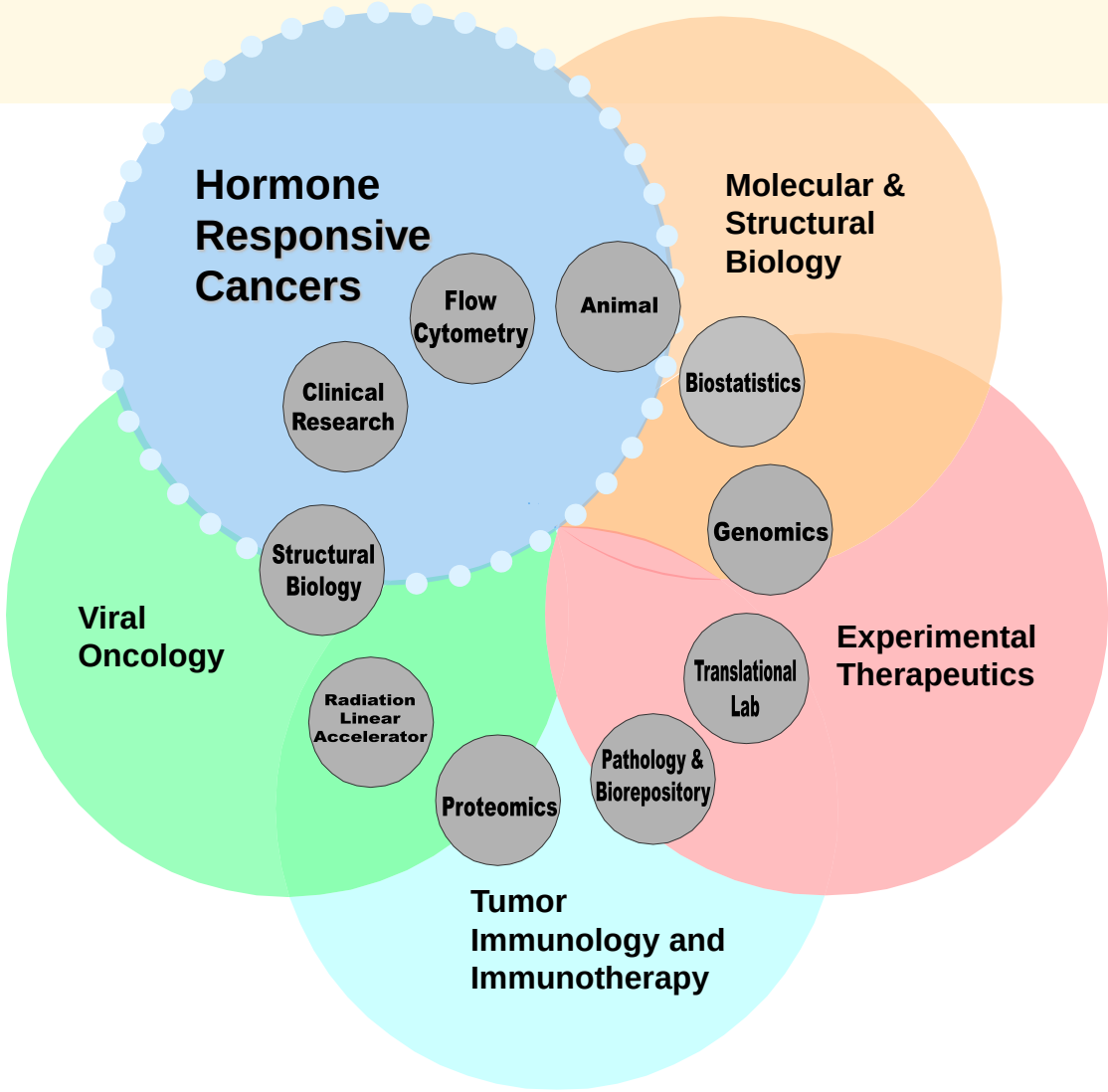
Hormone Responsive Cancers



Maryland State Council on Cancer Control

Amy Fulton, Ph.D.

December 5, 2012

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Discovery & Development of a Multi-mechanistic Agent VN/124-1 (TOK-001 or Galeterone) for Prostate Cancer Therapy

Inventors: Vincent C. O. Njar, Ph.D., Professor
&
Angela M. H. Brodie, Ph.D., Professor

Department of Pharmacology &
Center for Biomolecular Therapeutics (CBT)

Prostate Cancer

- Most common cancer in males worldwide
- Advanced prostate cancer remains incurable despite significant advances in treatment options
- Identification of new strategies (prevention and therapy) are needed

Prostate Cancer & Androgens

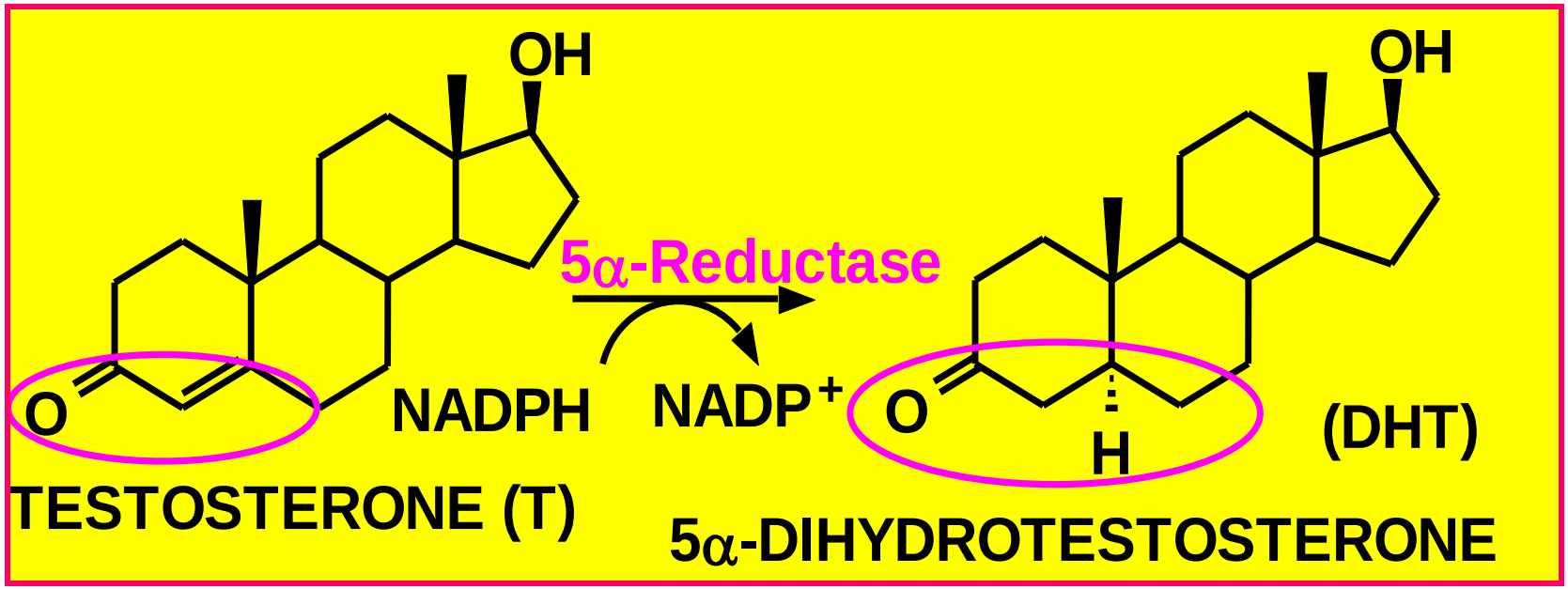
- ~ 90% Prostate cancers are androgen-dependent
- Blockage of androgen action = Effective treatment strategy

- Surgical castration/use of GnRH (LHRH) = current "gold standard" for therapy
  - *Eliminates testosterone production from testes but not from adrenals*

- Combination therapy: GnRH + antiandrogens – more effective

Androgens

- Steroids (testosterone and DHT) that stimulate male characteristics
- Implicated in prostate cancer progression

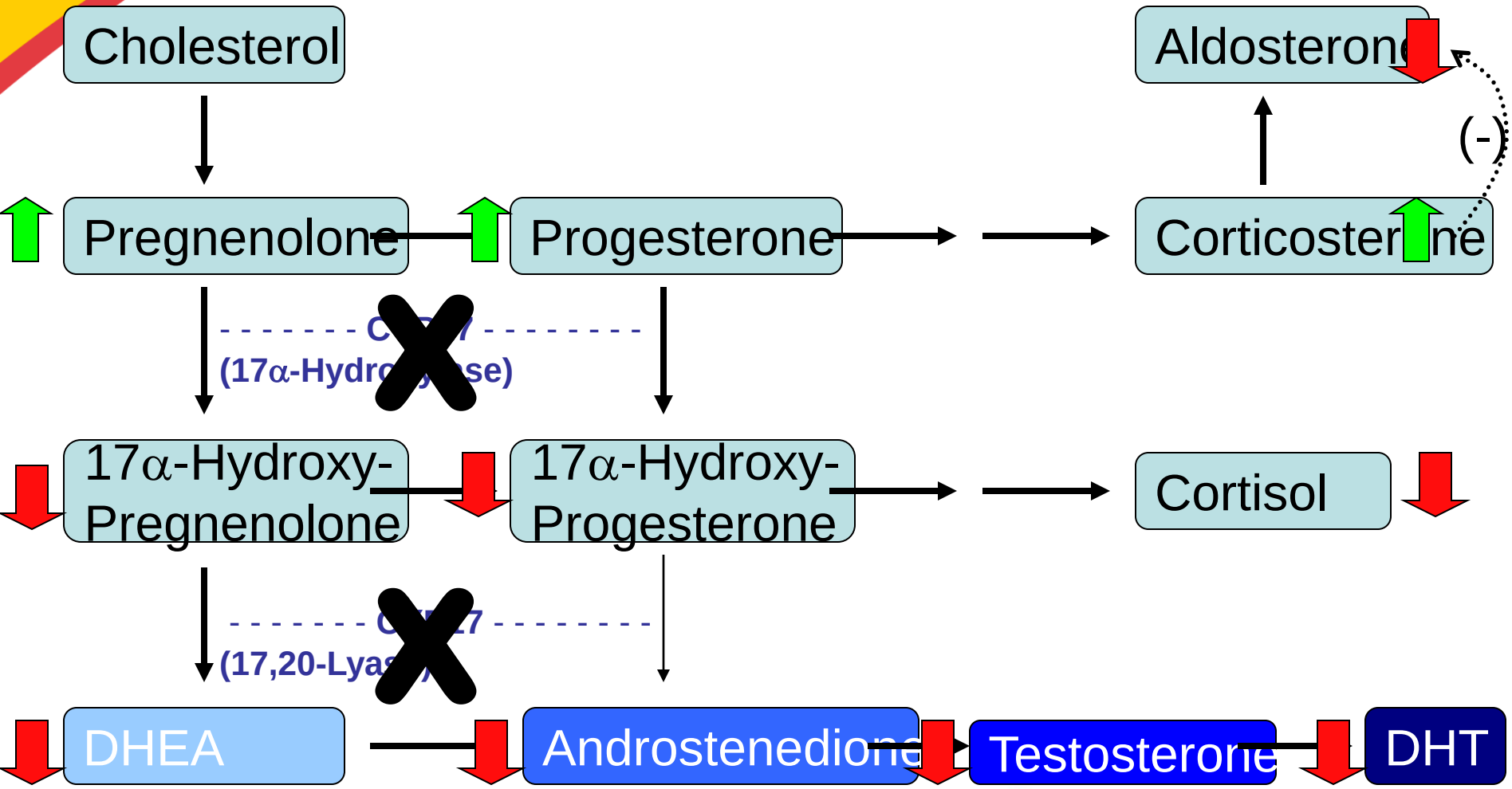


PCA Recurrence Following Anti-Hormonal Therapy

- Reasons advanced for PCA recurrence
  - Androgen receptor (AR) mutation
  - AR gene amplification and/or over expression
  - Androgen independent activation of AR

- However, **anti-hormonal therapies** produce most beneficial responses in multiple settings in PCA patients

Steroidal Biosynthetic Pathway



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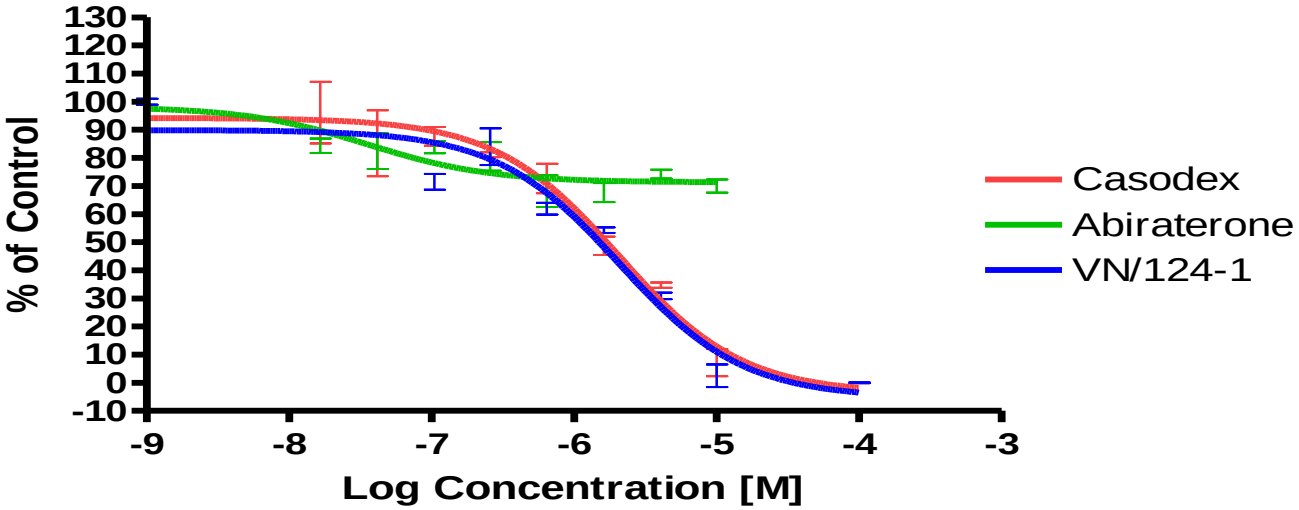
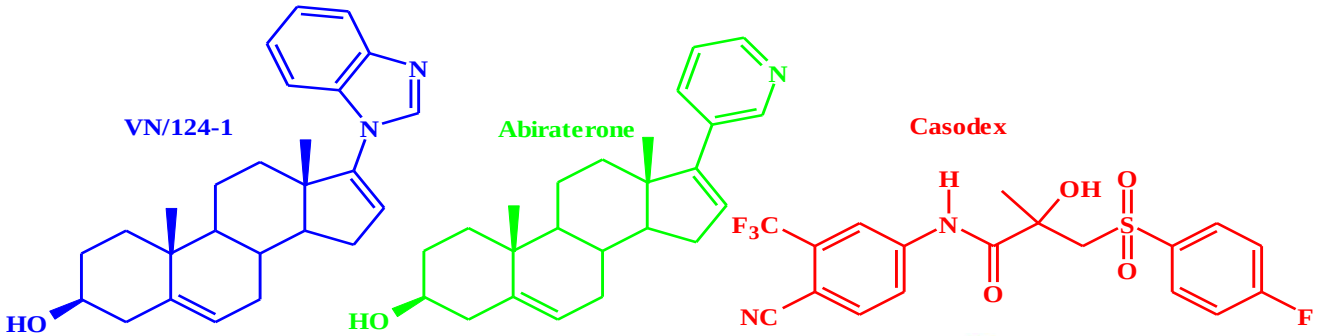
University of Maryland
Marlene and Stewart Greenebaum Cancer Center

Relative Binding Affinity Casodex, VN/124-1 & Abiraterone to Androgen Receptor (Wild-type)





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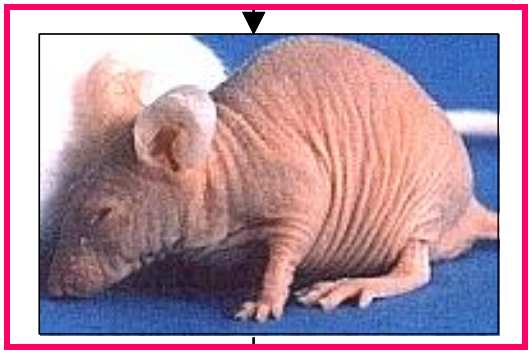
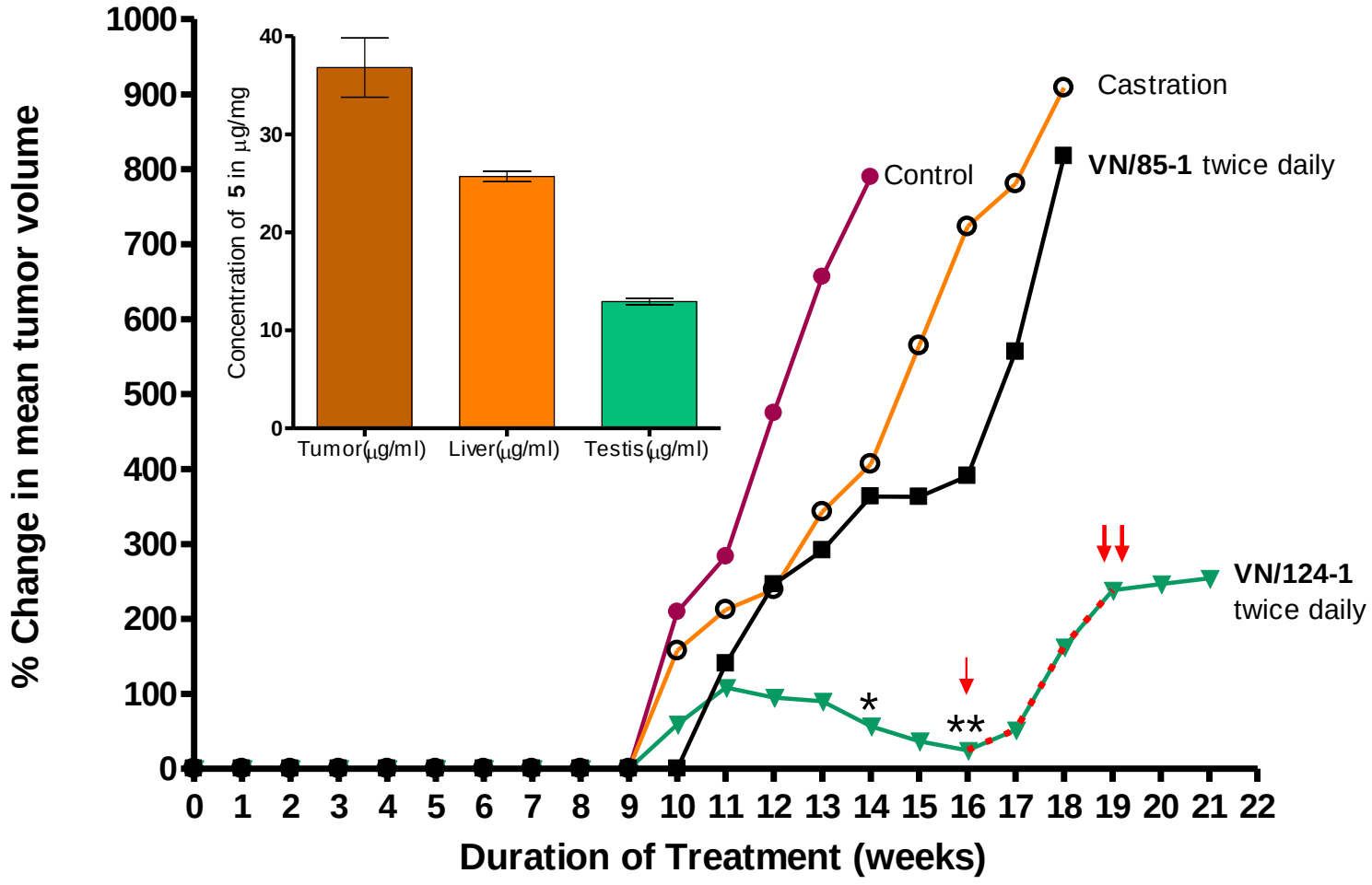
Antitumor Studies – Human LAPC4 Tumors in Male SCID Mice



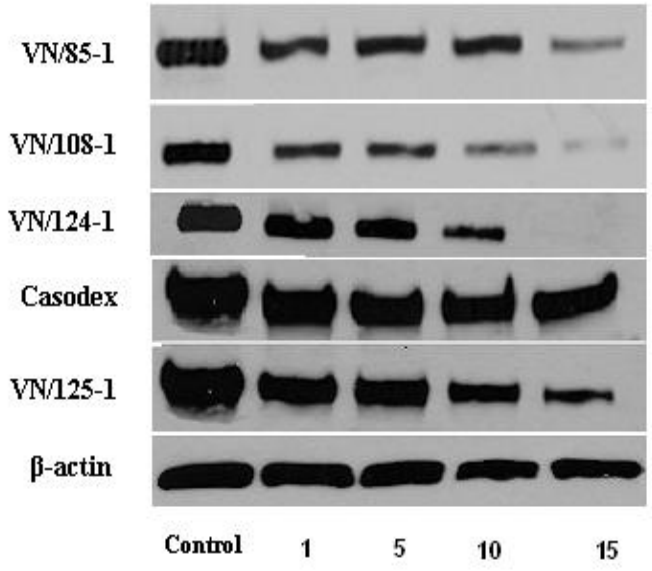
- Wild type androgen receptors (AR)
- Mice inoculated with LAPC4 cells/2 sites (n = 5 per group)
- Tumors ~ 300 mm^3
- Treated with 50 mg/kg, sc (x1 or x2) for 28 days

Effects of Castration, VN/85-1 & VN/124-1 on Formation & Growth of LAPC4 Tumor Xenografts

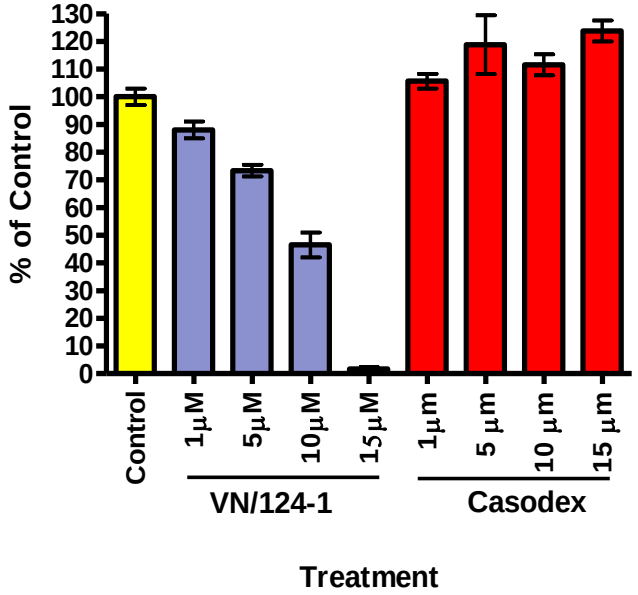


VN/124-1 Unlike Casodex Induces AR Degradation in LNCaP & LAPC-4 Cells

AR Expression in LNCaP cells after 24 h treatments



AR Protein Expression in LNCaP Cells Treated with VN/124-1 and Casodex



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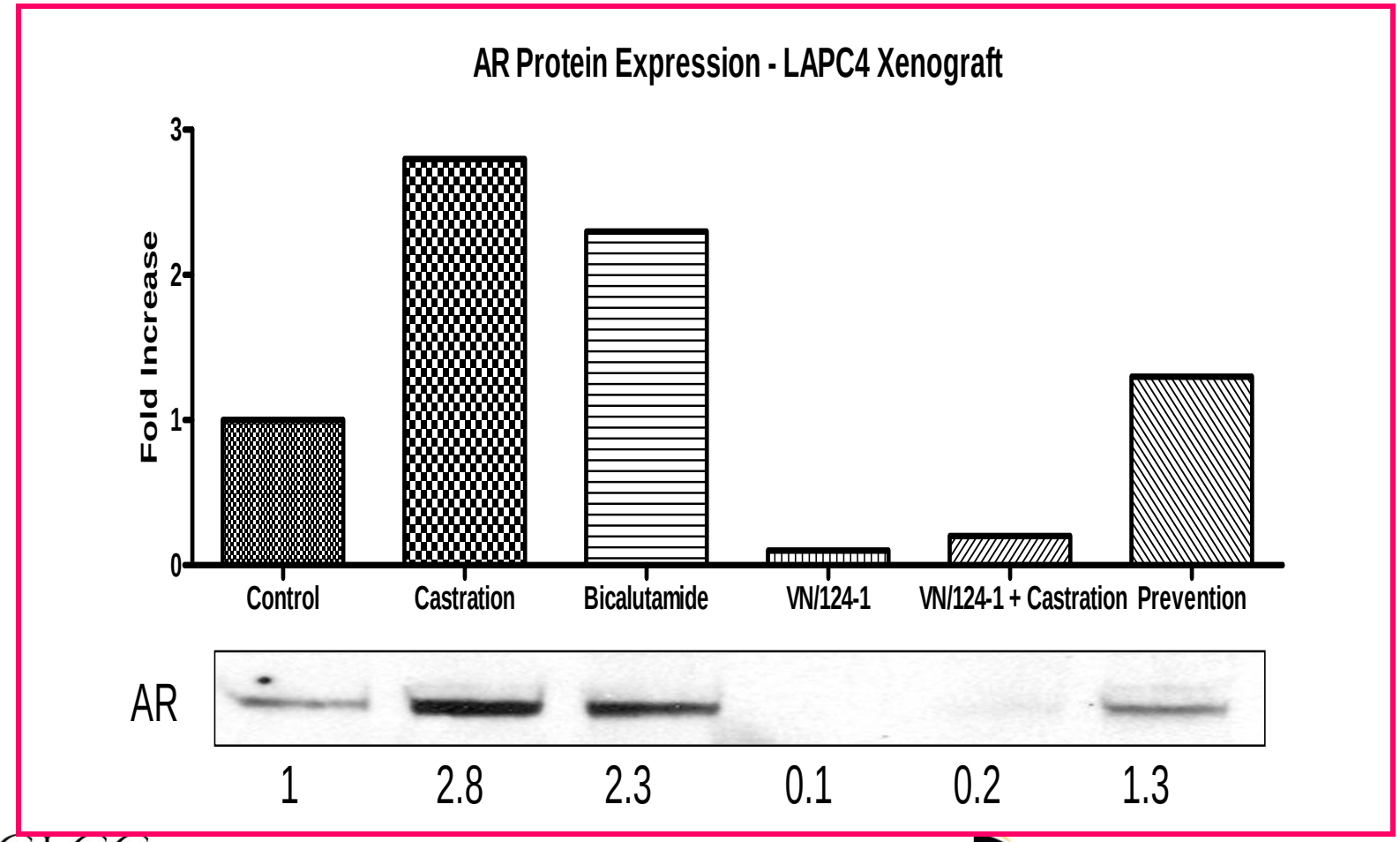
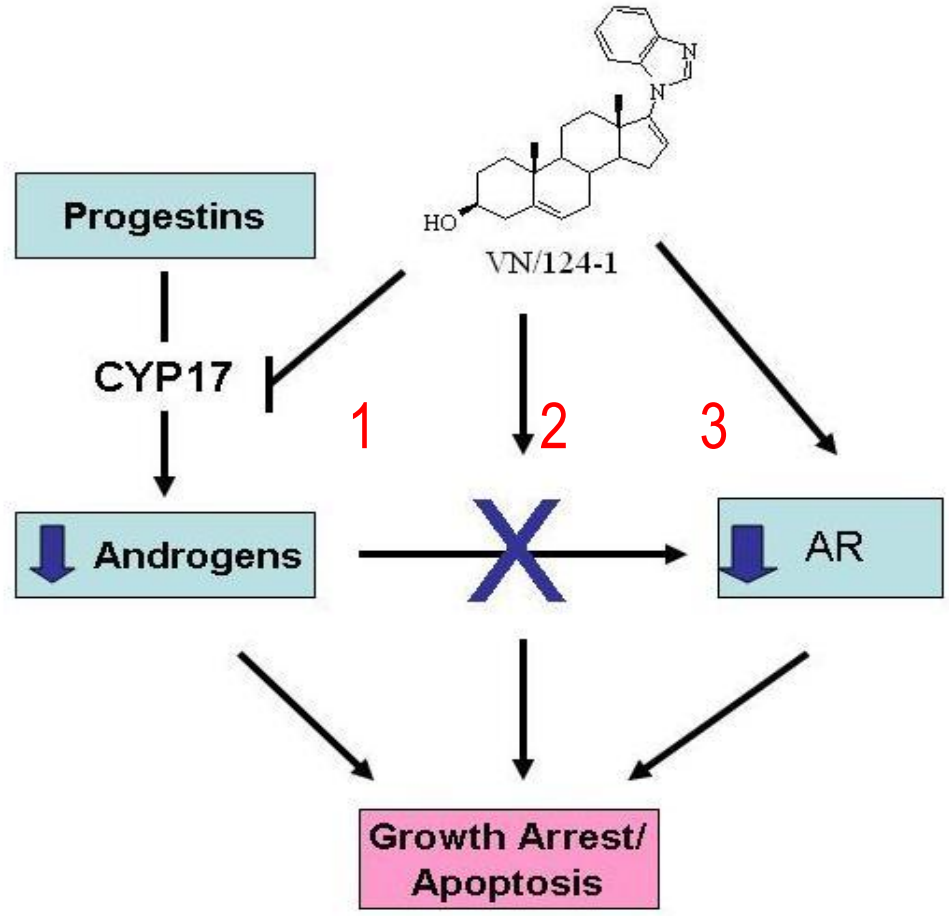
Vasaitis et al., Mol. Cancer Ther., 2008, 7: 2348-2357

Androgen Receptor (AR) Protein Expression from LAPC4 Tumors Following Various Treatments

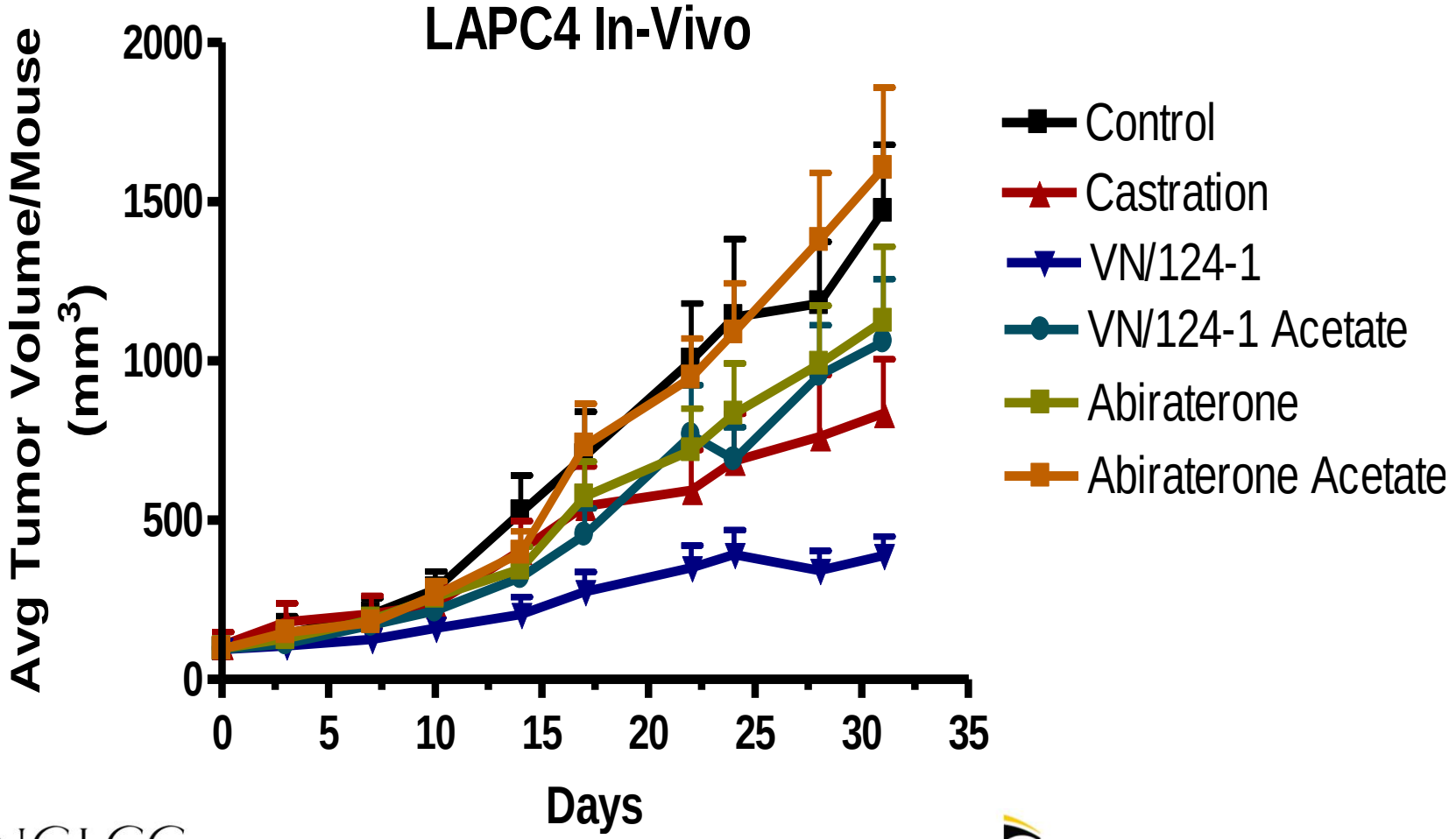


Vasaitis et al., *Mol. Cancer Ther.*, 2008, 7: 2348-2357

Multiple Mechanisms of VN/124-1 Inhibition Along Androgen Axis



Effects of VN/124-1 & Abiraterone on Growth of LAPC-4 Tumors *In Vivo*



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*Bruno RD et al., Steroids, **2011**, 76: 1268-1279*

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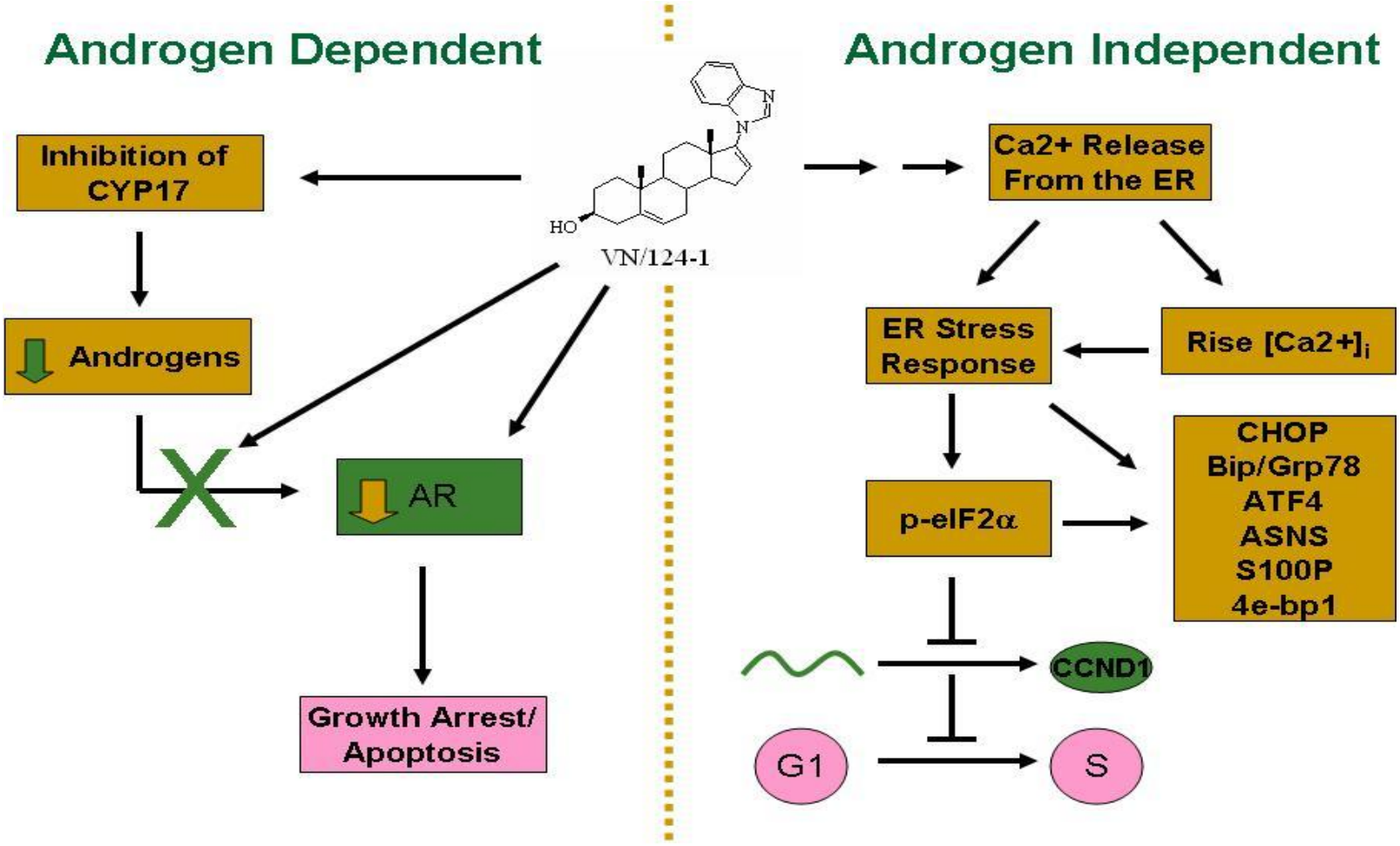
Androgen-dependent & -independent Mechanisms of Action of VN/124-1



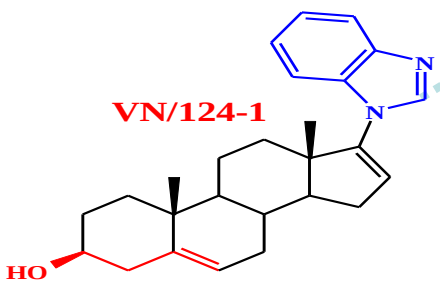
VN/124-1 May be Effective Treatment at All Stages of PCA Development

Radiation Therapy
Radical Prostatectomy

New Therapeutics
Proteasome inhibitors
(ARDA's)

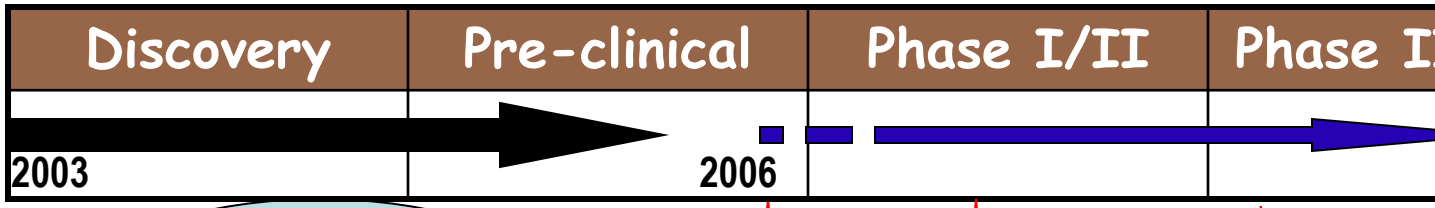
Chemotherapy
Docetaxel-based

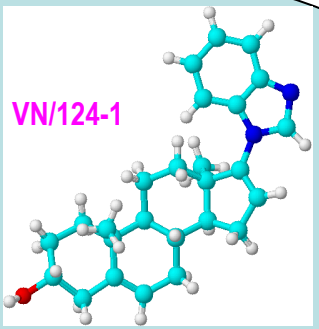
localized prostate cancer	recurrent cancer (rising serum PSA)	metastatic prostate cancer	Castration refractory cancer (rising serum PSA)	metastatic androgen-independent cancer



Development of VN/124-1 for the Treatment of Prostate Cancer: VN/124-1 Technology

- **Licensed to Tokai Pharmaceuticals Inc., Cambridge, Mass., USA - 2006**





Potent CYP17 inhibitor endowed with multiple desirable anti-prostate cancer activities

Tokai License of Technology

November 5, 2009 *(Completed)*

4th quarter of 2012

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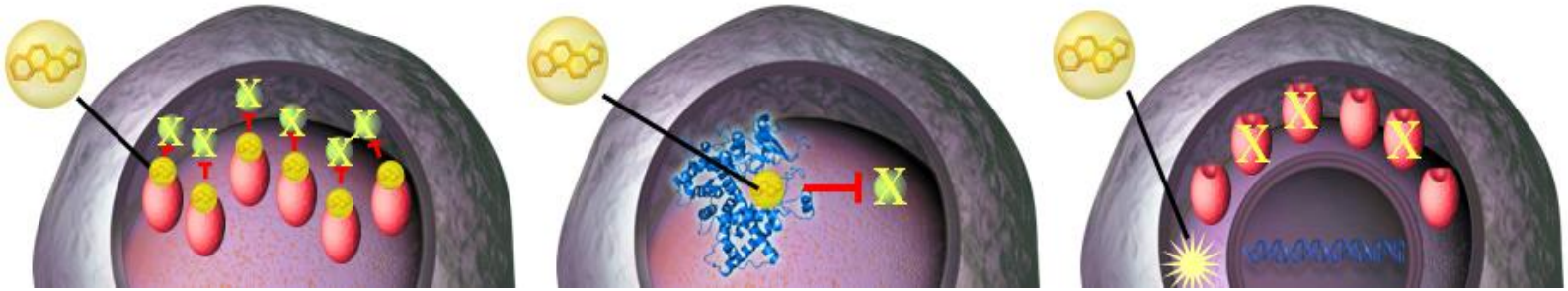
Galeterone (TOK-001 or VN/124-1)

- Oral small molecule for treatment of Castration Resistant Prostate Cancer (CRPC)
- Tokai licensed technology from University of Maryland, Baltimore in 2006
  - Inventors: Vincent C. O. Njar, Ph.D. & Angela M. H. Brodie, Ph.D.
- Three Mechanisms of Action (MOA):

Androgen Receptor (AR) antagonist

CYP17 Lyase inhibitor

Decrease AR levels



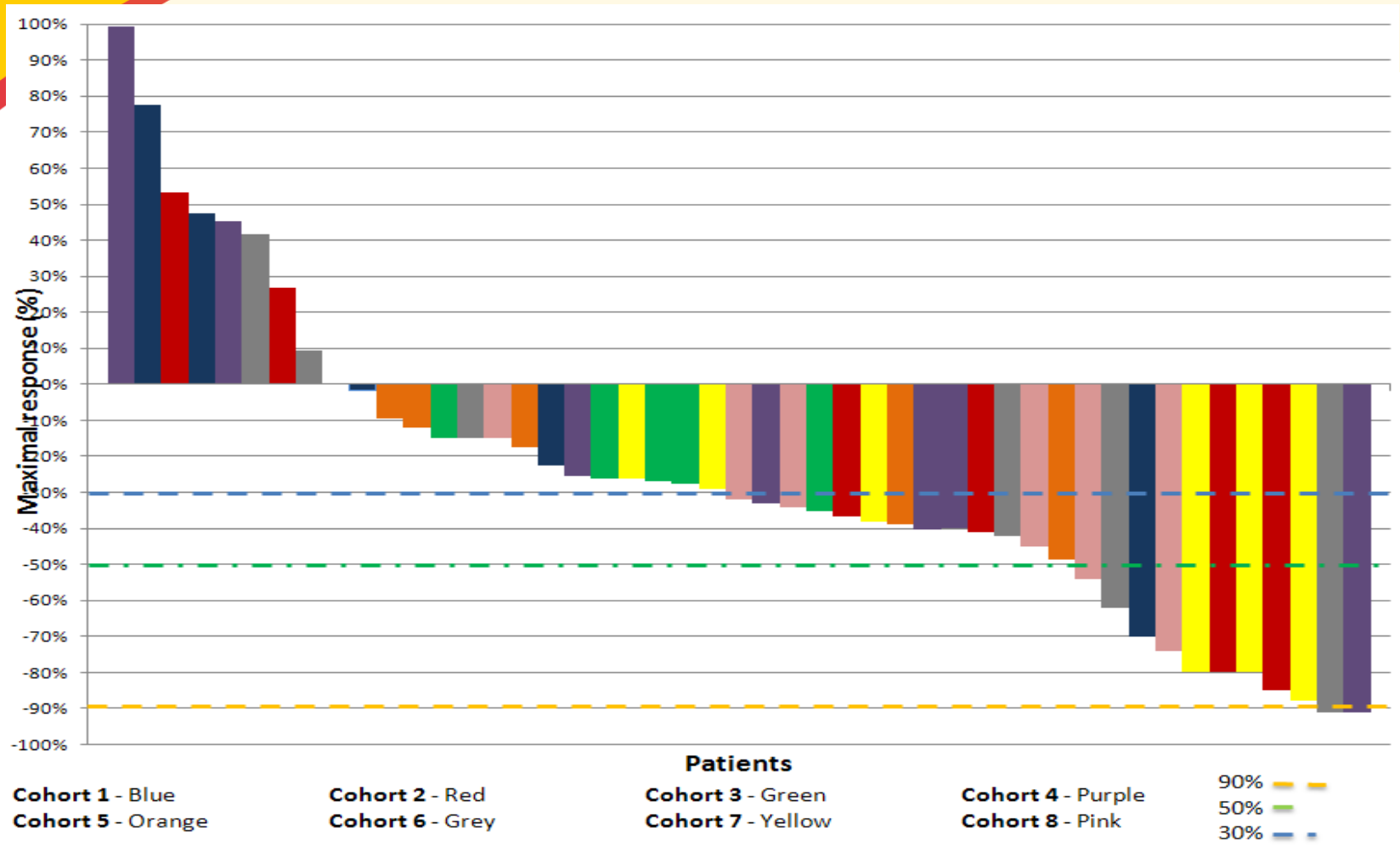
Galeterone: ARMOR1 (Androgen Receptor Modulation Optimized for Response) - Design

- **Dose escalation trial in eight clinical centers**
  - Standard dose escalation safety trial; 6 patients per group
  - Doses: 650 mg/day, 975 mg/day, 1300 mg/day, 1950 mg/day, 2600 mg/day
  - Single agent
  - Patient instructed to take galeterone with food

- **Dosing daily for 12 weeks (followed by optional continued dosing for eligible patients)**
  - Single and Split oral dosing
  - With and without supplement

- **Entry Criteria**
  - CRPC patients $\geq$ 18 y.o.
  - Metastatic and non-metastatic disease
  - Chemotherapy and ketoconozole naive

Maximal PSA Response: Waterfall Plot



An increase in response rate was seen with higher doses

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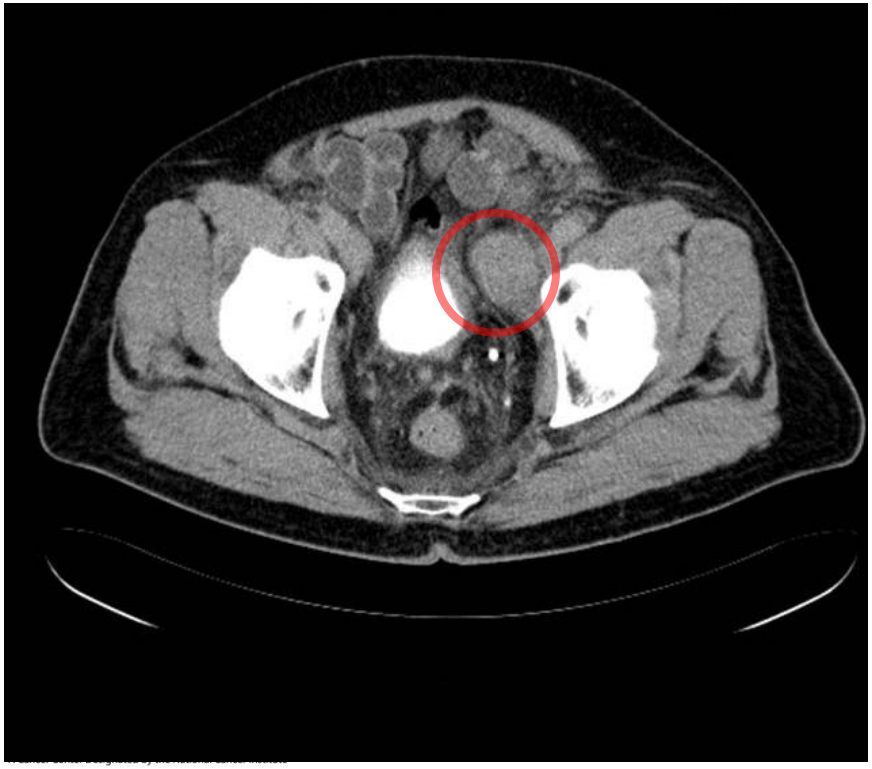
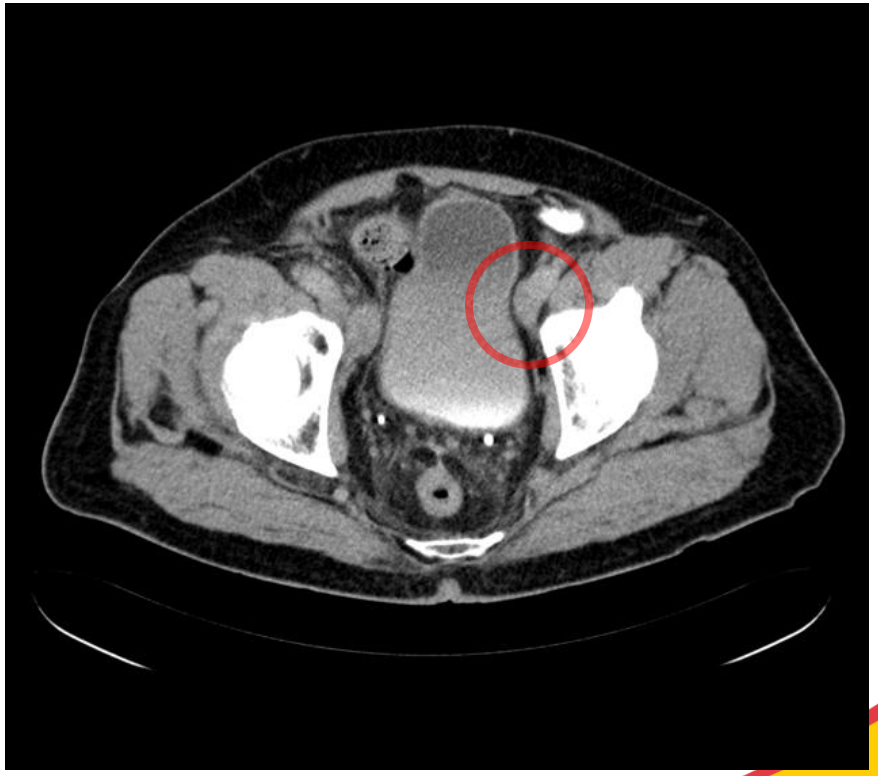
Reduction in tumor size reported in 3 patients treated with high doses of Galeterone

- Decrease in left pelvic lymphadenopathy
- Corresponding 80% PSA reduction

Baseline (2/9/2011): 3.9 x 2.9 cm



3 month (5/6/2011): 2.8 x 1.3 cm



Summary of Clinical Trials & Further Development of Galeterone

- Galeterone, well tolerated
- Significant & long-term PSA responses observed
- Excellent safety profile
- Tumor reduction observed radiologically
- Human proof-of-concept achieved: PSA reductions with soft tissue disease shrinkage
- Undergone successful formulation optimization
- Phase 2b trials planned for 4th quarter of 2012

On June 12, 2012 Galeterone (TOK-001 or VN/124-1) received Fast Track designation from the U.S. Food and Drug Administration (FDA) for the potential treatment of metastatic castration-resistant prostate cancer (CRPC)

Thank You

Vincent Njar, Ph.D
Njar Laboratory
Members

Angela Brodie, Ph.D.
Brodie Laboratory
Members

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