

# Induction of Tolerance to Immunotoxins Using Nanoparticle Delivery of Rapamycin

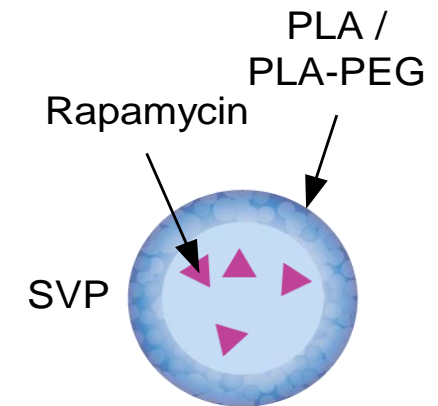
Ronit Mazor and Ira Pastan  
Immunogenicity summit  
October 2016

# Outline

- **Nanoparticle Delivery of Rapamycin (SVP)**
- **Combination of recombinant immunotoxins with nanoparticles**
  - Immunocompetent mouse model
  - Mice with pre-existing antibodies
  - Anti tumor activity in Syngeneic mice
  - SVP do not accelerate tumor growth
  - Localization of SVP
  - Adoptive transfer of tolerance

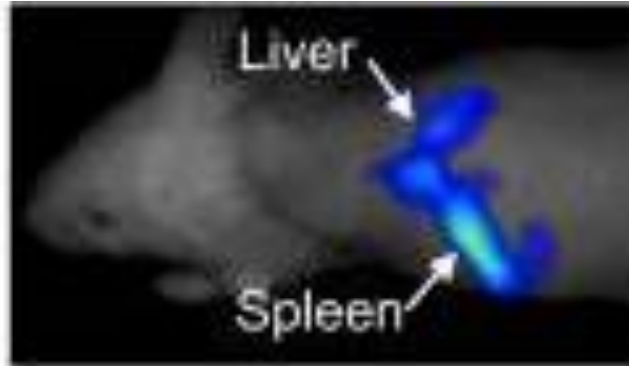
# Synthetic vaccine particles (SVP) for tolerance induction

- poly(lactidecoglycolide) (PLGA)
- Self assembled
- Bio degradable (lactic acid and glycolic acid)
- PLGA has FDA approval for drug delivery
- Preferable uptake by APC due to **size, Shape** and surface **charge**
- Encapsulation of Rapamycin (**SVP**)
- Successfully prevented immunogenicity of: Factor VIII, KLH, OVA and adalimumab in mice, rats and monkeys (Zhang et al. Cell Immunol, 2016 , Kishimoto et al. Nat Nanotechnol, 2016)

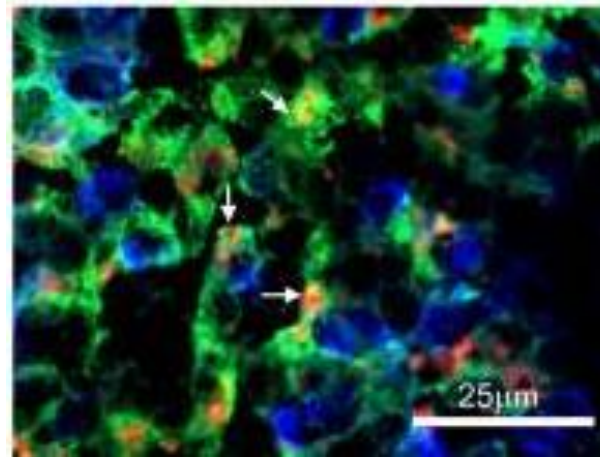
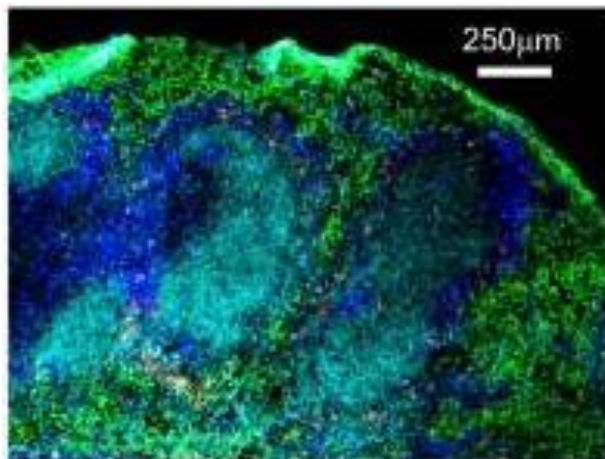


# SVP localize to Macrophages and DC in the spleen and lymph nodes (Maldonado et al. 2015 PNAS)

I.V.



S.C

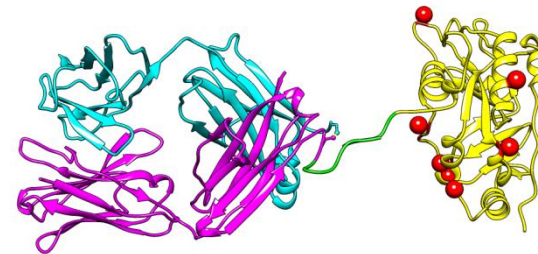


Macrophages (F4/80, green)  
DCs (CD11c, dark blue)  
B cells (B220, cyan)  
SVP (red)

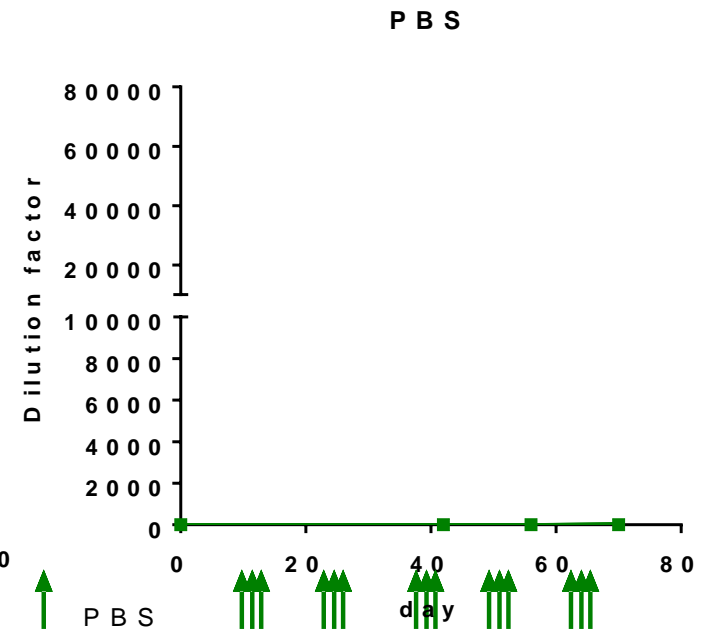
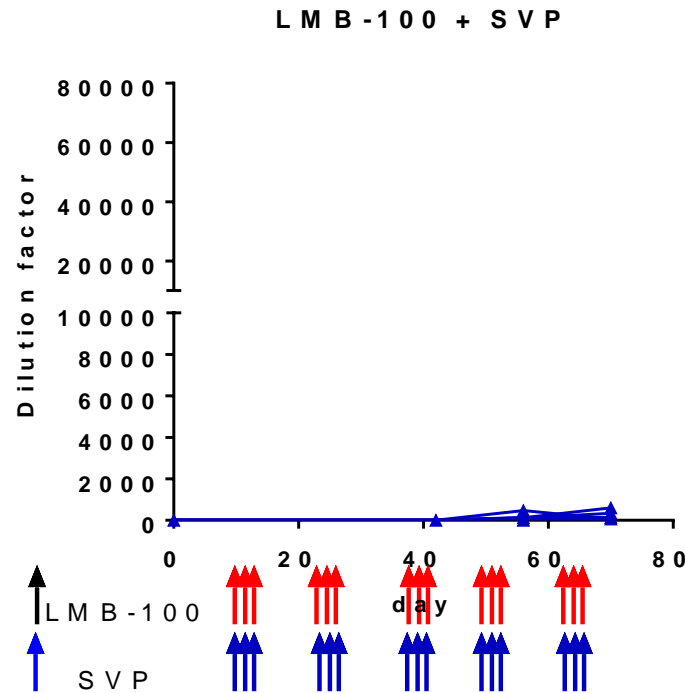
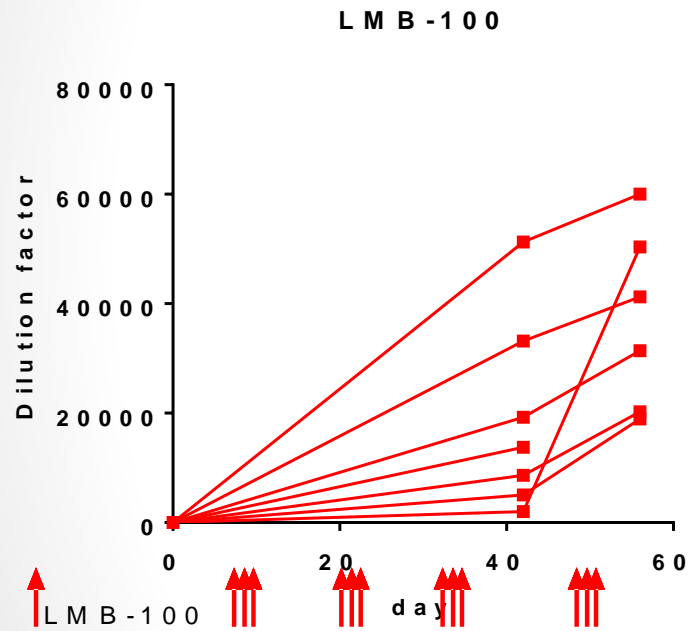
# Can we use SVP to induce immune tolerance against a foreign bacterial protein?



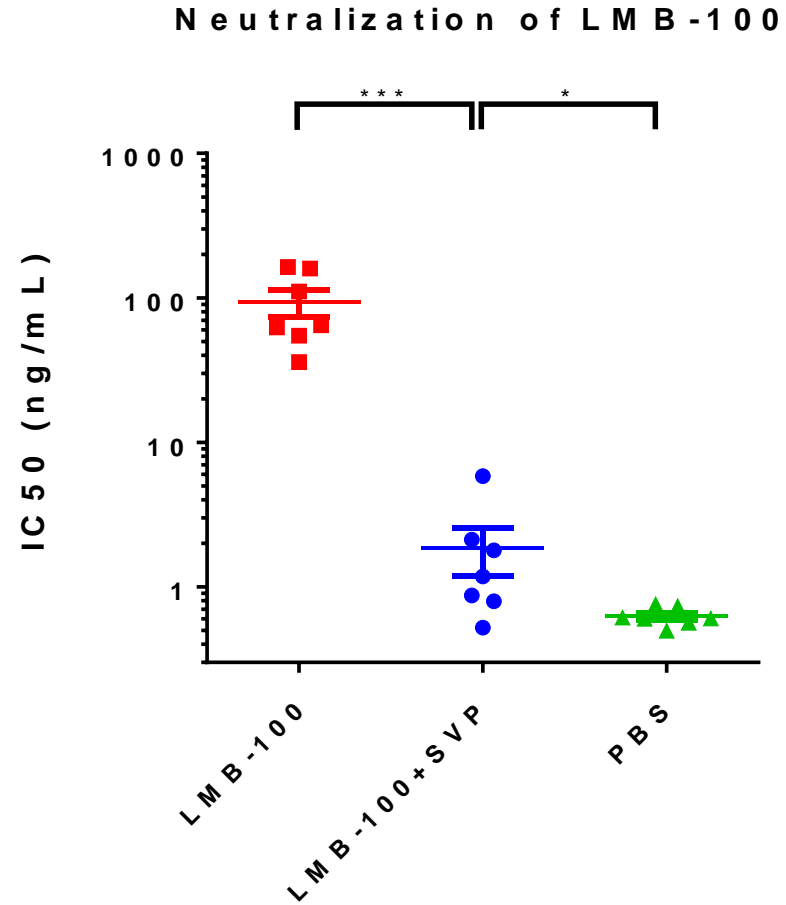
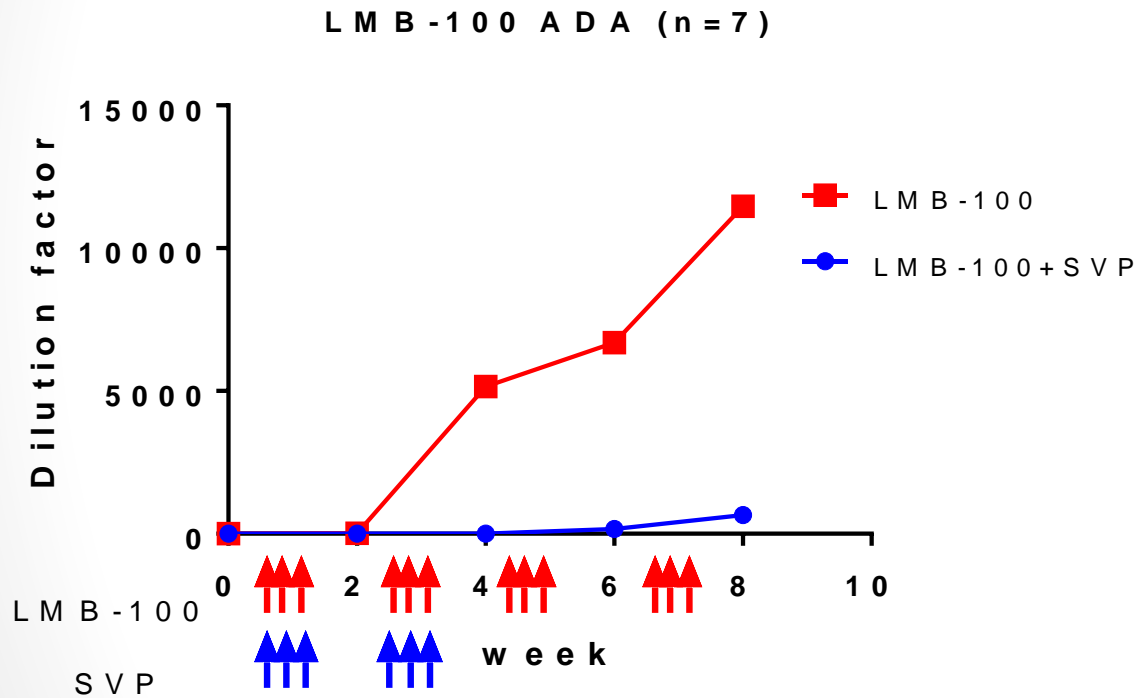
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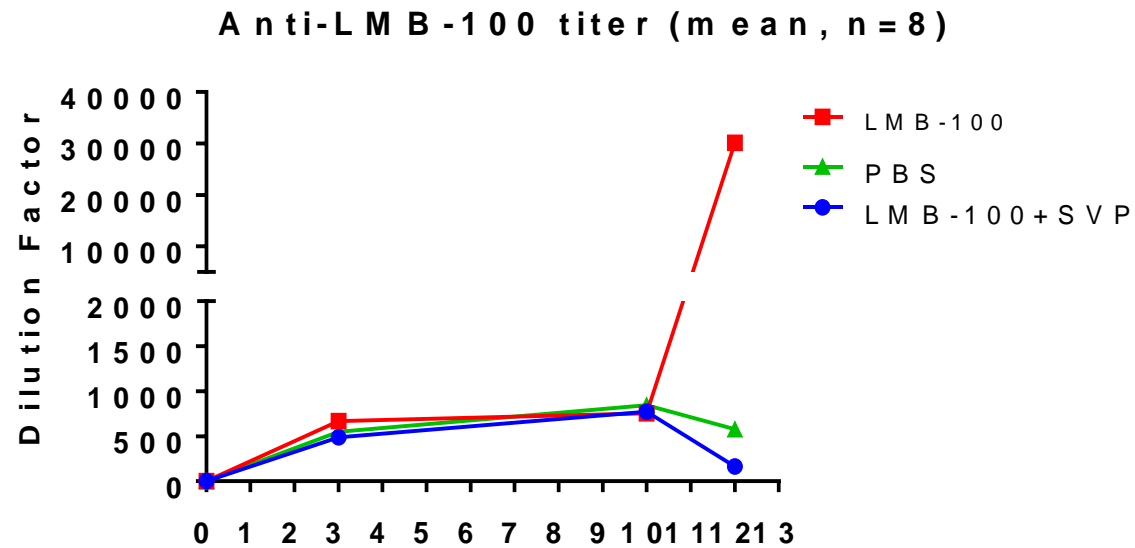
# Combination of LMB-100+SVP prevents formation of ADA against LMB-100 (n=7)



# Combination of LMB-100+SVP induces tolerance and prevents formation of neutralizing and ADA



# Combination of LMB-100 with SVP prevent ADA formation in mice with Pre-existing antibodies

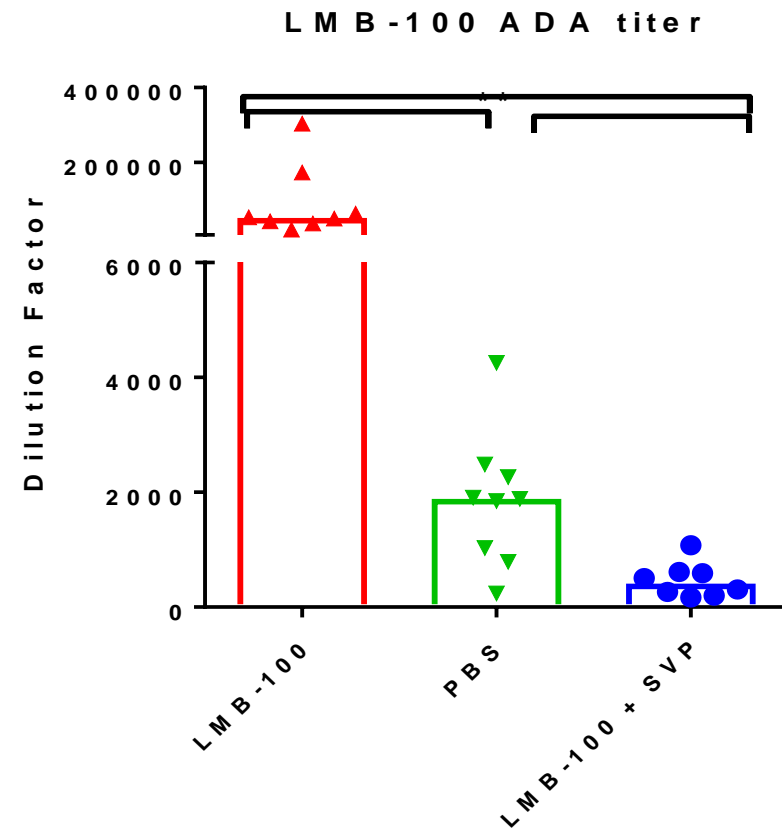


LMB-100 Immunization: ↑↑↑↑

Week

Challenge: ↑↑↑

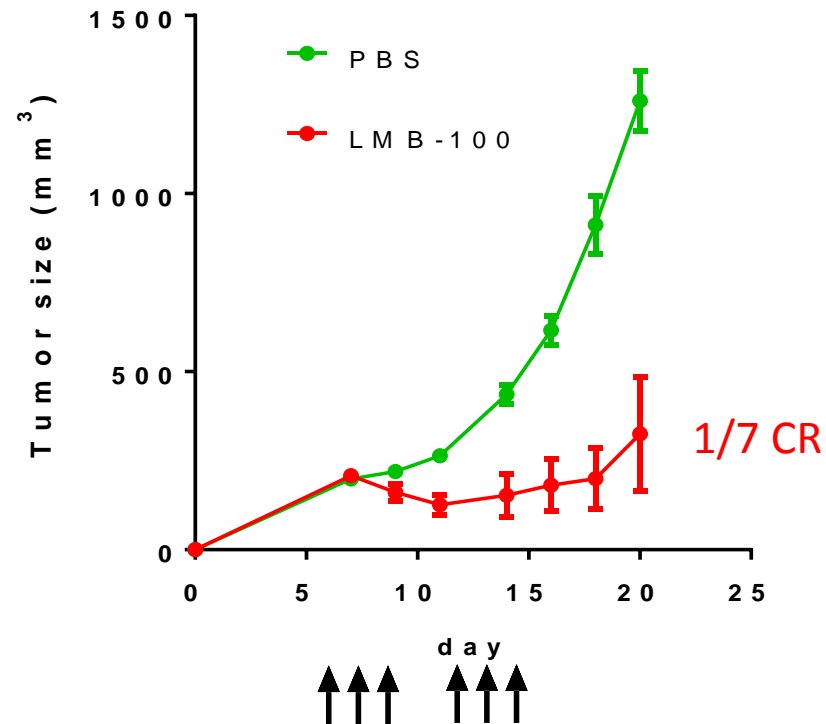
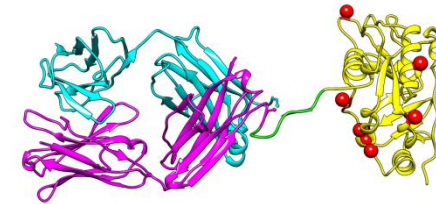
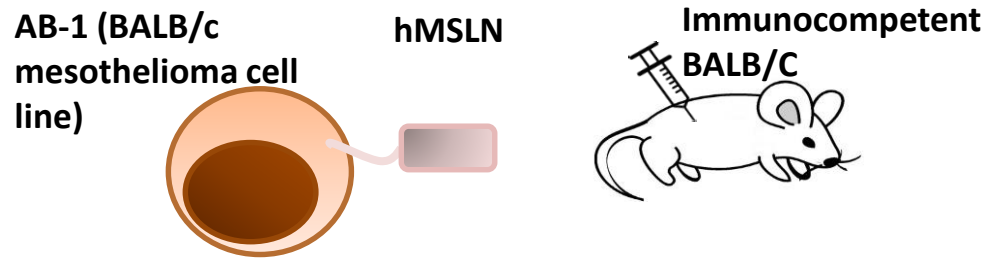
↑↑↑



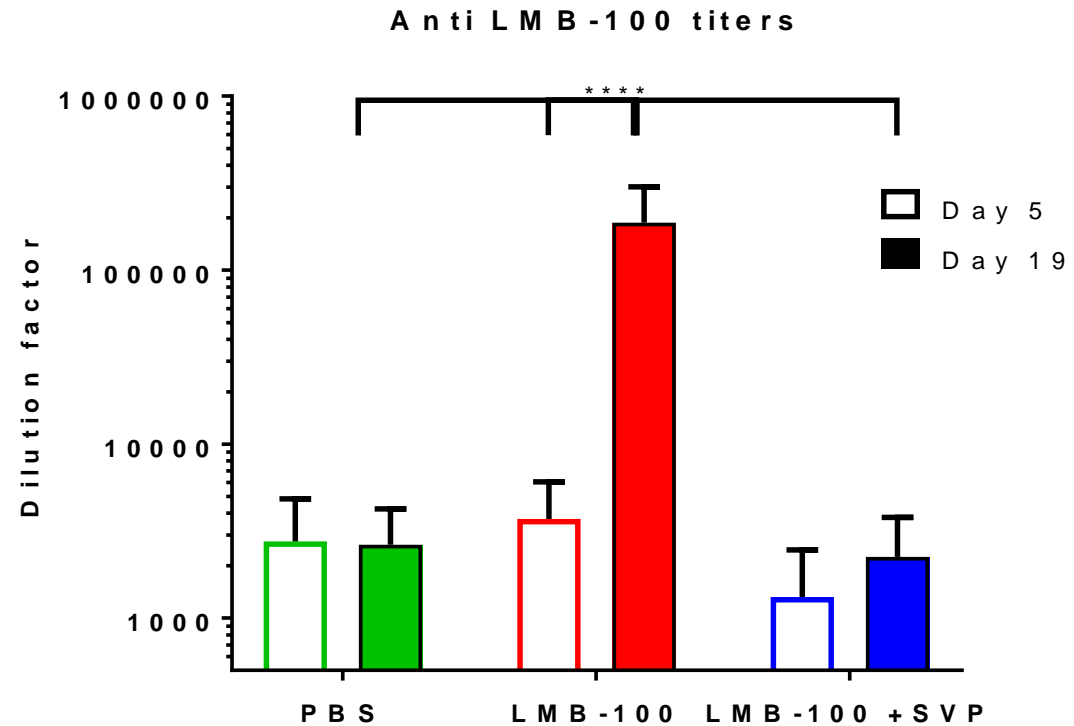
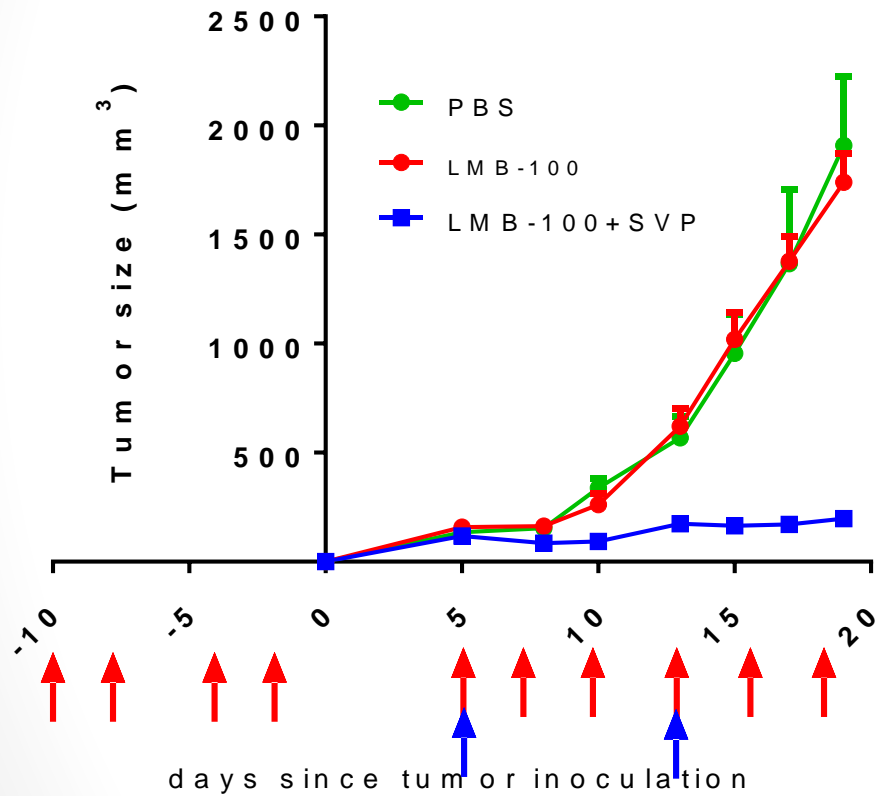
More information on Pre-existing model in Emily king's poster



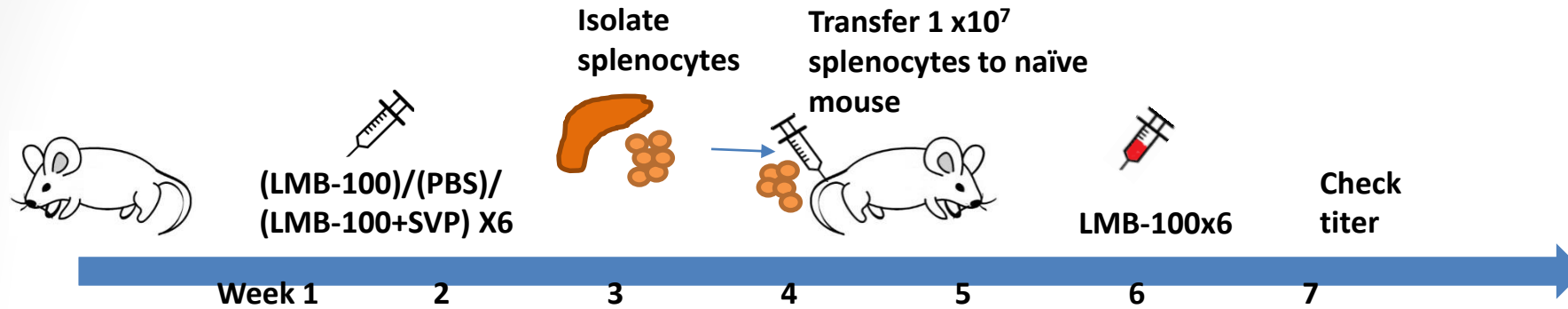
# AB1 hMSLN tumors grow in immunocompetent syngeneic BALB/c mice and are sensitive to LMB-100 (n=7)



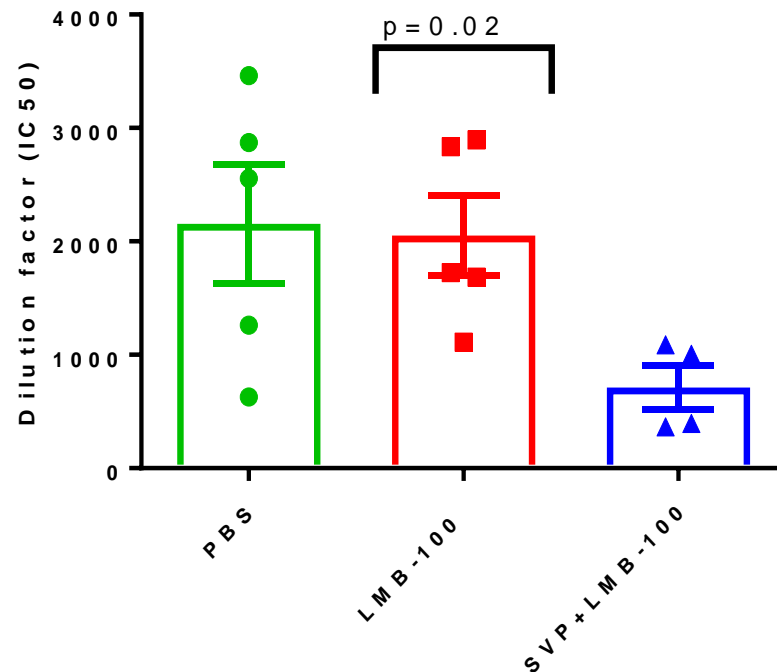
# Combination of LMB-100 with SVP restored the efficacy of LMB-100 (n=7)



# 66% decrease in ADA formation after adoptive transfer of splenocytes treated with combination of SVP and LMB-100

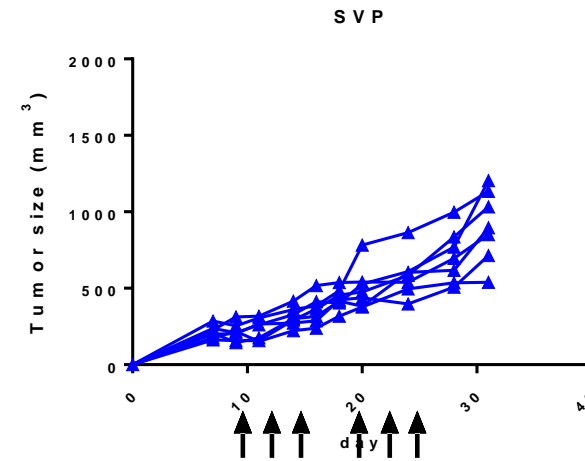
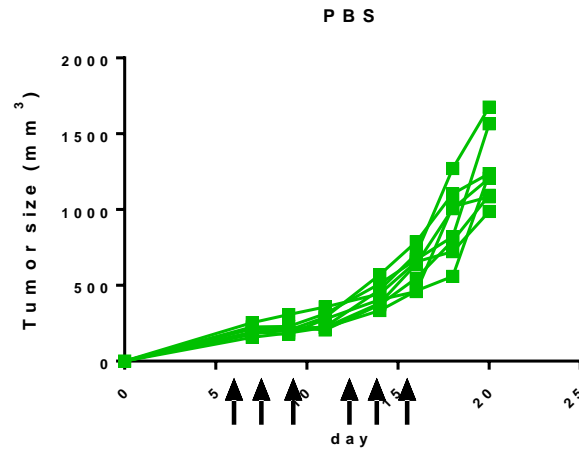


L M B - 1 0 0 A D A t i t e r a f t e r a d o p t i v e t r a n s f e r

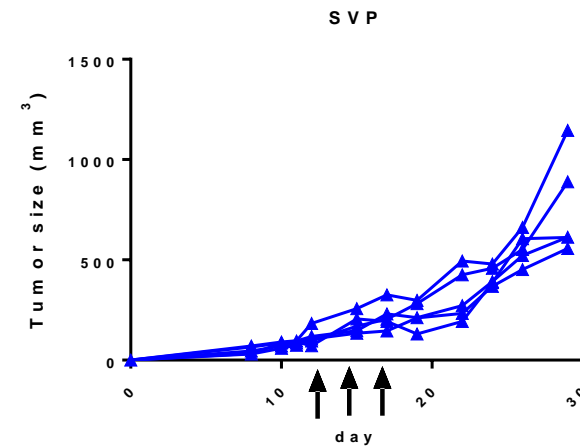
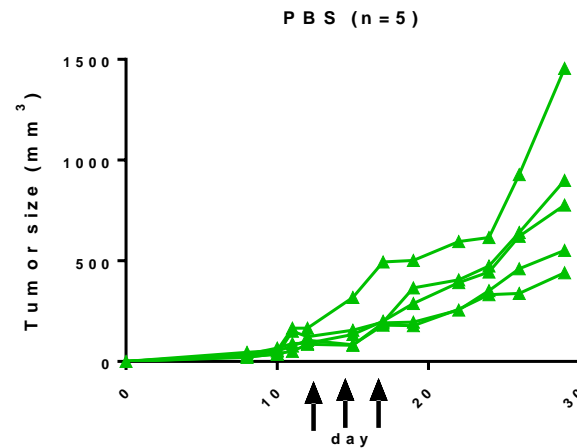


# SVP do not accelerate tumor growth

AB1 mouse  
mesothelioma  
tumor



66c14 mouse  
metastatic breast  
tumors



# Conclusions

- **Combination of LMB-100 with SVP prevents formation of neutralizing ADA**
- **prevents formation of ADA in mice with pre-existing antibodies**
- **The immune tolerance is transferable**

**Combination therapy can make immunotoxins more effective in cancer treatment because more treatment cycles can be given.**

# Acknowledgments

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