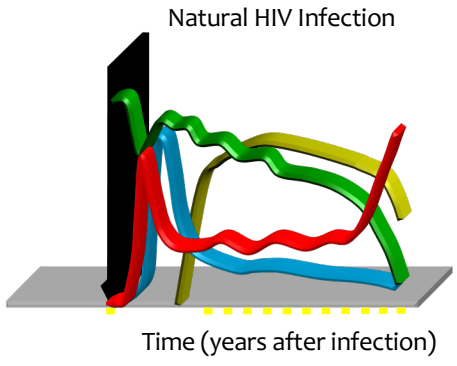




- Expansion of T-follicular cells, raising the question whether the observed anti-tumuor effect in mice involved also components of the humoral immunity (via parts of the innate NK cells , for instance)
- Effect may be HIV-specific as Tf are some of the most affected in that infection

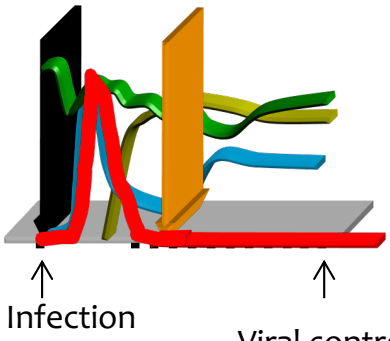
Cris Peligero, unpublished data

Can advances in HIV therapeutic vaccination inform HPV strategies ?



Viral Load
CD4 T cells
CTL response
Antibody response

Therapeutic Vaccine



Potential components of a <u>therapeutic</u> vaccine:

T cell response to viral proteins

- CD8 CTL "killer T cell" to kill infected cells
- CD4 T-helper cells to maintain functional CTL
- Combination approaches with nAb
- (Specific for HIV: Viral reservoir activators)

➢ **Common to HPV: Modulation of a pre-existing, ineffective immunity**

Immune correlates for prophylactic vs therapeutic vaccine development

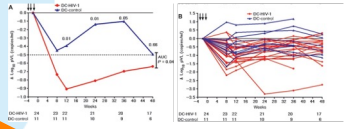
Prophylactic	Therapeutic
Induce an anti-HIV immune response in healthy individuals	Redirect/refresh the existing HIV immune response in HIV infected individuals
↓	↓
Generation of virus-specific B- and T cells	Selective expansion of virus-specific T cells
↓	↓
"De novo responses"	"Remodeling" of pre-existing immunity

→ **Different vaccine immunogen strategies and delivery approaches**

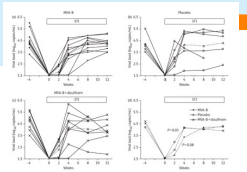
→ **What are the correlates of "immune control" ?**
- **Protection from infection**
- **Protection from disease progression**

HIVACAT Therapeutic HIV Vaccine Program

DCV-02

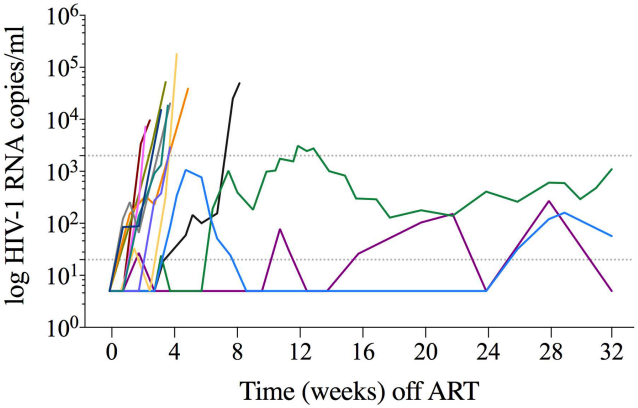


2010



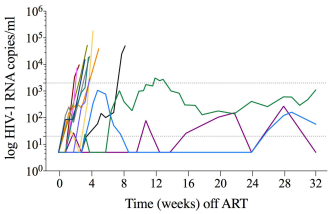
RISVAC 03

BCN-01/02 (Kick and kill strategy using ChAd and MVA vaccines expressing HIVCons plus Romidepsin)



Mothe et al Front Imm, 2020

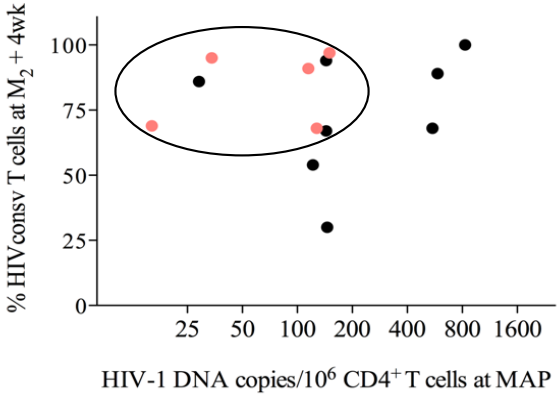
Insights gained from BCN02



1) No placebo control, what is the rate of Post-Treatment-Control (PTC: 8-13%)

2) Romidepsin safe yes, but effective ?
   - minor peaks in viremia
   - transient increase in apoptotic T cells
   - reduced polyfunctional cells
   - in vitro antiviral (VIA) activity preserved

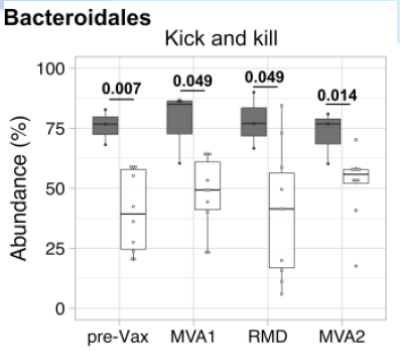
3) Reservoir possibly important, no reduction up to ATI (like RIVER, AELIX002, etc)

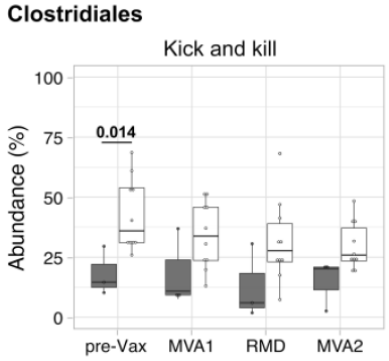


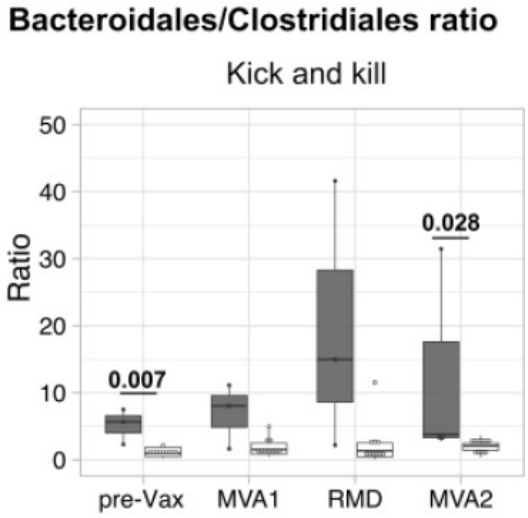
Mothe et al Front Imm, 2020
Rosas-Umbert Front Imm 2020

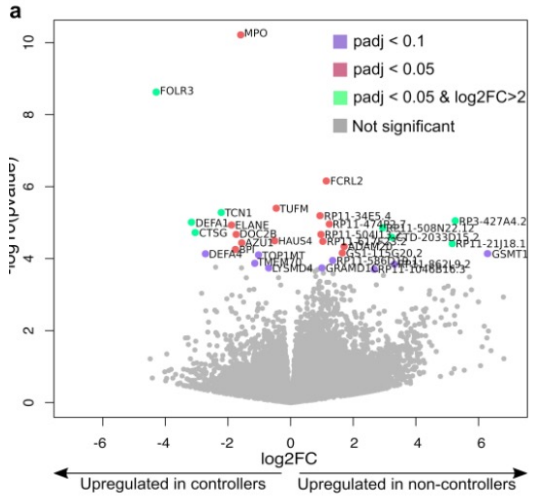
Insights gained from BCN02

4) Gut microbiome impacts therapeutic HIV vaccine response and virus control after treatment stop





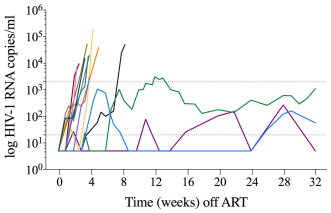




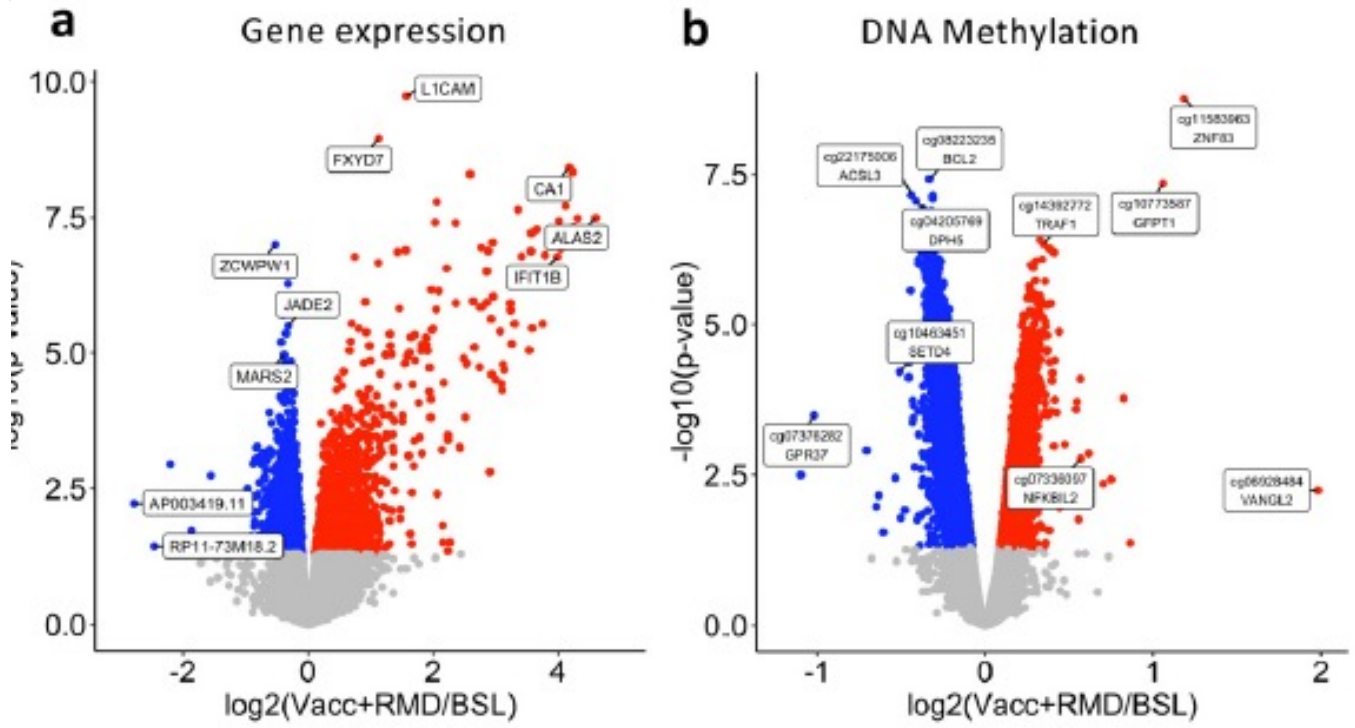
- Bacteroidales/Clostridiales ratio predicts HIV-1 reservoir size and virus control
- Baseline functional enrichment in levels of immune activation and inflammatory response

Borgogno MBIO, 2022

Insights gained from BCN02



5) Pre-ATI (and pre-vaccination) methylation imprints associated with ATI control



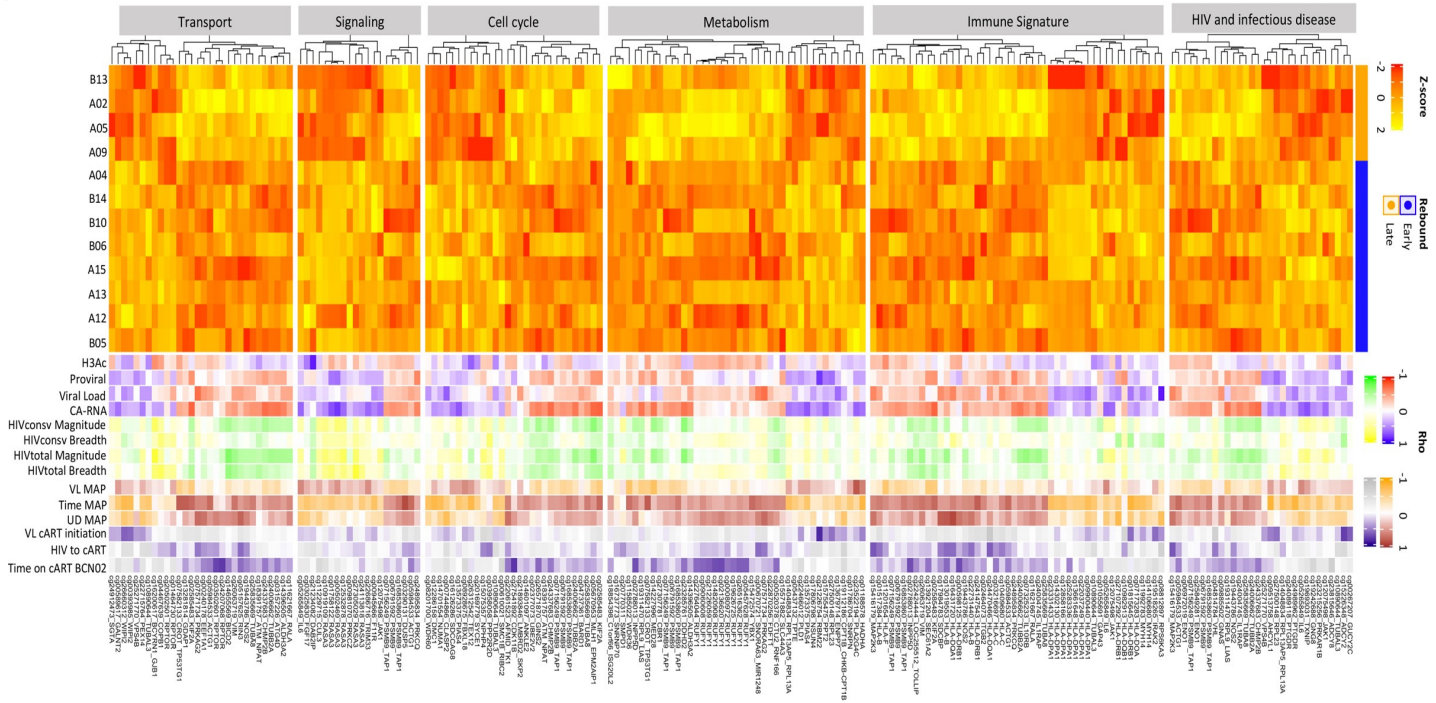
Epigenetic landscape in the kick-and-kill therapeutic vaccine BCN02 clinical trial is associated with antiretroviral treatment interruption (ATI) outcome

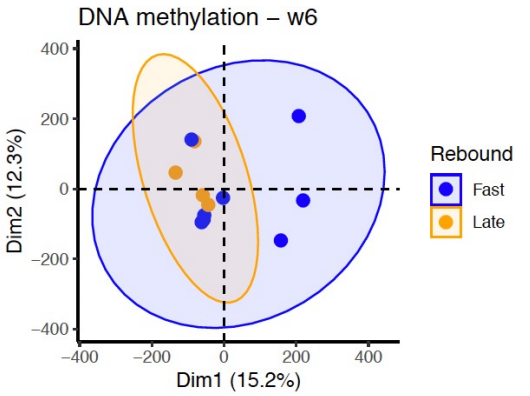
Bruna Oriol-Tordera,[a,b] Anna Esteve-Codina,[c,d] María Berdasco,[e,f] Miriam Rosàs-Umbert,[a,g] Elena Gonçalves,[h] Clara Duran-Castells,[a,b] Francesc Català-Moll,[a] Anuska Llano,[a] Samandhy Cedeño,[a] María C. Puertas,[a,i] Martin Tolstrup,[g] Ole S. Søgaard,[g] Bonaventura Clotet,[a,j,k] Javier Martínez-Picado,[a,j,k,l] Tomás Hanke,[m,n] Behazine Combadiere,[h] Roger Paredes,[a,j,k] Dennis Hartigan-O'Connor,[o,p] Manel Esteller,[q,r,s] Michael Meulbroek,[t] María Luz Calle,[u] Alex Sanchez-Pla,[v,w] José Moltó,[j] Beatriz Mothe,[a,j,k] Christian Brander,[a,k,l] and Marta Ruiz-Riol[a,*]

Oriol-Tordera Plos Path 2021
Oriol-Tordera EBioM, 2022
Duran-Castells BioMedicine. 2023

Insights gained from BCN02

5) Pre-ATI (and pre-vaccination) methylation imprints associated with ATI control





Commentary

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Immunotherapy

Can we just kick-and-kill HIV: possible challenges posed by the epigenetically controlled interplay between HIV and host immunity

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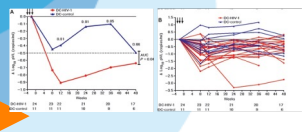
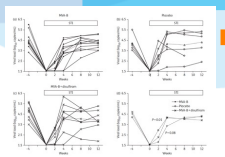
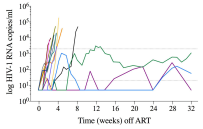
Therapeutic HIV Vaccine Program Barcelona

DCV-02

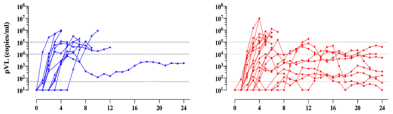




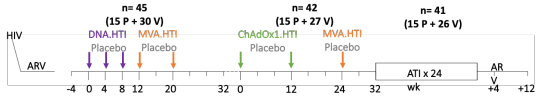
RISVAC 03



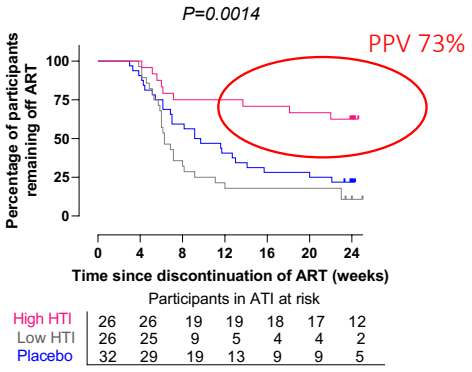
BCN-01/02



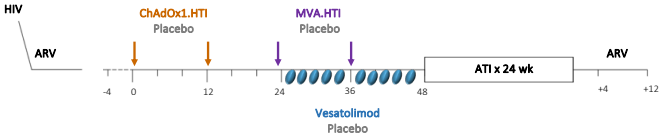
AELIX-002



Time off ART



AELIX-003 (HTI + TLR7)



BCN-03 (combined T and B cell vaccination)

Conclusions - Next steps

- Therapeutic vaccination against viral infections may need to contemplate
  - Existence of pre-existing, virus-specific immunity, be it exhausted or decoy and possibly interfering with vaccination
  - Immune modulation, including epigenetic alterations from early stages of infection, impeding the induction of an effective immunity
  - Different effector function profiles / immune cells compared to prophylactic vaccines
- Immunogen design and timing of vaccination need to be aligned with viral gene expression profiles and level of progressive alterations in the immune microenvironment
- The persistent nature of HPV infection may call for wider therapeutic vaccination, including individuals where “cleared” infection was accompanied by non-cancerous lesions
- Combination approaches may need to be tested that induce effective, long-lasting immunity able to exert anti-virus/cancer immunity, complicating clinical development

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