TG1050, A NOVEL IMMUNOTHERAPEUTIC TO TREAT CHRONIC HEPATITIS B, CAN CONTROL HBsAg AND PROVOKE HBsAg SEROCONVERSION IN HBV-PERSISTENT MOUSE MODELS

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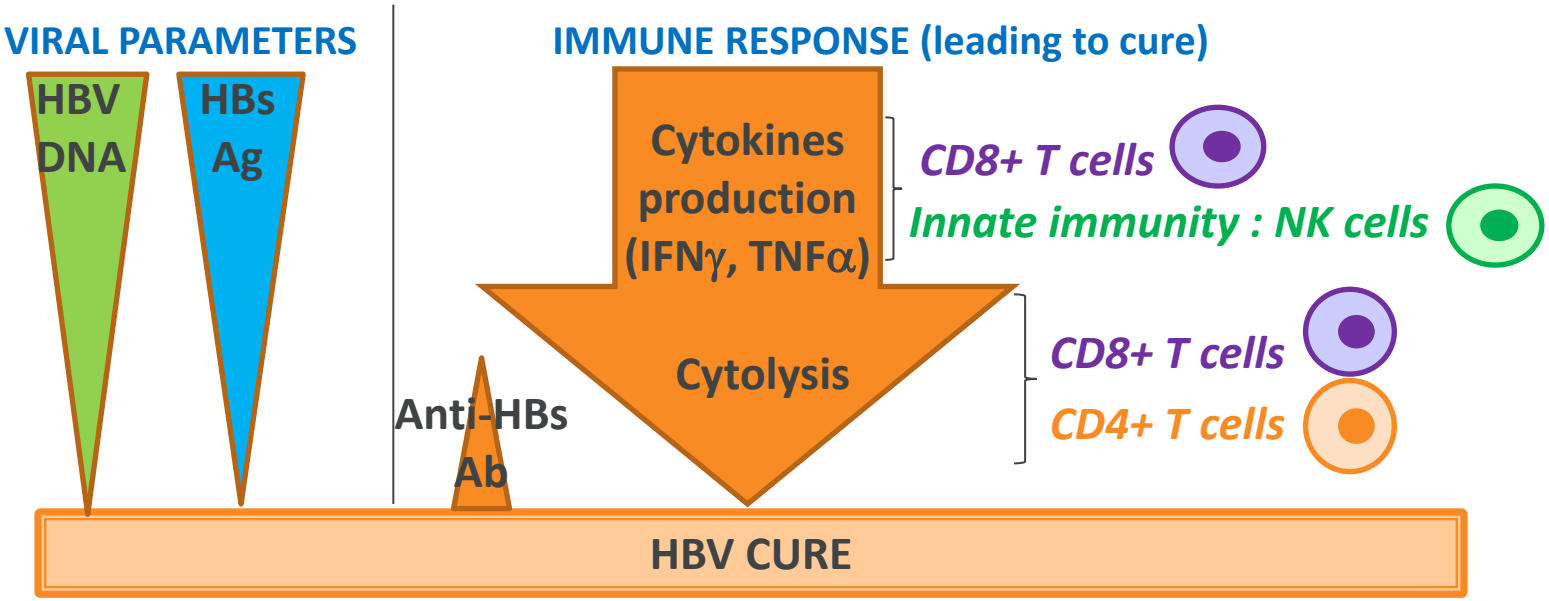
RATIONALE FOR AN IMMUNOTHERAPEUTIC IN THE TREATMENT OF CHRONIC HEPATITIS B (CHB)

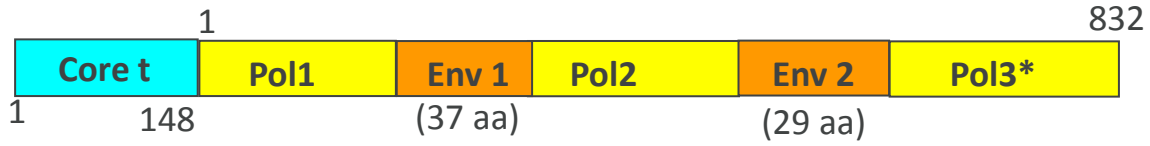
- HBV cure (HBsAg/anti-HBsAg seroconversion) rate is low with current therapies (3 to 5%)
- Small molecules aiming at treating CHB do not recruit the host immune system yet:
  - ✓ A strong correlation exists between HBV specific functional T cells and control/eradication of viremia *(Bertoletti and Ferrari, Gut, 2012, Dec; 61(12):1754-64)*



TG1050: PRODUCT DESCRIPTION

TG1050

Based on non-replicative E1 and E3 deleted human adenovirus serotype 5 encoding a fusion protein comprising truncated HBV Core fused to a deleted and mutated HBV polymerase and 2 selected HBsAg (Env) domains (genotype D sequence)



**mutations inserted in Pol3*

KEY FEATURES OF TG1050 IMMUNOGENICITY IN HBV-FREE MODELS

- **In HBV-free mice, TG1050 injected once by sc route induces**

High frequencies of HBV-specific T cells
targeting the **3 encoded HBV antigens**
Being mainly **CD8+ T cells**
(detected in spleens and/or livers)

Producing cytokines (mainly IFNγ and/or TNFα)

Long-lasting (up to 400 days) and displaying mainly an effector memory phenotype (CD44+/CD62L-)

Displaying in vivo cytolytic activities

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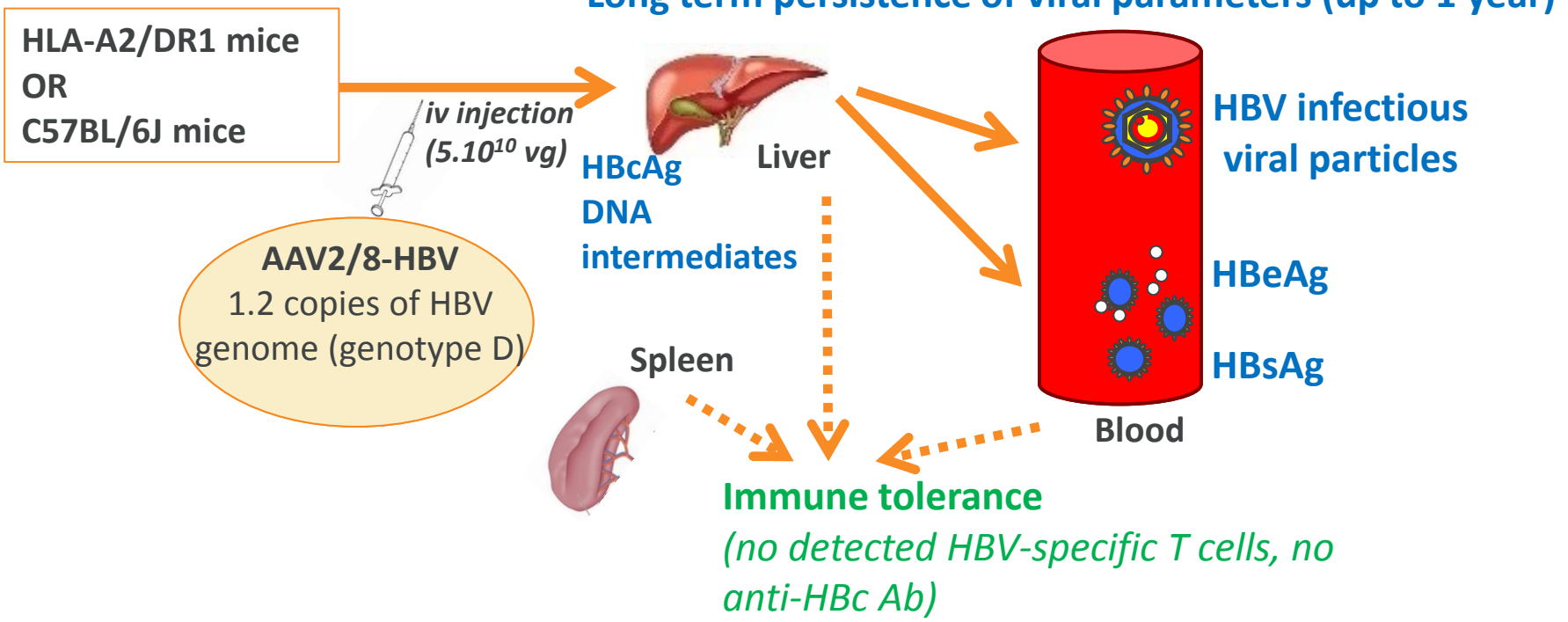
Martin P, et al. Gut 2014;0:1–11. doi:10.1136/gutjnl-2014-308041

AAV-HBV : A MURINE MODEL OF HBV PERSISTENCE



- ***Main differences with human HBV infection :***
  - *No detectable cccDNA*
  - *No de novo infection of hepatocytes with new viral particles*

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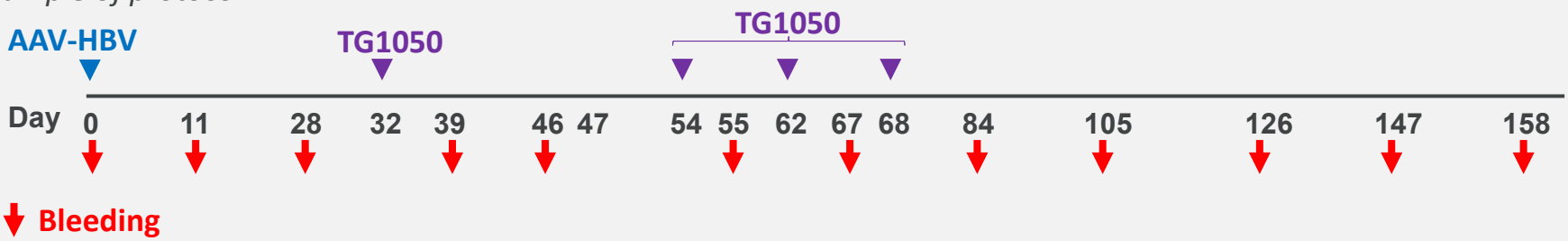
Dion et al, J Virol, 2013 May;87(10):5554-63 and unpublished data

AAV-HBV MURINE MODEL AND TG1050 IMMUNIZATION

- **AAV-HBV and TG1050 Injections**
  - **Mice (HLA-A2/DR1 or C57BL/6J) are transduced by the AAV-HBV**
  - **32 days post-transduction, mice are immunized with TG1050 (once or multiple times)**

Example of protocol



- **Parameters used for read-outs**
  - **Immune responses :**
    - HBV-specific T cells in spleens and/or livers (ELISPOT or ICS assays)
    - HBV-specific antibodies : anti-HBc Ab, anti-HBs Ab in blood (ELISA assays)
  - **Viral parameters** : HBV DNA (qPCR) and HBsAg (ELISA assay) in blood

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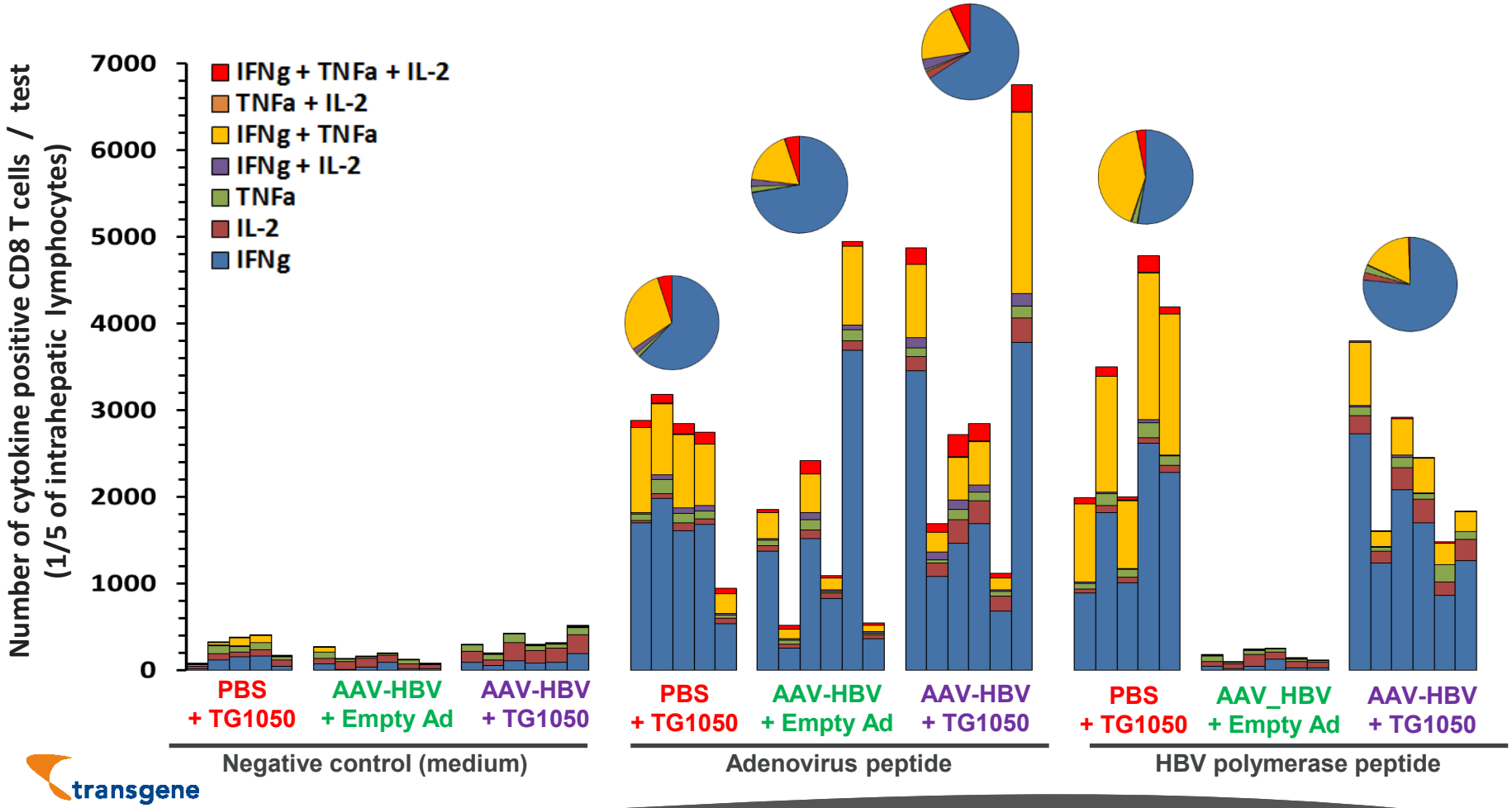
TG1050 INDUCES FUNCTIONAL T CELLS SPECIFIC OF HBV IN THE LIVER OF HBV PERSISTENT MICE

IFNγ/TNFα/IL2 ICS assays at day 47 on intrahepatic lymphocytes, after single TG1050 injection of C57BL/6J mice



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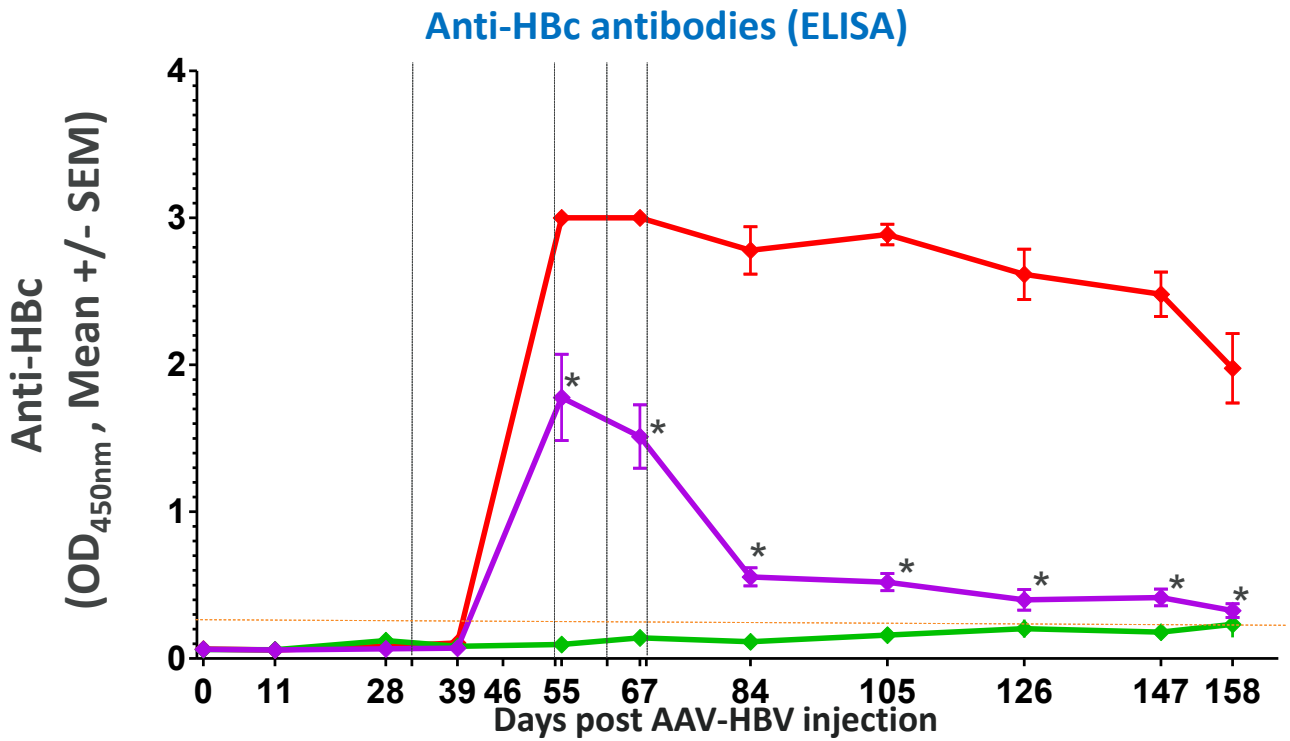
Martin P, et al. Gut 2014;0:1–11. doi:10.1136/gutjnl-2014-308041 and unpublished data

TG1050 INDUCES ANTI-HBV CORE ANTIBODIES IN HBV PERSISTENT MICE



AAV-HBV C57BL/6J mice immunized at day D32, D54, D62, D68 with
- TG1050 (2x10^{9}vp)
- Empty Ad (2x10^{9}vp)

Immunization (TG1050 or empty Ad)

*p<0,05 for comparison of AAV-HBV +TG1050 and AAV-HBV + Empty Ad

C57BL/6J mice immunized at day D32, D54, D62, D68 with
- TG1050 (2x10^{9}vp)

Cut-off (0.25 OD$_{450}$)

Plasma dilution : 1/2000

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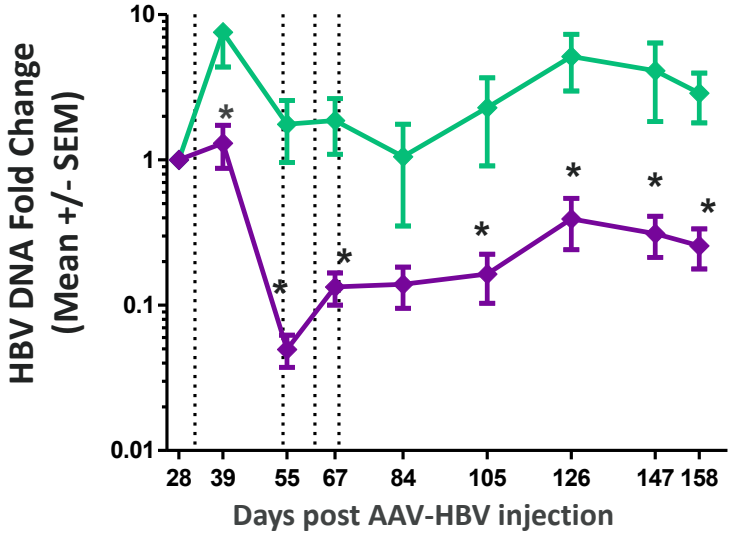
TG1050 HAS A SUSTAINED ANTIVIRAL EFFECT IN HBV PERSISTENT MICE

: *Significant decrease of HBV DNA and HBsAg levels*

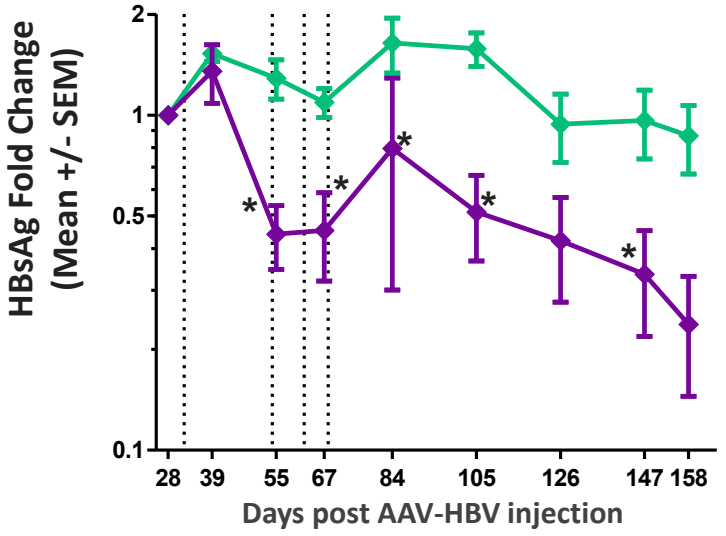
HBV DNA (viral load)

Mean viral load at D28 : 1.4x10^6 copies/mL



Circulating HBsAg

Mean HBsAg titers at D28 : 20µg/mL



AAV-HBV C57BL/6J mice immunized at day D32, D54, D62, D68 with
- TG1050 (2x10^{9}vp)
- Empty Ad (2x10^{9}vp)
- Immunization (TG1050 or empty Ad)

* p<0.05 for comparison of Empty Ad with TG1050 (statistical analysis based on a mixed model and post-hoc tests with multiplicity correction)

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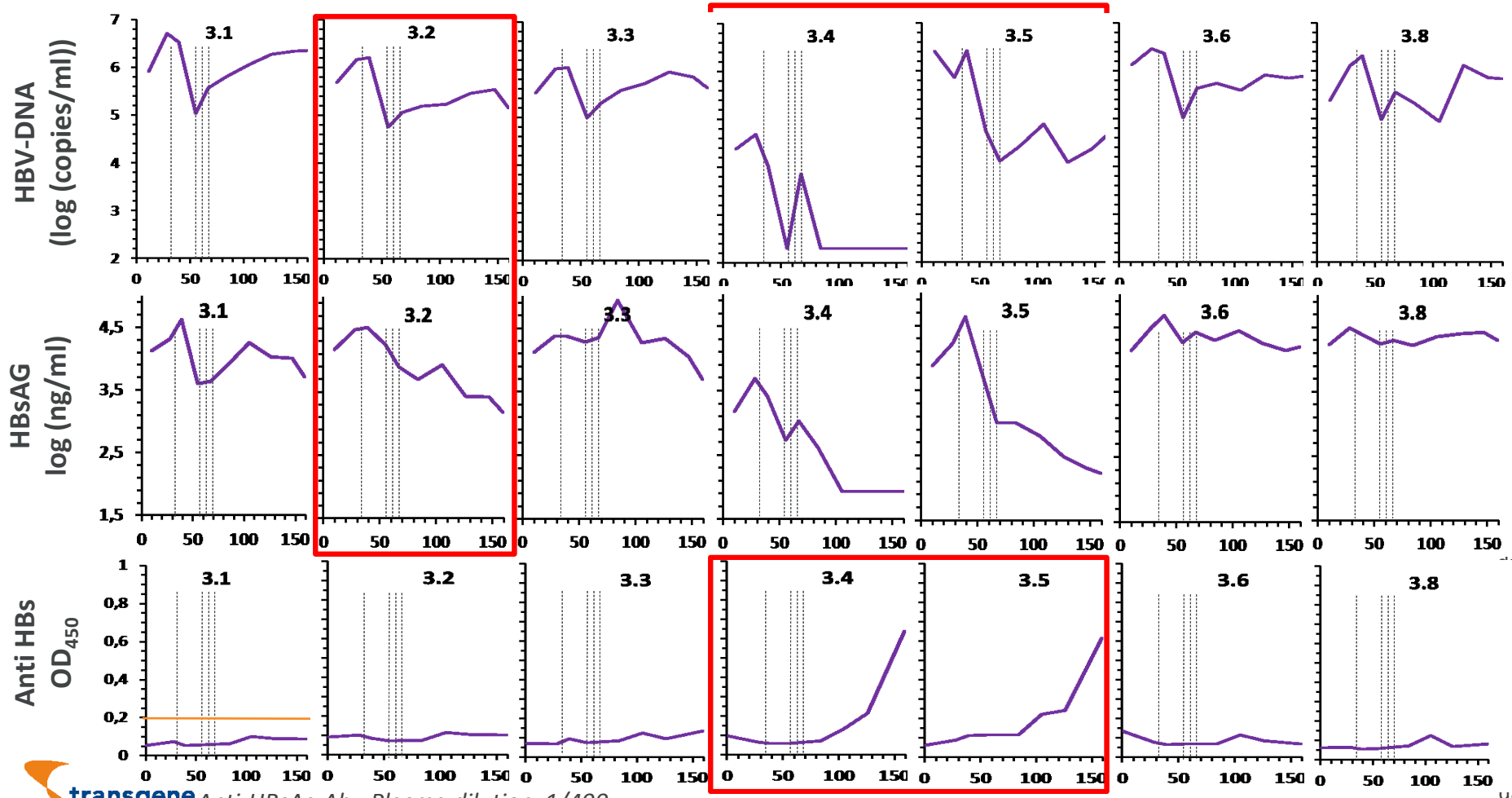
TG1050 INDUCES HBV DNA AND HBSAG DECLINE AS WELL AS HBSAG SEROCONVERSION IN SOME HBV PERSISTENT MICE

C57BL/6J mice 3.1 to 3.8 were HBV persistent and injected with TG1050 at days 32, 54, 62 and 68 (vertical dotted line)



transgene *Anti-HBsAg Ab : Plasma dilution 1/400*

SUMMARY

- **In the AAV-HBV model in C57BL/6J mice, TG1050 in stand alone was shown to be able to induce :**

  - ✓ **HBV-specific functional T cells detected in the liver** and producing cytokines

  - ✓ an **antiviral activity,** detected as soon as after the 1rst injection and which is sustained overtime
    - ✓ **100% of treated mice display a HBV DNA decrease**
    - ✓ **43% of treated mice display a strong (>1log) HBsAg decrease**

  - ✓ **30% of treated mice display appearance of anti-HBsAg antibodies**

CONCLUSION

- In a context of HBV persistence, TG1050 is immunogenic, exerts an antiviral activity and triggers HBsAg seroconversion

- TG1050 is capable of capturing key features required to acheive clinical cure

- A Phase 1/1b (First-In-Man and dose finding) study is underway, with recruitment expected in mid-2015

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