AIC649

Innate Activation with Inactivated Parapoxviruses for HBV Therapy

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Presentation

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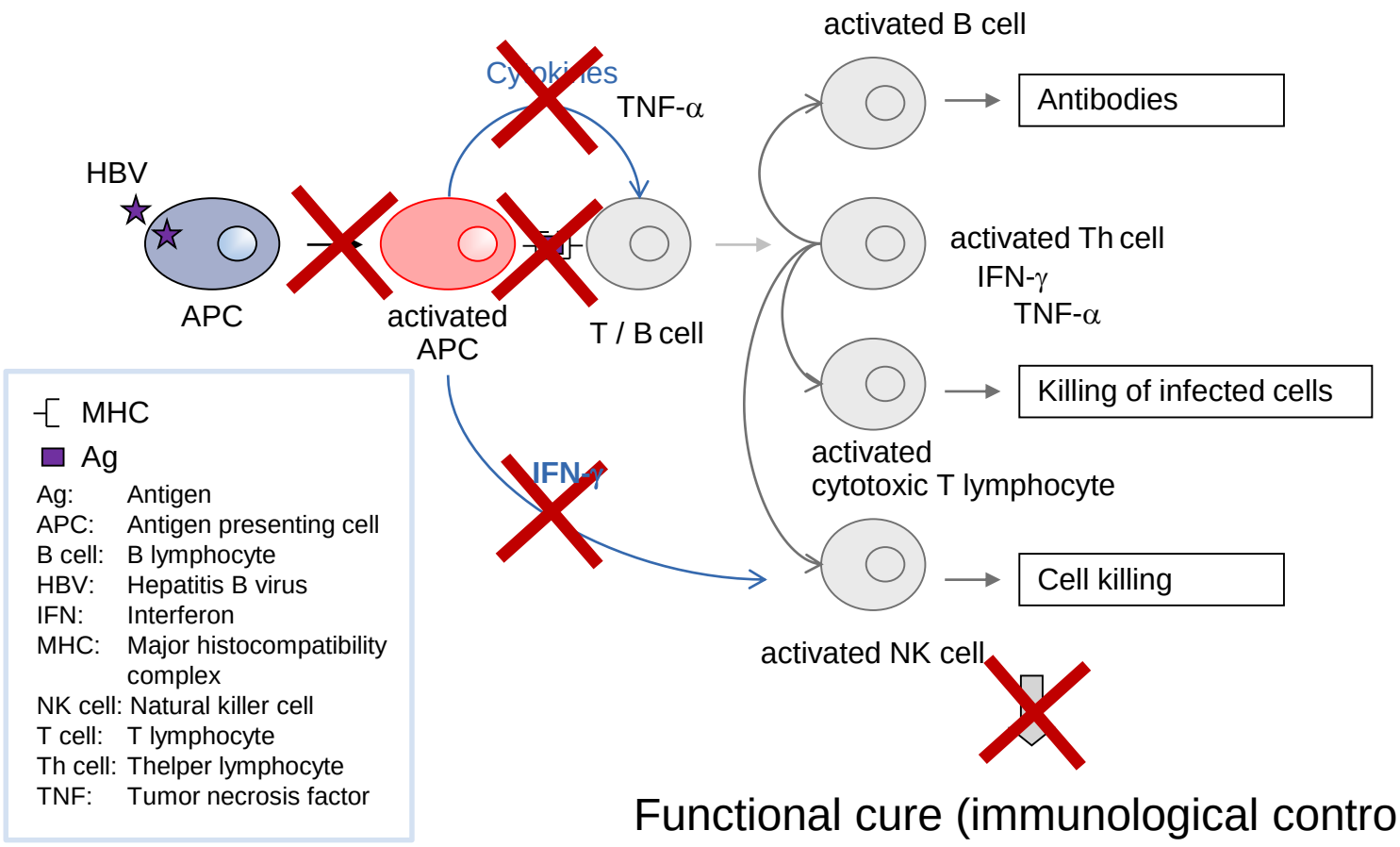
The Immunological Problem in cHB

Functional paralysis of APCs

Impairment of cytokine release

Weak / exhausted T cell responses
Defective NK cell responses

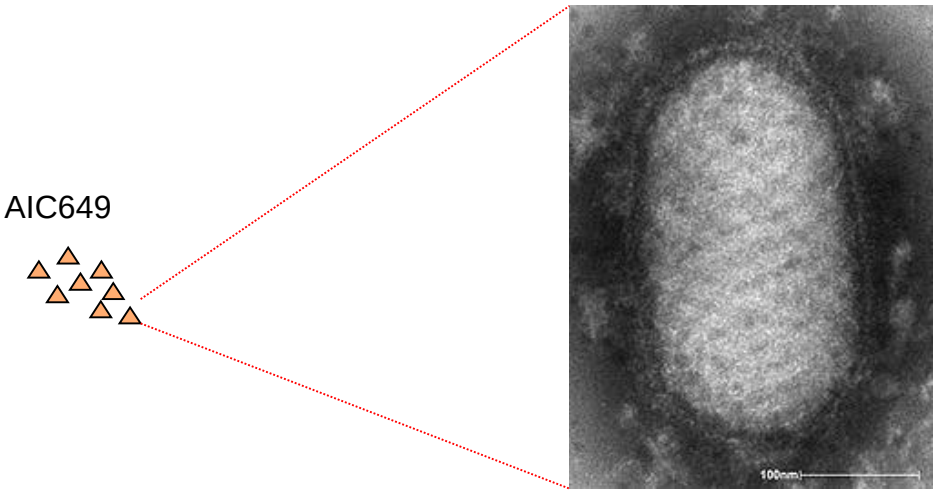


Functional cure (immunological control)

Dysregulated antigen-priming root cause for chronicity

AIC649 - HBV Cure

Introduction



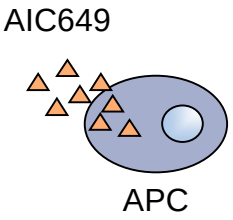
picture accessed Nov, 1st, 2018
https://de.wikipedia.org/wiki/Parapoxvirus

- AIC649 is an inactivated parapoxvirus particle (iPPVO)
  - Whole particle needed to maximally activate immune system

AIC649 under development for cHB by AiCuris

AIC649 - HBV Cure

Mode of Action



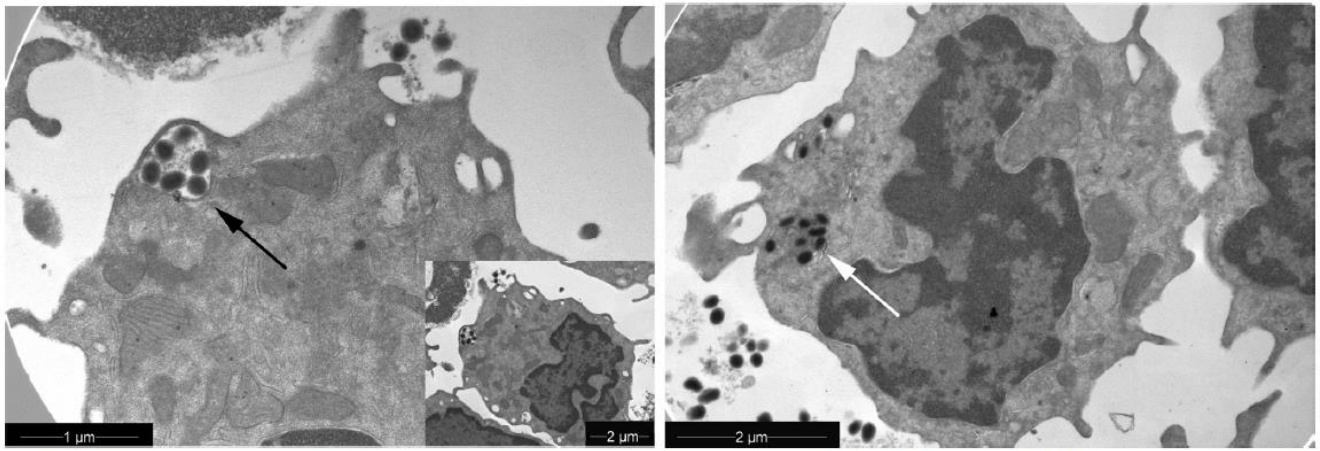


FIG. 4. Electron micrograph of Flt3L-generated BMDC cultured in the presence of iPPVO. Flt3L-generated BMDC cultured for 6 h in the presence of iPPVO (MOI = 5). iPPVO particles were located in the endosomal compartments of the cell (black arrow) and in the cytosol (white arrow).

Siegemund et al.: (2009) JV, 83, 9411

- Interaction of iPPVO with APCs?
  - Endosomal localization of iPPVO indicates phagocytosis as one mode of iPPVO uptake (Siegemund et al.: (2009) JV, 83, 9411).
  - Facilitated by opsonization? → Complement is necessary for IFN-γ induction by iPPVO (Friebe et al.: (2004) JV, 78, 9400).

AIC649 is taken up by antigen presenting cells (APCs)

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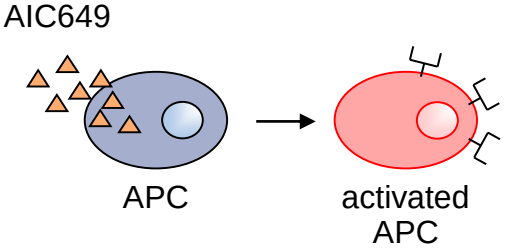
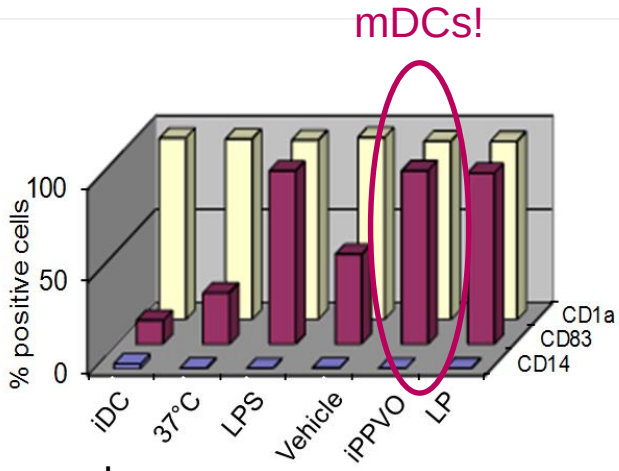
Mode of Action





CD14: marker for monocytes
CD1a: marker for dendritic cells
CD83: marker for activated DCs
HLA: human leukocyte antigen
iDC: immature dedritic cells
LP: Lipoprotein
LPS: lipopolysaccharide

Schütz et al, unpublished

- Effect of iPPVO on APCs?
  - Upregulation of activation markers:
    - (Human) dendritic cells (DCs) → upregulation of CD83, CD80, CD86, HLA-I and HLA-DR (Schütz et al, unpublished)
    - (Murine) pDCs und cDCs → upregulation of CD80, CD86, MHC-I and MHC-II (Siegemund et al.: (2009) JV, 83, 9411; von Buttlar et al.: (2014) PLoS One, 9, e106188).
    - Upregulation of MHC-II on (canine) monocytes (Schütze et al: (2009) VetMicrobiol, 140, 81)
  - Expansion of (murine) innate immune cells (DC and NK cells) in vivo (Rintoul et al.: (2012) Mol Ther, 20, 1148), accumulation of (ovine) MHC-II+ dendritic cells in skin lesions (Haig et al.: (1997) Comp Immun Microbiol InfectDis, 20, 197)

AIC649 induces activation / maturation of APCs

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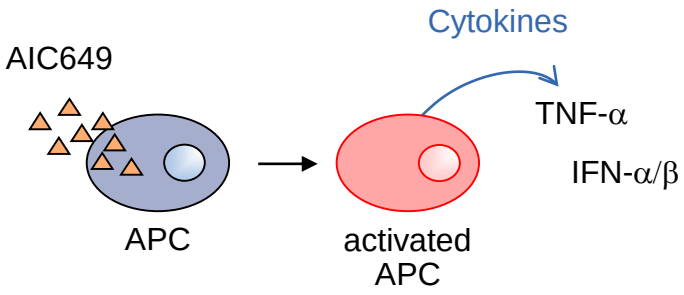
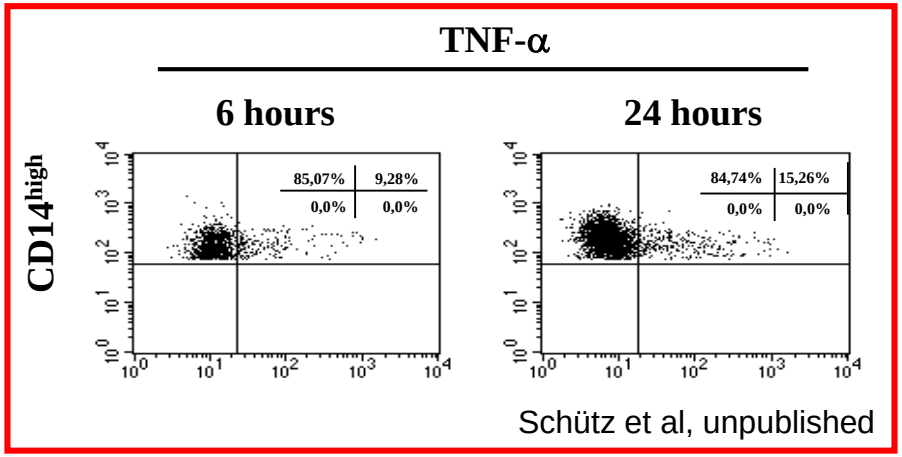
Mode of Action



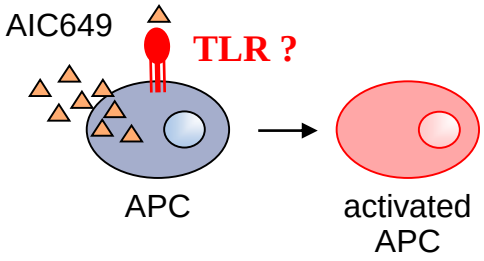


- Cytokine release by iPPVO activated APCs?
  - iPPVO induces a TNF- α production in (human) CD14+ monocytes/macrophages and immature DCs (Schütz et al, unpublished).
  - The CD14 receptor on (human) monocytes is involved in transducing the effects induced by iPPVO. Blocking of the CD14 receptor leads to decreased TNF- α levels after iPPVO stimulation (Friebe et al.: (2004) JV, 78, 9400)
  - (Murine) pDCs und cDCs secrete IFN α /β, BMDCs TNF- α and IL-12/23p40 in BMDCs in response to iPPVO (Siegemund et al.: (2009) JV, 83, 9411).

Activation of APCs by AIC649 induces cytokine release

AIC649 - HBV Cure

Mode of Action



cell types analyzed	TLR 1	2	3	4	5	6	7	8	9	10
murine pDCs									2	
murine cDCs									2	
mouse BMDCs		1		1						
human HEK transfected w/ TLR-3 or -7			1				1			
human PBMCs				3*						
human immature dendritic cells		4								

* iPPVO does not stimulate TLR-4, but crosses the pathway downstream

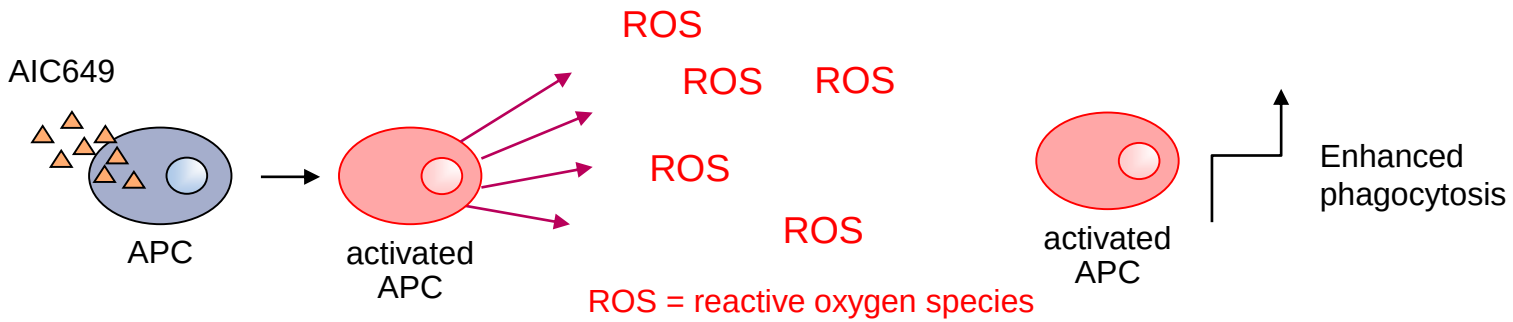
1 Siegemund et al.: (2009) JV, 83, 9411
2 von Buttlar et al.: (2014) PLoS One, 9, e106188
3 Friebe et al.: (2004) JV, 78, 9400
4 Schütz et al, unpublished

- Is the activation of APCs by iPPVO mediated by TLR?
  - "…our data identify endosomal TLR9 as the main receptor recognizing iPPVO in (murine) pDC" (von Buttlar et al.: (2014) PLoS One, 9, e106188).
  - But not in all cells: iPPVO activates (murine) cDCs by TLR-independent pathways (von Buttlar et al.: (2014) PLoS One, 9, e106188).
  - Experiments w/ human cells suggested no direct involvement of TLR2, -3, -4, and -7 in iPPVO sensing (Siegemund et al.: (2009) JV, 83, 9411; Schütz, unpublished; Friebe et al.: (2004) JV, 78, 9400).
  - Evidence for superantigen properties of iPPVO (Fachinger (2000) Eur J Immun, 30, 2962).

AIC649 acts via TLR-dependent and TLR-independent pathways

AIC649 - HBV Cure

Mode of Action



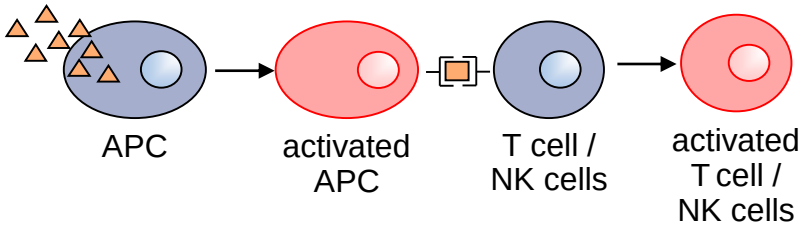
- Other effects of iPPVO in activated APCs?
  - iPPVO induces oxidative / respiratory burst and enhanced phagocytosis in (canine) monocytes (Schütze et al: (2009) VetMicrobiol, 140, 81) and (murine) macrophages (Anziliero et al.: (2014) Cellular Immunol, 289, 36).
- …and in non-professional APCs:
  - iPPVO induces oxidative / respiratory burst and enhanced phagocytosis in (canine) polymorphonuclear neutrophils (Schütze et al: (2009) VetMicrobiol, 140, 81) and (human + murine) neutrophils (Förster et al.: (1994) Arch Virol, 136, 219; Anziliero et al.: (2014) Cellular Immunol, 289, 36).

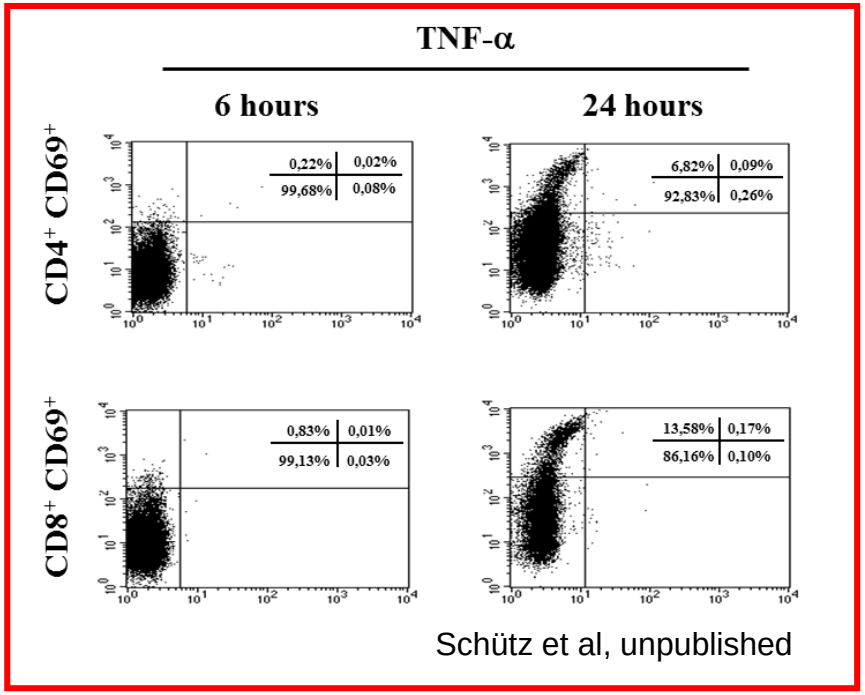
AIC649 induces functional priming of immune cells

AIC649 - HBV Cure

Mode of Action

AIC649





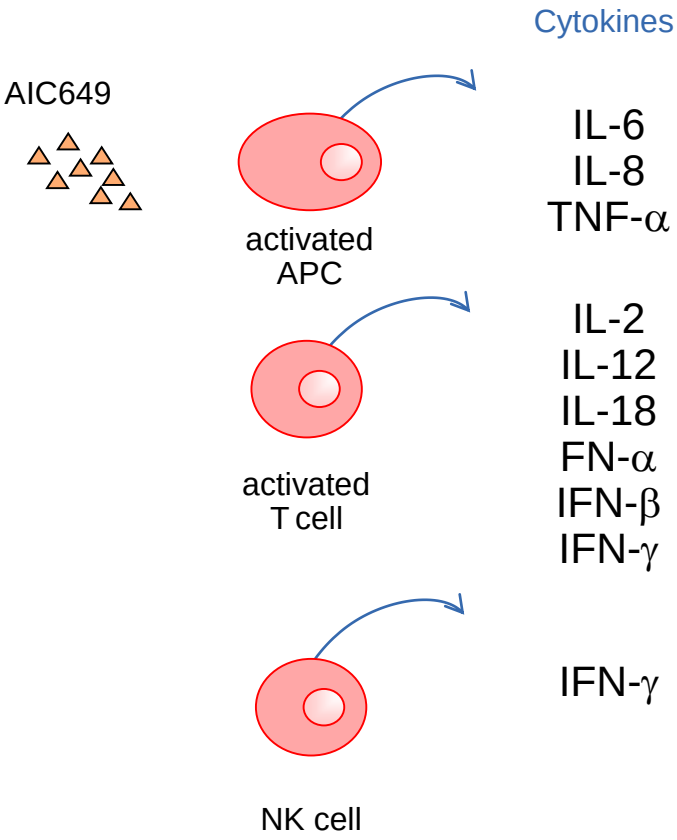
Schütz et al, unpublished

- Which cells respond to iPPVO activated APCs?
  - interactions between MHC class II and the CD3/CD4 TCR complex required for efficient stimulation of (procine) T cells by iPPOV (Fachinger (2000) Eur J Immun, 30, 2962).
  - iPPVO induces upregulation of activation marker CD69 in (human) CD4+ and CD8+ T cells (Schütz et al, unpublished) and (murine) NK cells (Rintoul et al.: (2012) Mol Ther, 20, 1148)

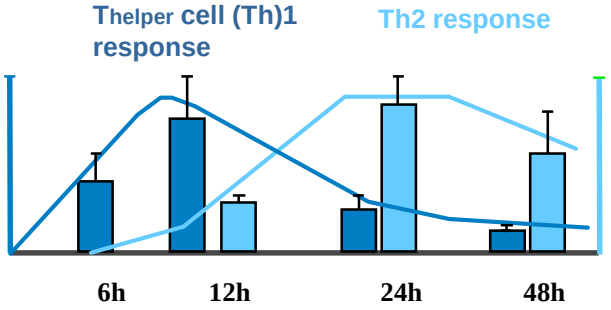
AIC649 induces activation of T cells and NK cells

AIC649 - HBV Cure

Mode of Action



- After iPPVO stimulation in vitro or in vivo all of these cytokines can be detected
- Non species specific (human, simian, murine, canine, porcine, ovine, equine…)
- Timely regulated (physiological response) w/ shift towards Th1

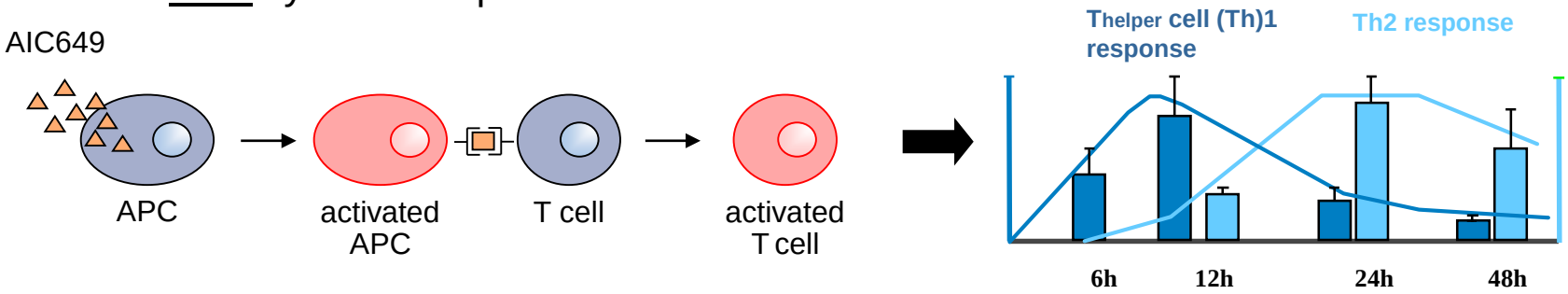


AIC649 induces complete antiviral cytokine response

AIC649 - HBV Cure

The Concept of Immune Reconstitution

- Goal: A tolerance-breaking therapy against chronic viral infections by activation of cellular AND cytokine responses

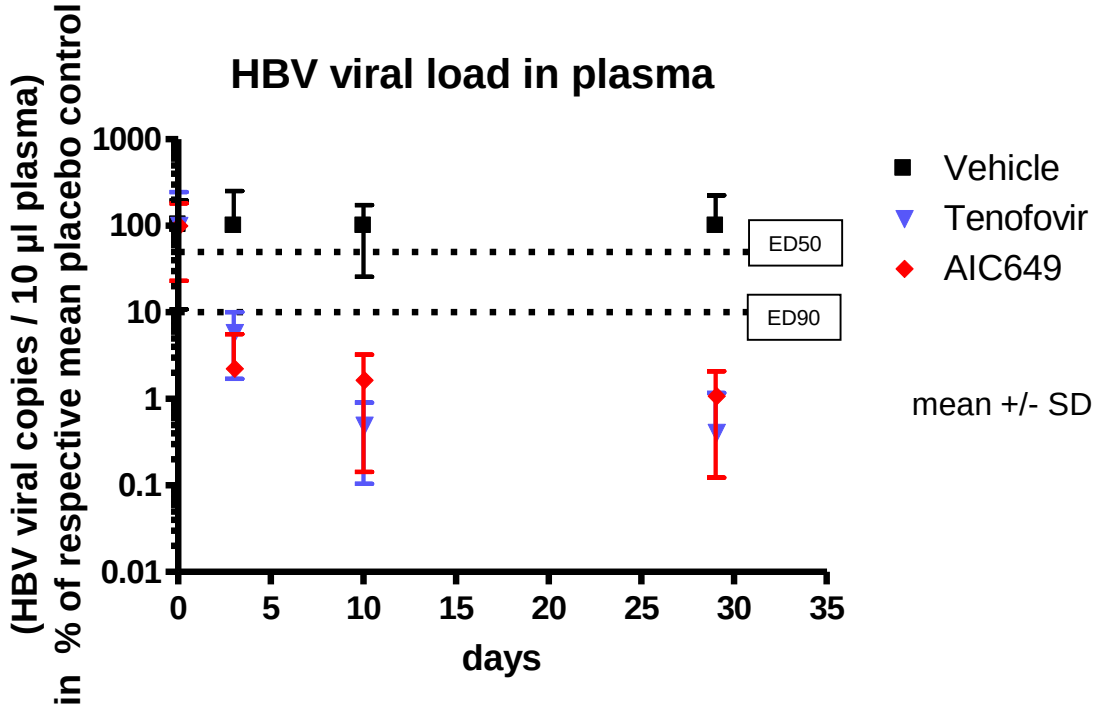


- AIC649 is an inactivated parapoxvirus particle
- Activation of the immune system via toll-like receptor (TLR)-dependent AND TLR-independent pathways
- Maturation and proliferation of cells: Antigen presenting cells (APCs; innate immunity), T cells (adaptive immunity)
- Cytokine release: Interleukin (IL)-6, IL-8, IL-12, Interferon (IFN)-γ, IFN-α, IFN-β, TNF-α and others

AIC649 induces a natural, self-limiting antiviral state

AIC649 – Preclinical Data

Antiviral Activity in the HBV tg Mouse Model



AIC649 or vehicle administered i.p. twice a week, 9 times in total

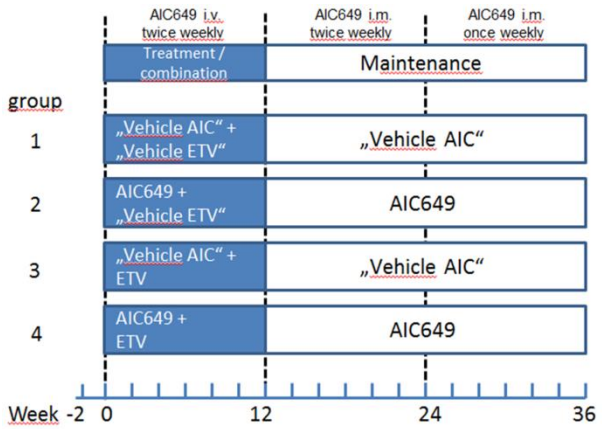
Tenofovir administered orally twice a day at 100 mg/kg for 28 consecutive days

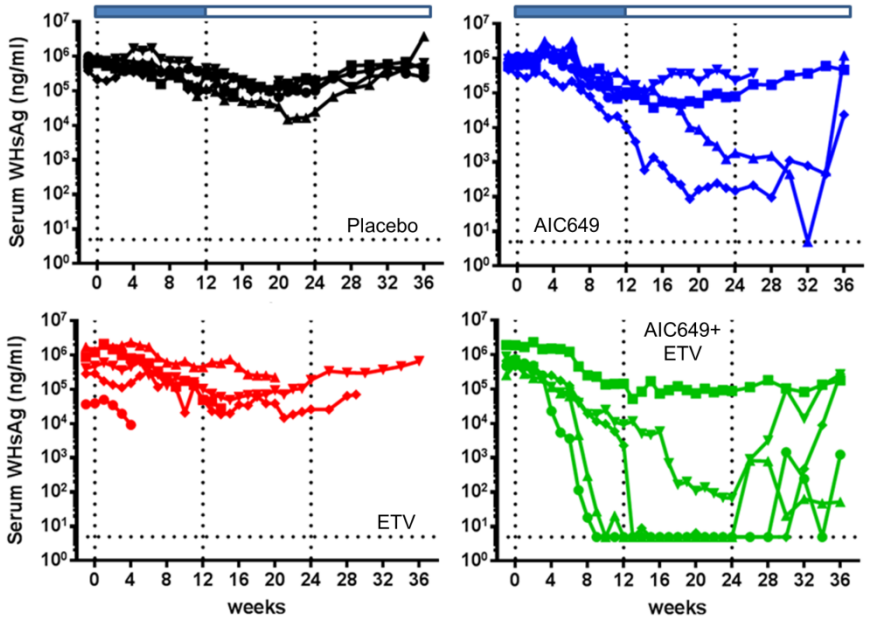
AIC649 reduces HBV load in the HBV tg mouse with comparable efficacy to tenofovir

AIC649 – Preclinical Data

Unique Efficacy in the Woodchuck Hepatitis Model

Paulsen D. et al. Hepatology, 2017
(Poster LB-22 AASLD 2017)





- AIC649 treament induced **WHsAg reduction / loss, anti-WHsAg antibodies, cell mediated immune responses (CMI), and normalization of liver enzymes** (already in monotherapy)
- Unique **bi-phasic** response pattern differing from all other competitors in development
- **Well tolerated**

AIC649 adds the immunological component to NUC treatment to achieve functional cure

AIC649 – Clinical Development

Phase I (SAD) – Study Design

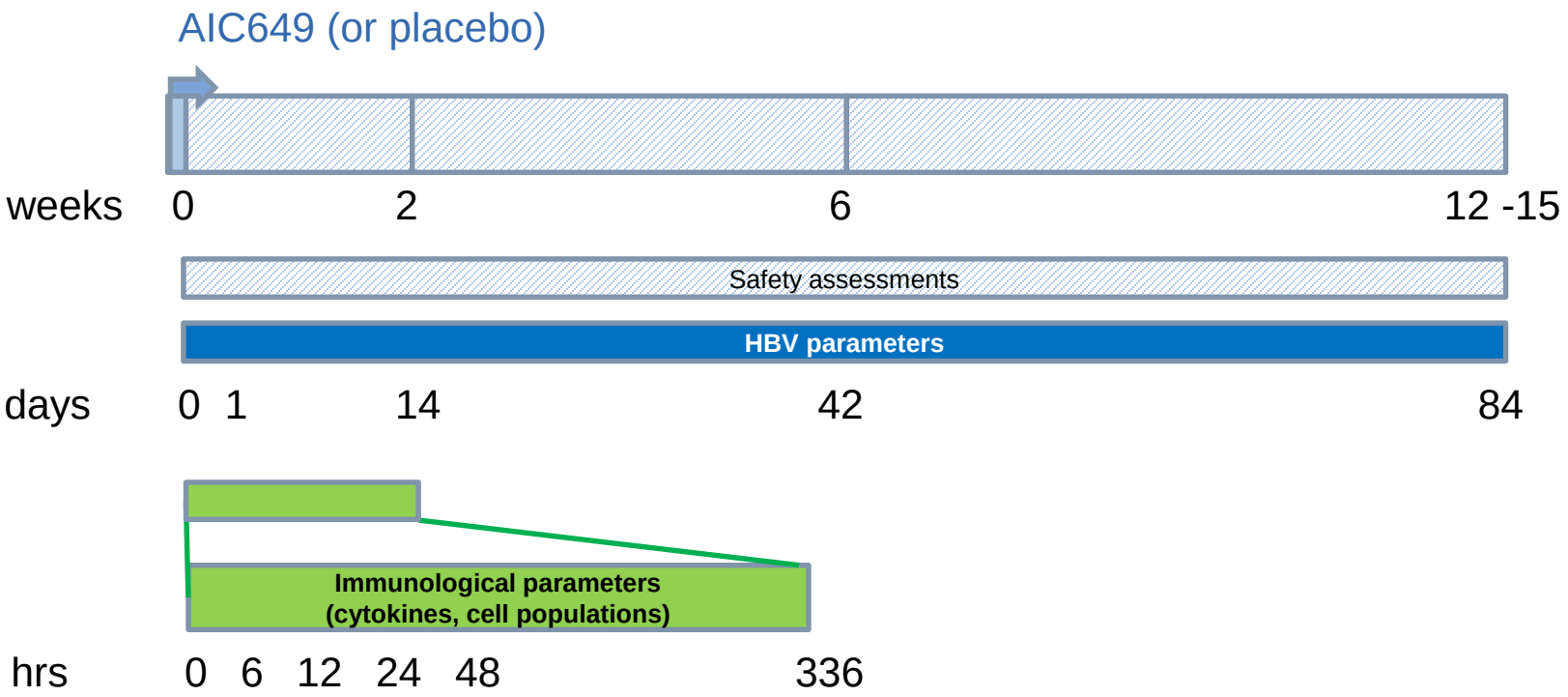
Evaluation of safety, tolerability and pharmacodynamics of different dose levels in a phase 1 clinical trial in HBV-positive volunteers

- Randomized, multi-center, double-blind, placebo-controlled trial
- Intravenous single ascending doses; 6+2 per dose
- 32 treatment-naïve and treatment-experienced patients with CHB
  - Male and female, 18 to 65-year-old
- HBeAg+ and HBeAg-, All HBV genotypes
- Dose group 3 and 4: Long-term follow up of HBV parameters: 2 visits at months 6-9 and 12-15) post treatment

AIC649 – Clinical Development

Phase I (SAD) – Study Design

Evaluation of safety, tolerability and pharmacodynamics of different dose levels in a phase 1 clinical trial in HBV-positive volunteers



AIC649 – Clinical Development

Phase I (SAD) – Safety Results

Evaluation of safety, tolerability and pharmacodynamics of different dose levels in a phase 1 clinical trial in HBV-positive volunteers

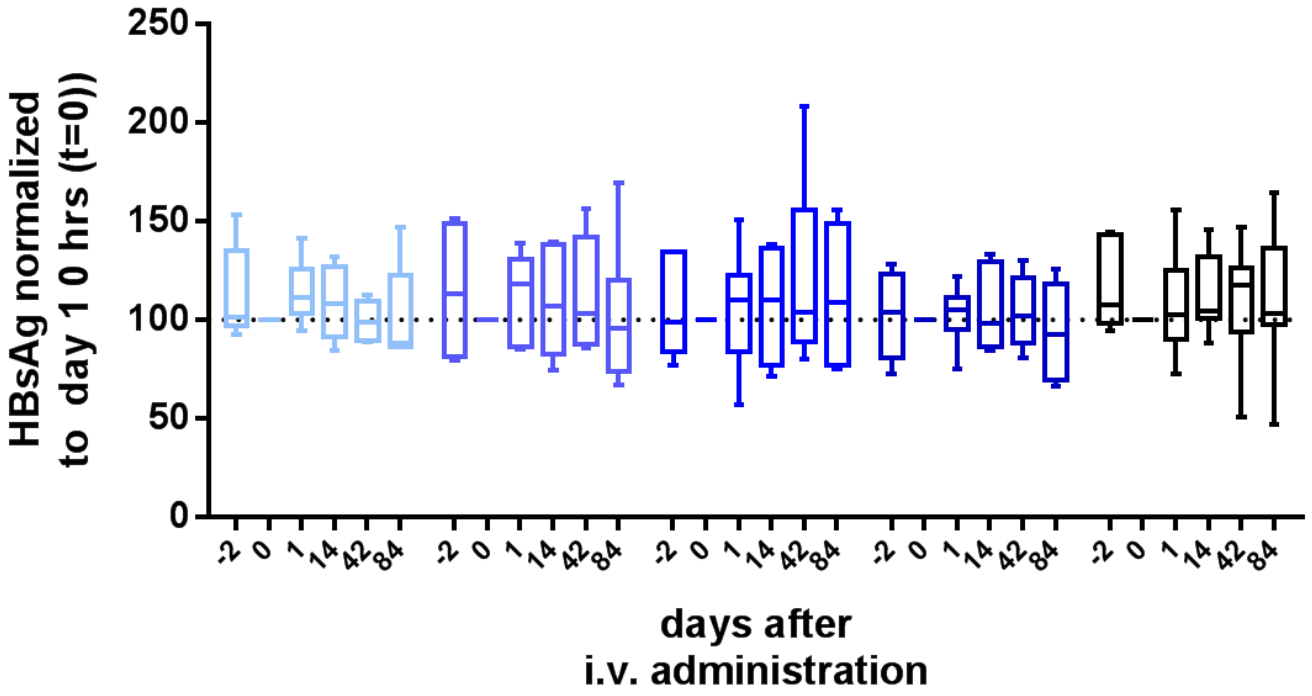
- No safety signal in form of adverse events
- No clinically significant abnormal value in
  - Hematology/blood chemistry
  - Vital signs including ECG parameters
  - No hepatic flares
- MTD was not reached with the highest dose tested (dose group 4)

A single intravenous dose of AIC649 was safe and well tolerated in all dose groups

AIC649 – Clinical Development

Phase I (SAD) – Virology Results

HBsAg levels



Dose group 1
Dose group 2
Dose group 3
Dose group 4
Placebo

Box-and-whisker plot: given are the minimum, the 25th percentile, the median, the 75th percentile, and the maximum.

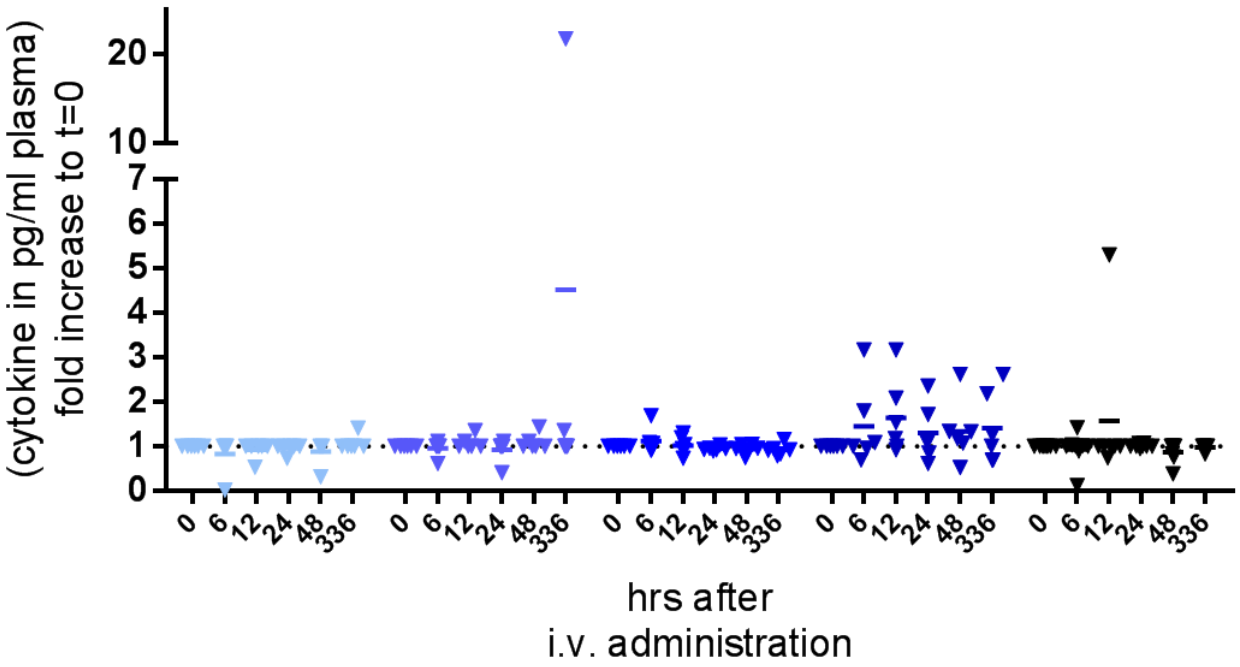
Dotted line: baseline at t=0. Screening values were set to -2

HBsAg levels did not substantially change in most patients

AIC649 – Clinical Development

Phase I (SAD) – Immunology Results

IFN-ɣ



- Dose group 1
- Dose group 2
- Dose group 3
- Dose group 4
- Placebo

Straight line: group mean per time point

Dotted line: baseline at t=0

Consistent increases in IFN-ɣ could be detected in dose group 4

AIC649 – Clinical Development

Phase I (SAD) – Summary

Evaluation of safety, tolerability and pharmacodynamics of different dose levels in a phase 1 clinical trial in HBV-positive volunteers

- A single intravenous dose of AIC649 was safe and well tolerated in all dose groups.
- There was no dose limiting toxicity and the MTD was not reached with highest dose tested.
- Despite the heterogeneity of the patients in the trial, there was evidence that a single dose of AIC649 stimulates immunity.

AIC649 will be investigated in further clincal trials

AIC649 – Acknowledgements

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