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TITLE: Using a Novel Transgenic Mouse Model to Study c-Myc Oncogenic Pathway in Castration Resistance and Chemoresistance of Prostate Cancer

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We previously made a PB-Cre4/Ai-Myc model for Cre-induced and androgen-independent expression of c-Myc and Luc2 in prostate. This is designed for concisely studying castration response and CRPC. However, most mice never developed significant tumors. Here, we showed that ablation of p53 in this model led to rapid growth of prostate tumors (expected based on our hypothesis) but with lethal epididymis tumors (unexpected). To solve this problem, we performed early castration together with testosterone pellet implantations in these mice. The mice were later divided into two groups, the control continued receiving pellet implantations whereas the "castration" group underwent a pellet removal procedure. We observed castration-response as evidenced by greatly reduced BLI signal and a lack of AR nuclear localization in the castrated tumors. However, we did not observe significant difference in overall survival and there were large seminal vesicle tumors associated with most prostate tumors in this model. These made it difficult to concisely assess prostate tumor response to castration. We have designed and will use alternative approaches to address this problem in the near future.
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Introduction

c-Myc is the most significantly amplified oncogene in human prostate cancer (PCa) [1, 2], and its gene amplification is associated with advanced disease grade and worse prognosis [3]. In addition, c-Myc overexpression is common in PCa as early as PIN [4]. These indicate its critical roles in PCa progression as well as in the development of therapy-resistance, such as castration resistance and chemoresistance. Dr. Sawyer’s group has developed the widely used Hi-MYC model using an enhanced probasin promoter to drive c-Myc overexpression in prostate epithelia [5]. These Hi-Myc mice develop invasive prostate carcinomas that share molecular features with human PCa. However, since probasin promoter activity is crucially dependent on androgen, the Hi-Myc tumors lose c-Myc expression after castration [5]. Therefore, the tumor regression in these androgen-depleted Hi-Myc mice represents the mixed effects of an artificial direct effect from loss of oncogene expression and a potential real effect from tumor responses to castration. These greatly complicate the system and make it difficult to concisely study c-Myc oncogenic pathway in androgen signaling, castration-responses, and the development of castration-resistant PCa (CRPC). Accordingly, we have generated the Ai-Myc (for expression of c-Myc and luc2 in any tissue in a Cre-inducible manner) model. After crossing with the PB-Cre4 mice overexpressing Cre in prostate epithelium [6], c-Myc and Luc2 expression will be specifically turned on in the prostate of the male PB-Cre4/Ai-Myc mice (Figure 1). Importantly, once turned on, the c-Myc and Luc2 expression will be driven by the P\textsubscript{CAG} promoter independent on androgen. This will allow us to concisely study c-Myc signaling pathway in (1) castration induced prostate tumor response, (2) the recurrence of CRPC tumors, and (3) the development of chemoresistance in CRPC tumors. The Luc2 expression will label the tumors in this model, which allows real-time in vivo bioluminescence imaging (BLI) for prostate tumor progression, tumor response to various therapeutic agents, and tumor relapse after the development of therapy resistance including castration resistance and chemotherapy resistance. Furthermore, by crossing PB-Cre4/Ai-Myc mice with mouse lines carrying loxP flanked gene of interest, such as p53, we will be able to concisely and efficiently knock out the gene of interest and turn on the expression of c-Myc and Luc2 within the same cell population.

![Figure 1. Diagram of the Ai-Myc transgenic model (expression of c-Myc in any tissue in a Cre-inducible manner).](image_url)

We observed delayed prostate tumor progression as well as apparent prostate epithelial cell death in our PB-Cre4/Ai-Myc model. mPIN, but not invasive prostate tumors were formed in most PB-Cre4/Ai-Myc transgenic mice up to 2 year of age. Since c-Myc overexpression may
induce p53 activation and lead to cell senescence or apoptosis [7], the subject of this grant is to cross our PB-Cre4/Ai-Myc mice with p53loxP/loxP mice [8] to conditionally knock out p53 and overexpress c-Myc in prostate for a rapid onset and progression of prostate tumors, and use these mice to study castration resistance and chemoresistance of PCa. Finally, although mutation or loss of p53 is not a very common event in human PCa at early stage, it is strongly correlated to PCa disease stages, metastasis, and castration-resistance [9, 10]. In fact, p53 is the most significantly altered gene in metastatic castration resistant prostate cancer [11]. Therefore, conditional ablation of p53 in the PB-Cre4/Ai-Myc mice is a valid approach to model a significant fraction of advanced PCa, which is the exact PCa type that should be targeted for our proposed studies on castration-resistance and chemoresistance of PCa.

Keywords:
c-Myc, prostate cancer, castration resistance, chemoresistance, prostate tumor model, Ai-Myc model, PB-Cre4, p53

Overall Project Summary
We observed that conditional ablation of p53 led to a rapid growth of lethal epididymis tumors (unexpected) and a greatly enhanced growth of prostate tumors (predicted based on our hypothesis) in the male PB-Cre4/Ai-Myc/p53loxP/loxP mice (Figure 2). Although our novel Ai-Myc model works as designed (overexpression of c-Myc and Luc2 in a Cre-inducible manner), this unexpected rapid growth of lethal epididymis tumors greatly limited our ability to directly use our model for prostate cancer study. This technical problem resulted from the Cre expression outside of prostate in the PB-Cre4 model; yet, to the best of our knowledge, there is no better model for more accurately targeting prostate epithelial cells. Finally, it is the unexpected Mother Nature that overexpression of c-Myc and loss of p53 lead to lethal epididymis tumor growth in mice. To overcome the rapid growth of lethal epididymis tumors in the PB-Cre4/Ai-Myc/p53loxP/loxP mice, we have modified our mouse model as demonstrated in Figure 5. Using this new research strategy, we have successfully produced lethal prostate tumors without the growth of epididymis tumors in the PB-Cre4/Ai-Myc/p53loxP/loxP mice. Three major tasks were proposed in our SOW.

Major Task1: Characterize the tumor development in the PB-Cre4/Ai-Myc/p53loxP/loxP mice and the control PB-Cre4/Ai-Myc mice. These include Subtasks (1) Generate and expand the population of PB-Cre4/Ai-Myc/p53loxP/loxP mice and PB-Cre4/Ai-Myc mice and (2) Perform full necropsy on mice from each group every two months after the BLI imaging. Collect prostate tissues/tumors for histopathology/immunohistochemistry (IHC), Western blot and/or qRT-PCR analysis.

For Subtask 1, we have crossed male PB-Cre4/Ai-Myc mice with p53loxP/loxP mice to generate the PB-Cre4/Ai-Myc/p53wt/loxP mice. We then crossed the obtained male PB-Cre4/Ai-Myc/p53wt/loxP with p53loxP/loxP mice to generate the targeted PB-Cre4/Ai-Myc/p53loxP/loxP mice for conditional knockout of p53 and overexpression of c-Myc in prostate epithelial cells. We have similarly generated a population of PB-Cre4/Ai-Myc mice, PB-Cre4/p53loxP/loxP mice, and PB-Cre4/Ai-Myc/p53wt/loxP mice as controls.
For Subtask 2, we have observed that the PB-Cre4/Ai-Myc/p53\textsuperscript{loxP/loxP} mice rapidly developed large tumors within 4-5 months. Full necropsy revealed that all mice developed large epididymis tumors that led to early euthanization (IACUC/ACURO approved protocol) and/or death. About 30% of mice also developed large prostate tumors at time of euthanization/death (Figure 2).

Figure 2. Conditional ablation of p53 in the PB-Cre4/Ai-Myc/p53\textsuperscript{loxP/loxP} model induces rapid growth of prostate tumors and lethal epididymis tumors. Representative prostate tissues/tumors and epididymis tissues/tumors from the male PB-Cre4/Ai-Myc/p53\textsuperscript{loxP/loxP} mice at 8, 12, 16, and 21 weeks of age.

We next performed detailed histopathological analysis including H&E staining and IHC staining for AR, c-Myc, E-Cad, and Ki67 on these lethal epididymis tumors as well as the epididymis tissue from the control PB-Cre4/p53\textsuperscript{loxP/loxP} mice. Loss of p53 alone did not significantly alter the histology of epididymis, with apparent normal tissue structure and epithelial cells stained positive for AR and E-Cad, and mostly negative for Ki67 and c-Myc (Figure 3). In contrast, overexpression of c-Myc together with loss of p53 induced largely poorly differentiated tumors that strongly overexpress c-Myc transgene, and are largely negative for AR and E-Cad, and highly proliferative as indicated by high expression of Ki67.

Figure 3. H&E and IHC staining of the epididymis tumor from a 4-month old PB-Cre4/Ai-Myc/p53\textsuperscript{loxP/loxP} mouse (lower panels) and the epididymis tissue from a control age-matched PB-Cre4/p53\textsuperscript{loxP/loxP} mouse (upper panels).
At the time of euthanization due to large epididymis tumor burden, about 30% of the PB-Cre4/Ai-Myc/p53loxP/loxP mice also developed significant prostate tumors, with microscopic prostate tumors and/or mPIN presented in all mice (Figure 4). This is in sharp contrast to the much delayed prostate tumorigenesis in the PB-Cre4/Ai-Myc mice. Detailed histological analysis revealed that these prostate tumors and mPIN foci express high levels of c-Myc transgene, and are positive for AR and E-cad, indicating that they are well differentiated. These prostate tumors and mPIN are also highly proliferative, as indicated by the presence of a large number of Ki67 positive cells. It is interesting that the number of Ki67 positive cells in these prostate tumors (Figure 4) are significantly lower than those in the epididymis tumors (Figure 3), which may partially explain the outgrowth of lethal epididymis tumors over prostate tumors in these PB-Cre4/Ai-Myc/p53loxP/loxP mice. Altogether, these data suggest that as we have predicted, knockout of p53 greatly enhanced prostate tumor progression in our PB-Cre4/Ai-Myc model, although the outgrowth of lethal epididymis tumors greatly limited our ability to directly use it to study prostate cancer, therapy response, and therapy resistance.

Figure 4. H&E and IHC staining of the prostate tumor from a 4-month old PB-Cre4/Ai-Myc/p53loxP/loxP mouse. Both mPIN (upper panels) and invasive prostate tumor loci (lower panels) are presented.

Although PB-Cre4 transgenic mice have been extensively used in prostate tumor modeling and research, we have observed significant off-target Cre activity in the epididymis. This resulted in overexpression of c-Myc and knockout of p53 in the epididymis, which led to extensive cell proliferation and rapid growth of the lethal epididymis tumors in our PB-Cre4/Ai-Myc/p53loxP/loxP model (Figure 3). However, tumor of epididymis is a rare type of cancer in human, and most of them are benign. Therefore, this may significantly limit the potential clinical application of our model as a model of epididymis tumor.

The rapid growth of tumors from epididymis has brought a significant technical problem when directly using our PB-Cre4/Ai-Myc/p53loxP/loxP mice to study prostate cancer, therapy response, and therapy-resistance as we have proposed in Major Tasks 2 and 3. Therefore, we proposed to perform castration to remove testis and epididymis altogether in the young PB-Cre4/Ai-Myc/p53loxP/loxP mice at 6-week old. This will eliminate the concerns on epididymis tumors. We also proposed to perform subcutaneous implantation of testosterone pellets to continue supporting prostate tumor growth. We have re-written the animal protocol to include such procedures, and received approvals from the local IACUC and the USAMRMC ACURO.
Figure 5. Scheme of the surgical manipulations on the male PB-Cre4/Ai-Myc/p53<sup>loxP/loxP</sup> mice.

**Major Task 2:** Study how the PB-Cre4/Ai-Myc/p53<sup>loxP/loxP</sup> prostate tumors respond to castration and the molecular signatures of castration resistance of these tumors. These include Subtask (1) At time to be optimized, PB-Cre4/Ai-Myc/p53<sup>loxP/loxP</sup> mice will be performed castration or sham operated. Prostate tumors will be collected for histopathology/IHC, Western blot and/or qRT-PCR analysis for their acute response to castration and the development of castration-resistant prostate tumors. Subtask (2) cDNA Microarray will be performed on the above tumors for the molecular signature of castration-resistant prostate tumors.

As outlined in Figure 5, we have performed surgical manipulations on the male PB-Cre4/Ai-Myc/p53<sup>loxP/loxP</sup> mice to prevent growth of lethal epididymis tumors. In brief, we performed castration surgery on the male PB-Cre4/Ai-Myc/p53<sup>loxP/loxP</sup> mice at 6-week of age. The epididymis is fully removed during this procedure, which prevents the otherwise outgrowth of lethal epididymis tumors. To provide androgen ligand supporting prostate tumor growth, androgen pellets (testosterone at 25 mg/pellet, one pellet per mouse) were implanted subcutaneously into the castrated mice, initially at 6-week and re-implanted at 11-week of age. At 16-week of age, the castrated and androgen pellet implanted mice were randomly divided into two groups. The control group continued receiving a third androgen pellet implantation and the experimental group underwent a "pellet-removal" surgical procedure that removed any observable leftover of the previously implanted pellet. We use this pellet removal procedure to simulate "castration" in these castrated/androgen pellet implanted PB-Cre4/Ai-Myc/p53<sup>loxP/loxP</sup> mice.

We have observed that the castrated/androgen pellet implanted PB-Cre4/Ai-Myc/p53<sup>loxP/loxP</sup> mice developed observable prostate tumors in about 16 weeks and by 24-weeks all mice have to be sacrificed due to large tumor burden (n=21) and/or died with confirmed presence of prostate tumors (n=2). We performed weekly BLI imaging after 16-week. As expected, the BLI signal in these mice mostly increased/maintained indicating growth of prostate tumors (Figure 6). However, we did observe that BLI signal in some mice decreased shortly
before or at the conclusion of the study and we suspect that this decrease is at least partially due to poor accessibility of the luciferin substrate into large prostate tumors. Full necropsy revealed that these mice (n=21 available for the last BLI imaging and fresh tissue collection) developed large prostate tumors with gross metastases to lung, lymph nodes and/or other tissues as evidenced by BLI imaging (Figure 6).

We also observed extensive involvement of greatly enlarged seminal vesicle and growth of seminal vesicle tumors associated with prostate tumors in about 90% of mice (Figure 7). This has brought some technical issues in our studies as discussed below.

To assess prostate tumor response to castration, as described above (Figure 5), we performed BLI imaging on all mice before the androgen pellet removal surgeries at 16-week. We
then performed weekly BLI imaging on the "castrated" mice after surgery. We observed greatly decreased BLI signal in most "castrated" mice, indicating a "castration" response of these prostate tumors. This was followed by increased BLI signal to various extents until the conclusion of the study (Figure 8). Of the 23 experimental mice, 22 were sacrificed due to large tumor burden and one died with confirmed presence of prostate tumors.

**Figure 8.** Weekly bioluminescence imaging (BLI) on castrated/androgen pellet implanted male PB-Cre4/Ai-Myc/p53loxP/loxP mice after removal of androgen pellet at week 16. Day 0 indicates BLI imaging performed before "pellet-removal" / "castration". BLI imaging was also performed on mice after full necropsy. BLI signal indicated primary prostate/seminal vesicle tumors and metastatic tumors. Upper panel: A representative mouse without gross metastasis. Lower panel: A representative mouse with metastasis indicated by BLI signal outside of prostate/seminal vesicle tumor. PT: prostate tumor; SV: seminal vesicle tumor; H&L: heart and lungs; LI: Liver; KI: kidney; IN: intestine; SP: spleen; ST: stomach, GI: Gastrointestinal tract.

Although we observed greatly decreased BLI signal intensity in prostate tumors in the "castrated" mice, to our surprise, there is no significant change in overall survival between the "castrated" group and the control group (data not shown). The tumors we collected in the "castration" group tend to be smaller, which may partially contribute to this observation (data not shown). We further confirmed this castration-response by demonstrating a lack of AR nuclear translocation in the "castrated" prostate tumors (Figure 9). However, since there was a great involvement of seminal vesicle tumors in the majority of prostate tumors in this model (such as the representative prostate/seminal vesicle tumor in Figure 7), it is very difficult to concisely assess the prostate tumor response to "castration". Therefore, the nature of the current apparent lack of significant therapeutic effect of "castration" remains to be determined. Further studies are needed to carefully evaluate the "castration" response of these prostate tumors.
Figure 9. Representative H&E and AR staining on the control and "castrated" prostate tumors. Upper panel: AR and H&E staining on a representative prostate tumor from an androgen pellet implanted (control) mouse. Lower panel: AR and H&E staining on a representative prostate tumor from an androgen pellet removed ("castrated") mouse.

Major Task 3: Study how the castration-resistant PB-Cre4/Ai-Myc/p53loxP/loxP prostate tumors respond to chemotherapy (docetaxel) and the molecular signatures of chemoresistance of these tumors. These include Subtask (1) PB-Cre4/Ai-Myc/p53loxP/loxP mice with castration-resistant prostate tumors will receive weekly intravenous administration of docetaxel or solvent control. Prostate tumors will be collected for histopathology / IHC, Western blot and/or qRT-PCR analysis for their acute response to chemotherapy and the development of chemo-resistant prostate tumors. Subtask (2) cDNA microarray will be performed on the above tumors for the molecular signature of chemo-resistant CRPC tumors.

As discussed above, it remains to be determined whether clinical relevant CRPC tumors (such as prostate tumors underwent great regression followed by recurrence together with prolonged host survival) have been obtained in our model, which is the basis for the proposed studies in Major Task 3. In addition, we have observed unexpected growth of large seminal vesicle tumors along with prostate tumors even in our modified model (Figure 7), which significantly complicated the system. Therefore, no study has been carried out directly on these PB-Cre4/Ai-Myc/p53loxP/loxP mice in Task 3.

To directly investigate the growth, castration-response, the intrinsic or acquired resistance to castration, and tumor response to chemotherapy and the development of chemoresistance of "pure" prostate tumors in the absence of large seminal vesicle tumors, although out of the scope of this grant, we are alternatively in the process of establishing multiple mouse derived xenograft (MDX) models directly from freshly collected prostate tumors from the male PB-Cre4/Ai-Myc/p53loxP/loxP mice. Specifically, we have successfully established a MDX model from a piece of a small prostate tumor from a male PB-Cre4/Ai-Myc/p53loxP/loxP mouse sacrificed due to large epididymis tumor burden. This small piece of prostate tumor (free of epididymis tumor and seminal vesicle tumor) was implanted subcutaneously into a male FVB mouse (syngeneic host,
Figure 10A and data not shown). 45 days after implantation, a MDX tumor of 2.6 grams with bright BLI signal was obtained (Figure 10B). This has provided the proof-of-concept study for generating "pure" prostate tumor (without seminal vesicle tumors and/or epididymis tumors) using this approach.

Figure 10. A mouse-derived xenograft (MDX) model for studying growth, therapy response, and therapy-resistance of "pure" prostate tumors induced by overexpression of c-Myc and loss of p53. (A) A small prostate tumor from a male PB-Cre4/Ai-Myc/p53^{loxP/loxP} mouse sacrificed due to large epididymis tumor burden was sliced into small pieces and implanted subcutaneously into male FVB mice (one piece per site). (B) The growth of a MDX prostate tumor with confirmed BLI signal in a male FVB mouse.

Although out of the scope of this grant, we will similarly establish multiple lines of MDX models of PCa from multiple male PB-Cre4/Ai-Myc/p53^{loxP/loxP} mice. This will create an animal hospital with "patients" with prostate tumors induced by overexpression of c-Myc and loss of p53. We will then carefully examine the castration-response, the potential development of castration-resistance of these "pure" prostate tumor xenografts in these syngeneic hosts. We will then perform weekly intravenous administration of docetaxel or solvent control into the host mice with established prostate MDX xenografts with intrinsic or required resistant to castration (to be determined), and investigate how these MDX xenografts respond to chemotherapy and the development of chemo-resistance.

Key Research Accomplishments

- Generation of the PB-Cre4/Ai-Myc/p53^{loxP/loxP} mice along with various controls for Cre-mediated knockout of p53 and overexpression of c-Myc in prostate epithelia.

- Characterized tumor progression in the PB-Cre4/Ai-Myc/p53^{loxP/loxP} mice and identified the unexpected rapid growth of the lethal epididymis tumors along with prostate tumors.

- Characterized the histopathology of the epididymis tumors and prostate tumors, including H&E staining and IHC staining for c-Myc, AR, E-Cad, and Ki67 etc.

- Designed, developed, and optimized the new research strategy, which allows the development of lethal prostate tumors in the male PB-Cre4/Ai-Myc/p53^{loxP/loxP} mice by
successfully preventing the development of lethal epididymis tumors. This involved early castration to fully remove testis and epididymis at 6-week of age, initial testosterone pellet implantation at 6-week, and pellet re-implantation at 11- and 16-week.

- Designed and optimized the protocol to simulate castration in the castrated/testosterone pellet implanted male PB-Cre4/Ai-Myc/p53$^{loxP/loxP}$ mice by removal of testosterone pellet at 16-week.

- Successfully demonstrated a castration-response of prostate/seminal vesicle tumors as evidenced by greatly decreased BLI imaging signal in the "pellet-removed"/"castrated" mice.

- Characterized the histopathology of the prostate tumors and confirmed a lack of AR nuclear localization (indicating lack of AR activation) in the prostate tumors from the "pellet-removed"/"castrated" mice.

- Designed an alternative approach to generate mouse-derived xenograft (MDX) prostate tumor model from the PB-Cre4/Ai-Myc/p53$^{loxP/loxP}$ mice. The MDX xenografts ("pure" prostate tumor xenografts) will be passaged in syngeneic hosts (FVB mice) for future investigation on the growth, castration-response, the intrinsic or acquired resistance to castration, and tumor response to chemotherapy and the development of chemoresistance.

**Conclusion**

We have carried out detailed studies on the tumorigenesis in the PB-Cre4/Ai-Myc/p53$^{loxP/loxP}$ mice (lethal epididymis tumors and rapidly growing prostate tumors). Due to the unexpected technical problem, the outgrowth of lethal epididymis tumors greatly limited our ability to directly use our model for prostate cancer study. Please note, our novel Ai-Myc model works as designed (overexpression of c-Myc and Luc2 in a Cre-inducible manner). This technical problem resulted from the Cre expression outside of prostate in the PB-Cre4 model; yet, to the best of our knowledge, there is no better model for more accurately targeting prostate epithelia. In addition, it is the un-predicted Mother Nature that overexpression of c-Myc and loss of p53 led to lethal epididymis tumor growth in mice. Accordingly, we have designed, developed and optimized a new research strategy by performing early castration together with testosterone pellet implantations. This allows the development of lethal prostate tumors in the PB-Cre4/Ai-Myc/p53$^{loxP/loxP}$ mice without interruption from the epididymis tumor. We have also demonstrated a castration-response of the obtained prostate/seminal vesicle tumors as evidenced by greatly reduced BLI imaging signal after androgen pellet removal/"castration". We further confirmed this castration-response by demonstrating a lack of AR nuclear translocation in the "castrated" prostate tumors. However, since there was great involvement of seminal vesicle tumors in the majority of prostate tumors in this model (such as the representative prostate / seminal vesicle tumor in Figure 7), it is very difficult to concisely assess the prostate tumor response to "castration". In addition, we did not observe significant difference in overall survival between the control and the "castrated" groups although the BLI imaging clearly indicating castration-responses. Currently, it remains unclear on the nature of the apparent "castration"
responses of these prostate tumors and whether the clinically relevant CRPC tumors have been generated in our model. Finally, we have designed a new strategy to generate the mouse-derived xenograft (MDX) prostate tumor model from the PB-Cre4/Ai-Myc/p53\textsuperscript{loxP/loxP} mice. The MDX xenografts ("pure" prostate tumors free of epididymis tumors and seminal vesicle tumors) will be passaged in syngeneic hosts (FVB mice) for future investigation on the prostate tumor growth, castration-response, the prostate tumor intrinsic or acquired resistance to castration, and prostate tumor response to chemotherapy and the development of chemoresistance.

Publications, Abstracts, and Presentations:

Publications:


Abstracts and Presentations:


Inventions, patents and licenses: Nothing to report

Reportable Outcomes: Nothing to report

Other Achievements: Nothing to report
References:


Appendices: None