

Transgenic Adenocarcinoma of the Mouse Prostate Model TRAMP; PB-Tag Line 8247

Recommended Breeding Scheme

The TRAMP model was generated by direct microinjection of a transgene construct comprised of a -426/+28 bp rat probasin (PB) regulatory element fused to the SV40 early genes (T and t antigen; Tag) into the male pronucleus of a C57BL/6 zygote.

In order to maintain the genetic integrity of the TRAMP model, please adhere to the recommended breeding scheme:

1. Maintain a pure C57Bl/6 heterozygous (hemizygous) colony

To maintain a pure C57Bl/6 heterozygous colony we recommend crossing heterozygous (TRAMP+/-) females with non-transgenic C57BL/6 breeder males. You may cross heterozygous (TRAMP+/-) males with non-transgenic C57BL/6 breeder females, but note that the TRAMP males may be infertile by 18 weeks of age due to obstructions arising as a consequence of prostate disease. Following this simple breeding strategy will ensure the maintenance of a pure C57BL/6 colony. All mice must be screened for the presence of the transgene by recommended PCR based protocols.

2. We do not recommend breeding homozygous mice

Although it is possible to generate homozygous (TRAMP+/+) mice by inbreeding heterozygous TRAMP(+/-) mice, this strategy is NOT recommended because the site of transgene integration in fact represents an insertional event and while chances are slim that the transgene inactivates an essential gene, double (homozygous) transgenix would have the increased possibility of being "double knockouts" at this site (this would severely complicate analysis). Single allele transgenix are at worse heterozygous at the site of integration meaning the "sister" chromosome would still (probably) be wildtype and fully functional. As well, the possibility exists that a divergent inbred strain will be established that will no longer be syngeneic with the TRAMP-C cell lines derived from the TRAMP mice or with other C57BL/6 colonies. Outcrossing the heterozygous C57BL/6 TRAMP(+/-) mice with C57BL/6 breeder mice will prevent such "drift".

3. Crossing TRAMP into other backgrounds

Once a pure C57BL/6 TRAMP(+/-) colony is established, you may generate mice for experimentation in either a) the pure C57BL/6 background or b) in hybrid genetic backgrounds. To date, we have experience with the following backgrounds:

- a. C57BL/6
- b. C57BL/6 x FVB
- c. C57BL/6 x DBA2

4. If I follow these recommendations what can I expect?

If you generate the [C57Bl/6 TRAMP(+/-) x C57Bl/6] F1 mice, you can expect PIN by 12 weeks of age. The tumors will arise by 24 weeks of age mostly in the dorsal and lateral lobes of the prostate. These will appear as well differentiated adenocarcinoma. By 30 weeks of age most mice will display evidence of metastatic spread to the lymph nodes and / or lungs. The mice will also display seminal vesicle invasion and these tumors may also exhibit phylloides appearance. Note that pure C57Bl/6 TRAMP(+/-) mice can live to 52 weeks of age.

If you cross C57Bl/6 TRAMP females to FVB non-transgenic males to generate [50% C57Bl/6 TRAMP(+/-) x 50% FVB] F1 mice you can expect all transgenic males to have primary pathology by 12 weeks or so (see Figure 1). They will display mostly hi grade PIN and some well differentiated prostate cancer. There is unfortunately no way at present to confirm this except for histology. In fact greater than 70% should have very large tumors by 18 weeks with lymph node mets. Some (25%) will also have lung mets. By 30 weeks 100% will have tumors with mets to lymph nodes and approximately 40% will have lung mets too. These mice rarely live beyond 32 weeks of age. Bone mets have been observed in these F1 mice.

5. Other considerations

We do not yet understand the difference between [C57Bl/6 TRAMP(+/-) x C57Bl/6] and the [C57Bl/6 TRAMP(+/-) x FVB] mice (we're working on that), but in both cases the incidence is still 100% tumor and lymph node mets by 30 weeks.

If you decide to generate the [C57Bl/6 TRAMP(+/-) x FVB] F1 mice, we do not recommend using the F1 mice for further breeding because we do not know the consequence of the altered genetic background (i.e. 25%C57/75%FVB vs 75%C57/25%FVB) on incidence or pathology.

To date, the [C57Bl/6 TRAMP(+/-) x DBA/2] F1 mice appear to mimic the phenotype observed with the [C57Bl/6 TRAMP(+/-) x FVB] F1 mice. Please keep us informed of your experiences with these and other crosses.

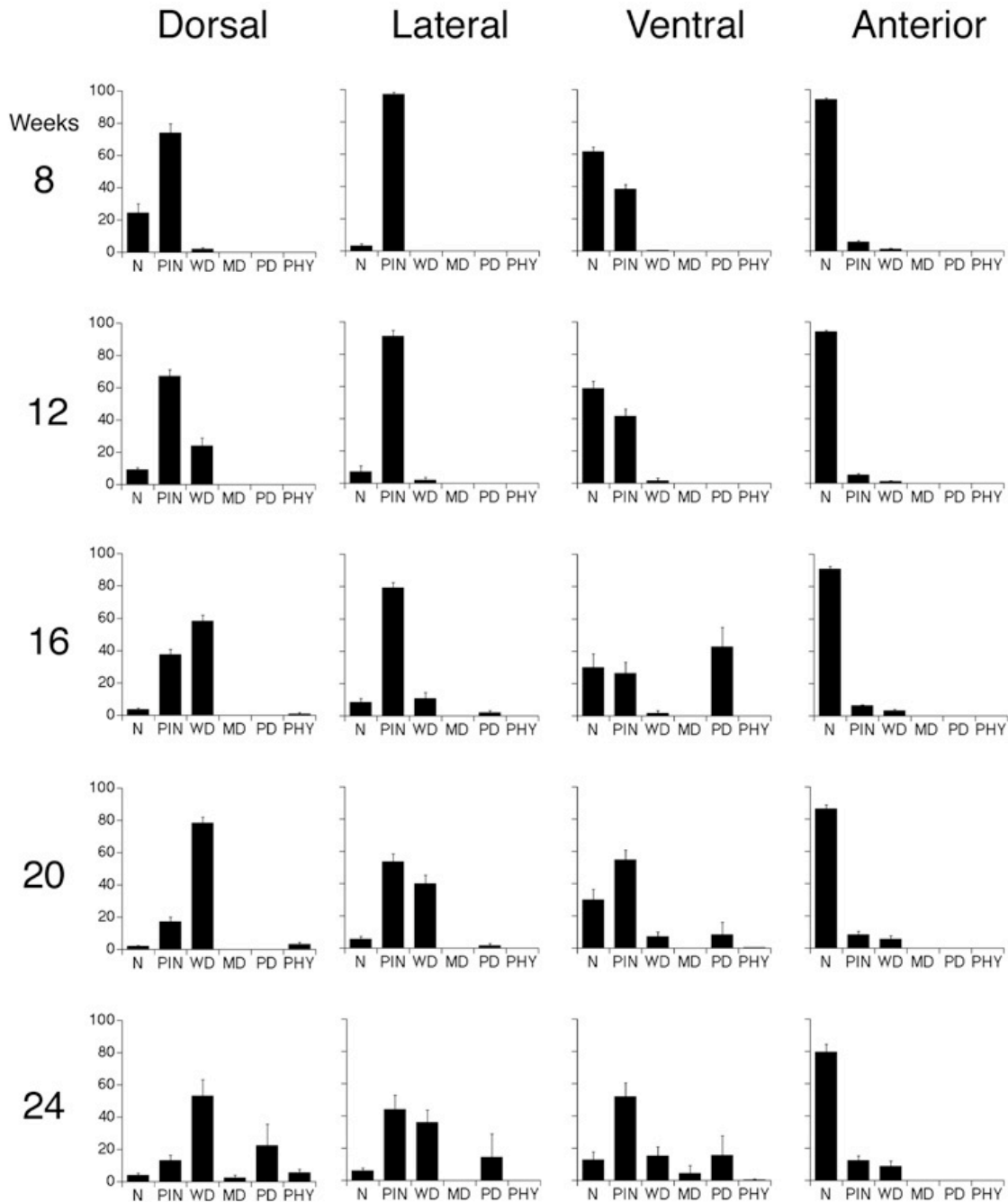


Figure 1. **Distribution of pathologic grade per prostatic lobe in TRAMP mice with age.** H&E stained slides were graded by three independent pathologists. Each prostatic lobe was scored for percentage of each pathological stage present in that lobe. The scores of all graders were averaged. Each graph represents the average percentage (\pm SEM) of each pathologic grade in the dorsal, lateral, ventral and anterior lobes of the prostate in TRAMP mice at 8 (N=10), 12 (N=10), 16 (N=14), 20 (N=13) and 24 (N=9) weeks of age. Pathologic grades: N, normal; PIN, prostatic epithelial neoplasia; WD, well differentiated adenocarcinoma; MD, moderately differentiated adenocarcinoma; PD, poorly differentiated adenocarcinoma; PHY, phylloides-like cancer. From Kaplan-Lefko, et al. *The Prostate* 55:219-237, 2003