

Targeting ZIP9 with (Anti)Androgenic Peptides

Group Seminar

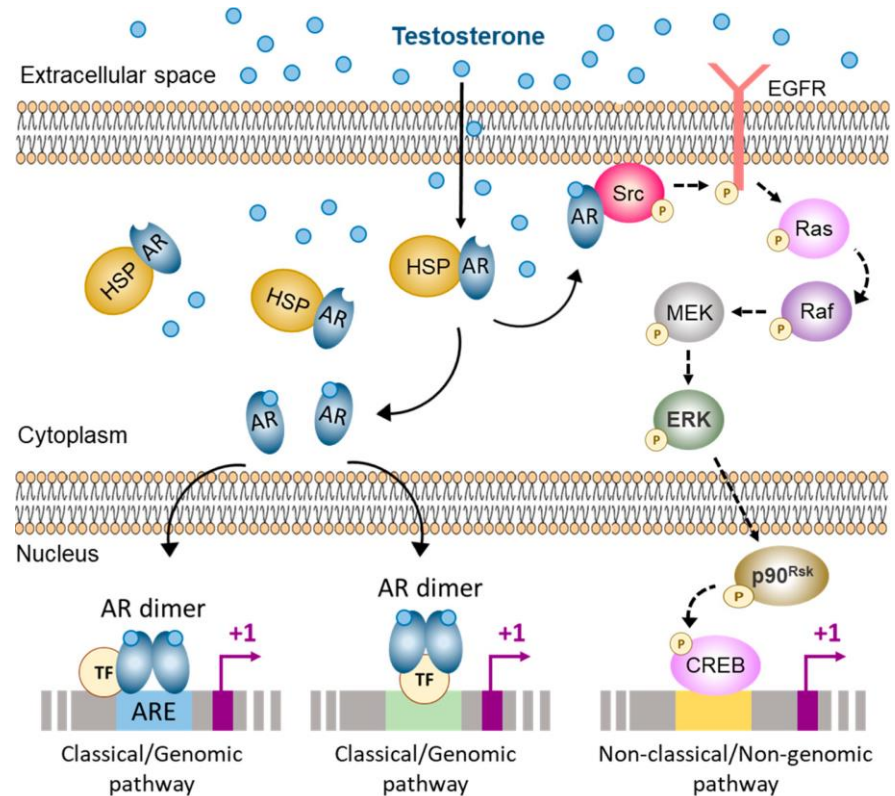
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- Osteoporosis, myodegenerative diseases, and male infertility are treated with, *e.g.*, testosterone
- Involves interactions with the classical androgen receptor (AR)
- Proandrogenic substances used for treating muscle- or bone- related disorders lead to undesirable effects
- Diseases based on malfunction of cells that contain **ZIP9**

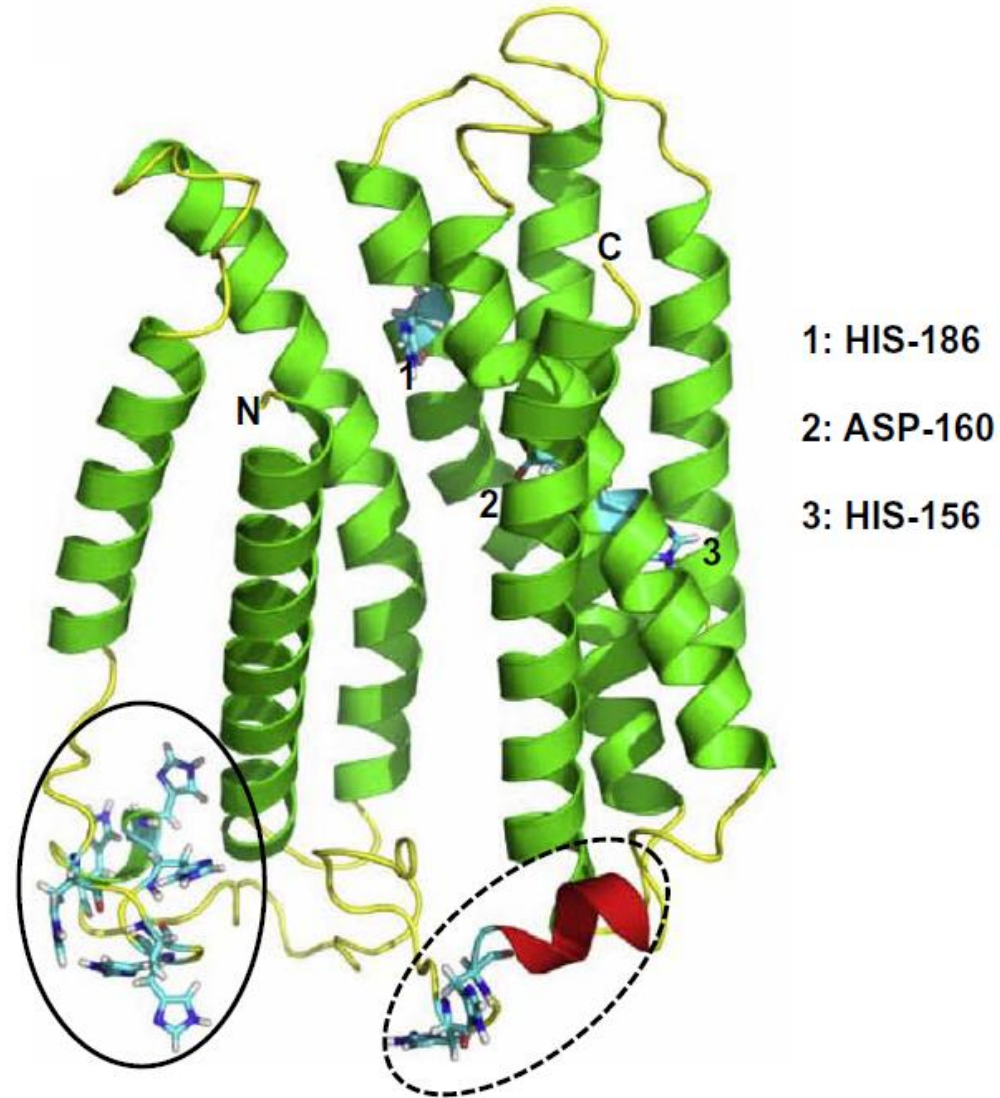


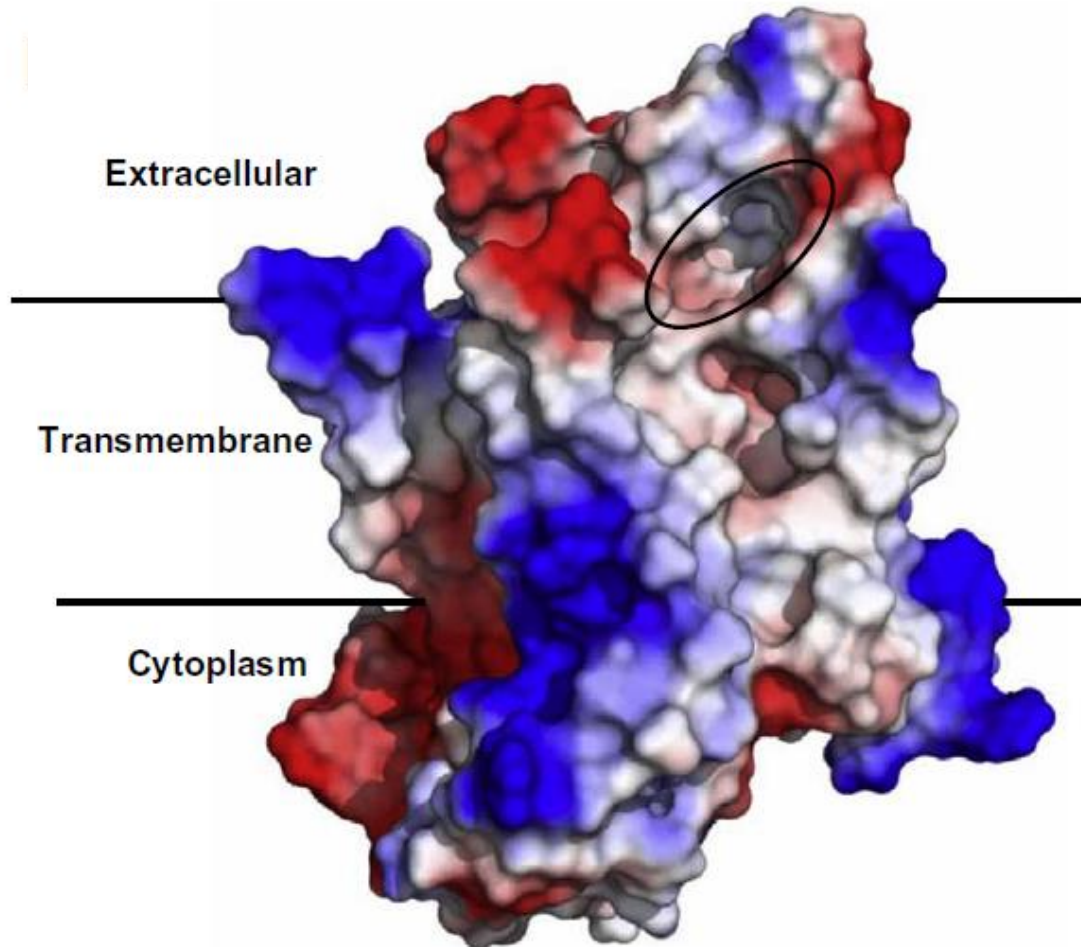
Positive androgenic effects by circumventing the AR by selective androgen receptor modulators (SARM)?

The Zinc Transporter ZIP9

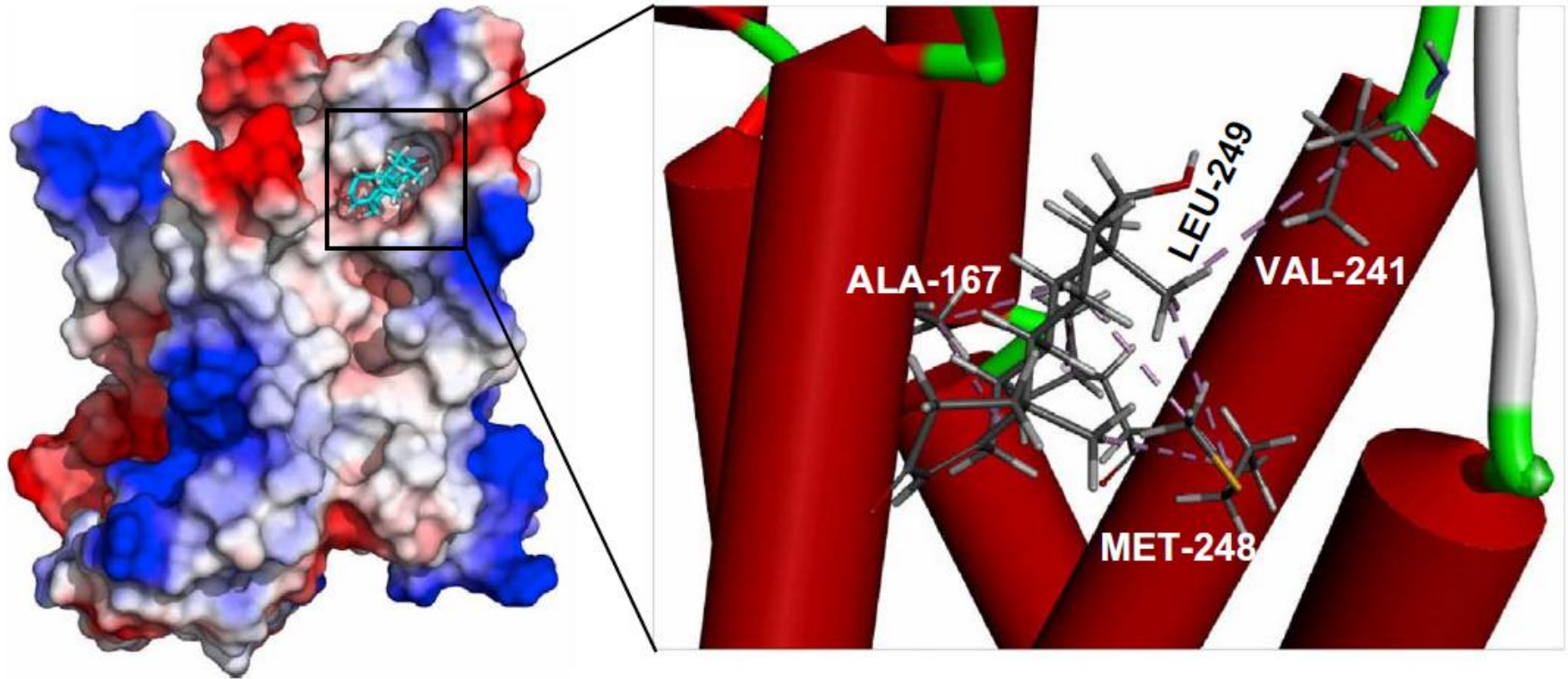
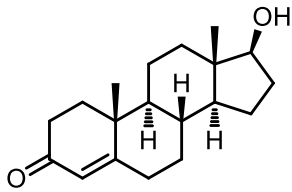


- Membrane-bound protein originally identified as a Zn²⁺ transporter
- Also binds testosterone
- Triggers the activation of the Src, Ras, Raf, Erk1/2, CREB, and ATF-1 signaling cascade
- Cascade is mediated through the interaction of ZIP9 with G-proteins
- Represents an interesting pharmacological target



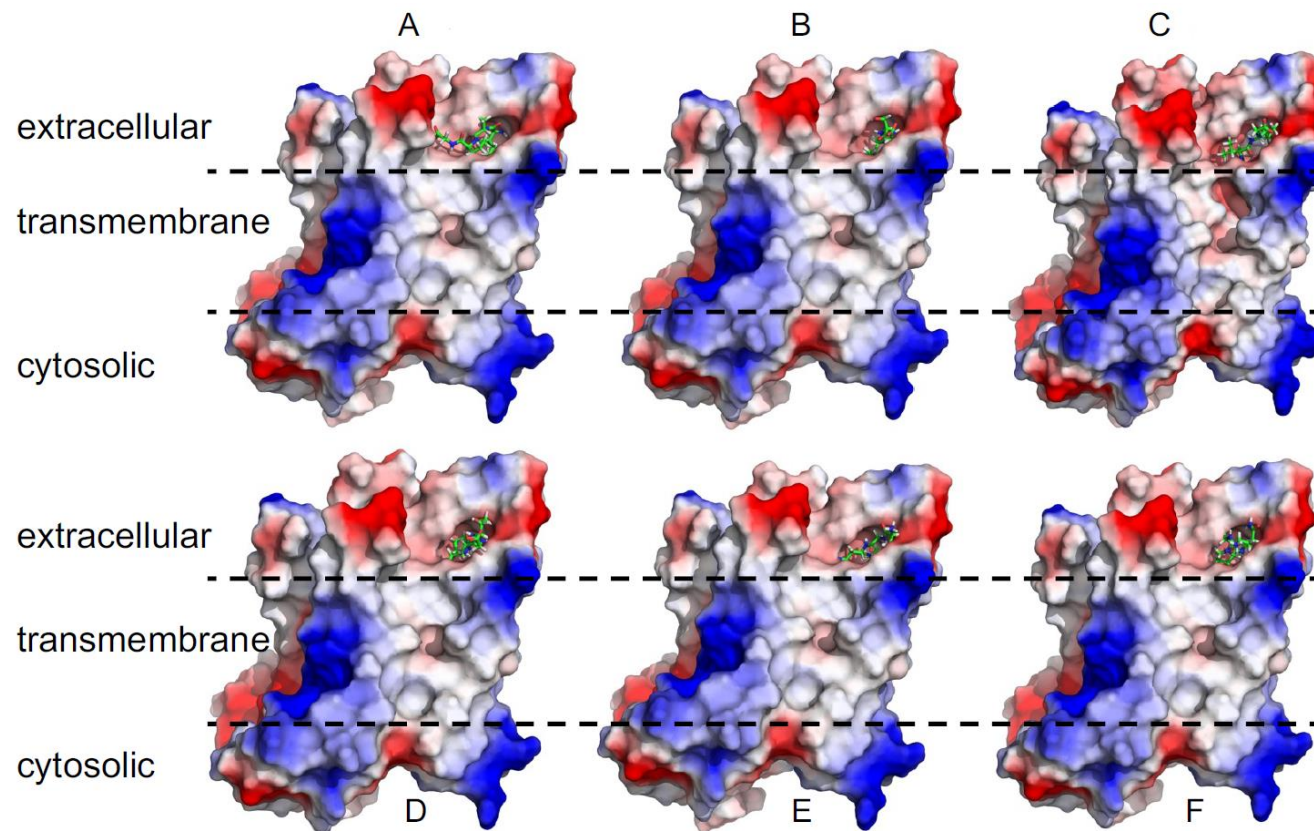


Binding of Testosterone



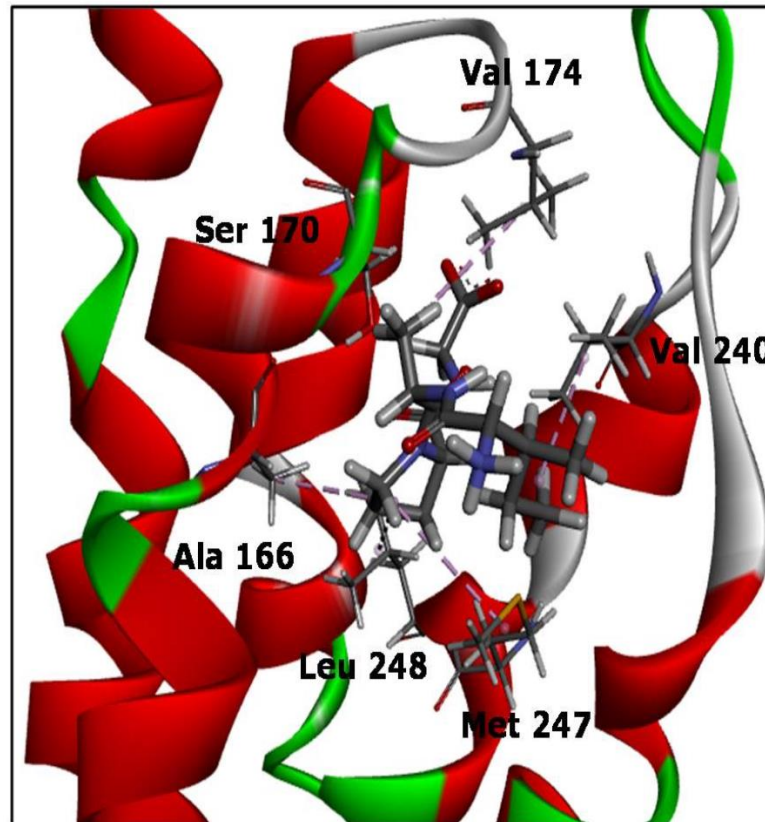


- *In silico* design of potential peptides
- Six candidates identified that may bind to proposed binding site of ZIP9 (IAPG, GVSG, GVVG, PQTG, SGNL, QAPG)

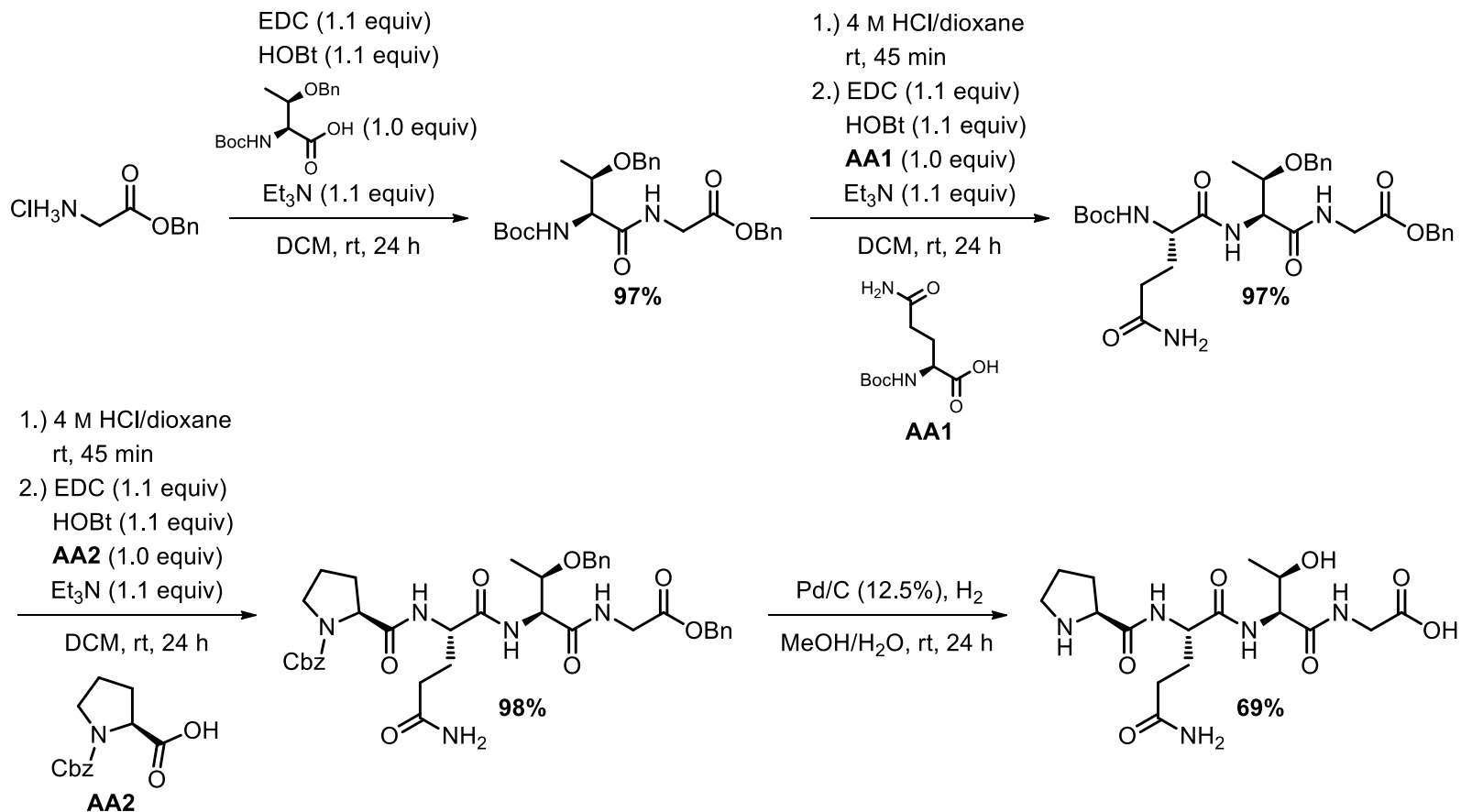


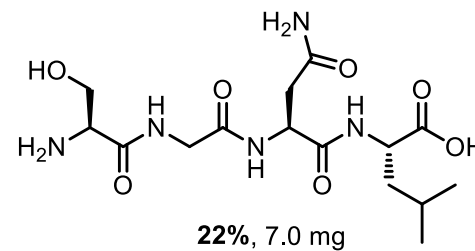
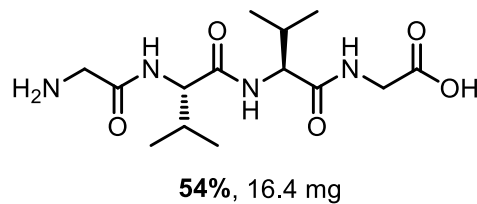
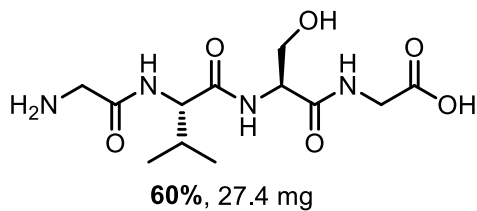
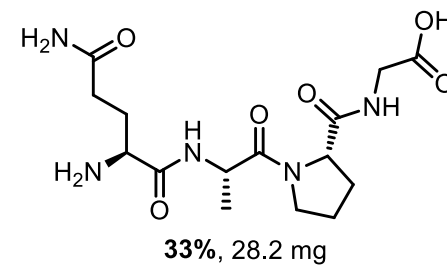
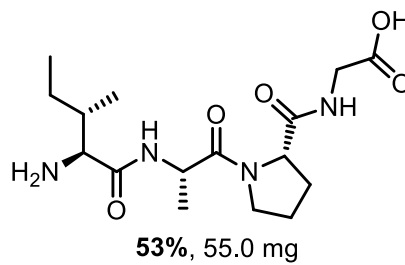
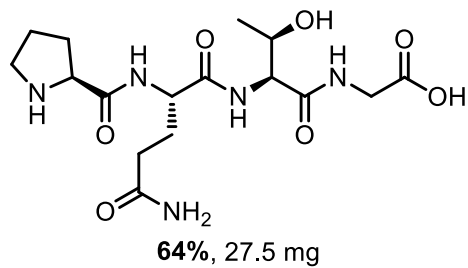


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- Six candidates identified that may bind to proposed binding site of ZIP9



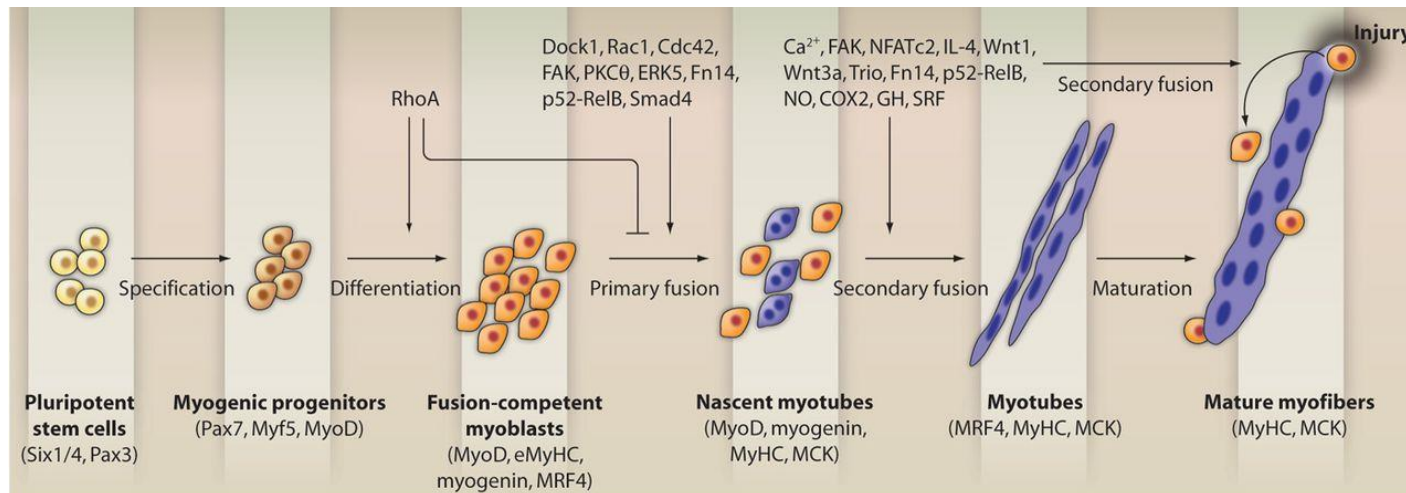
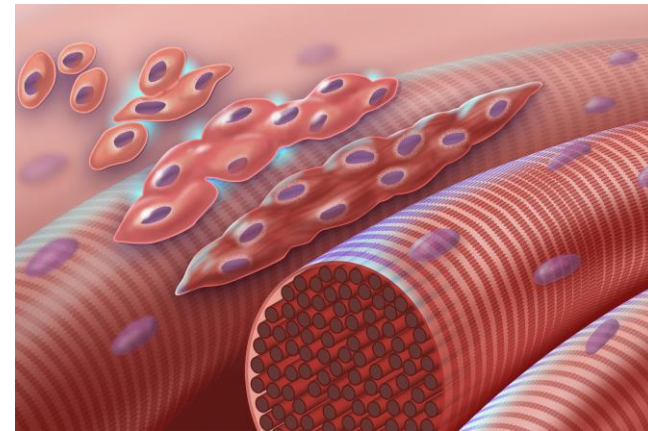
Synthesis of Andromimetic Peptides

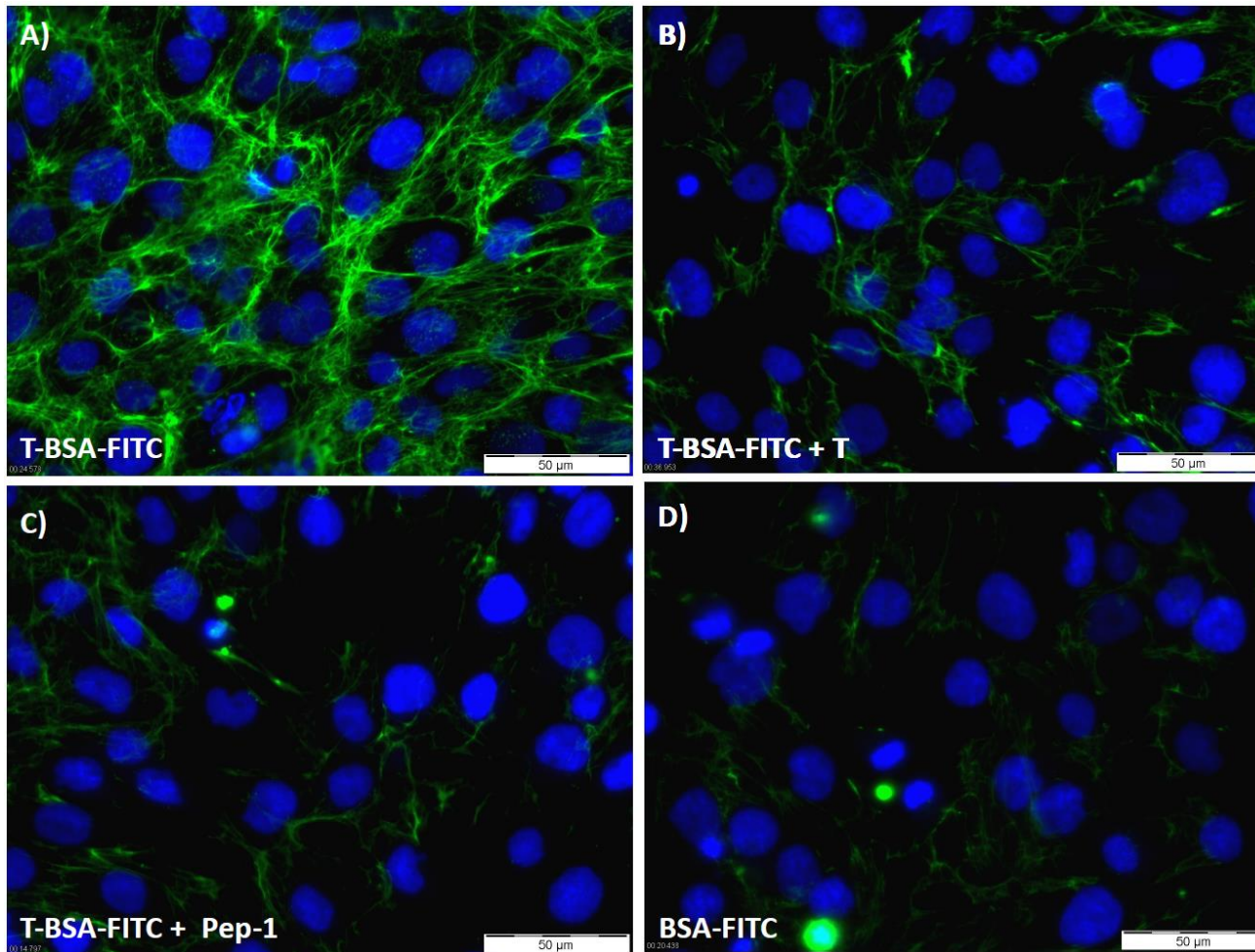


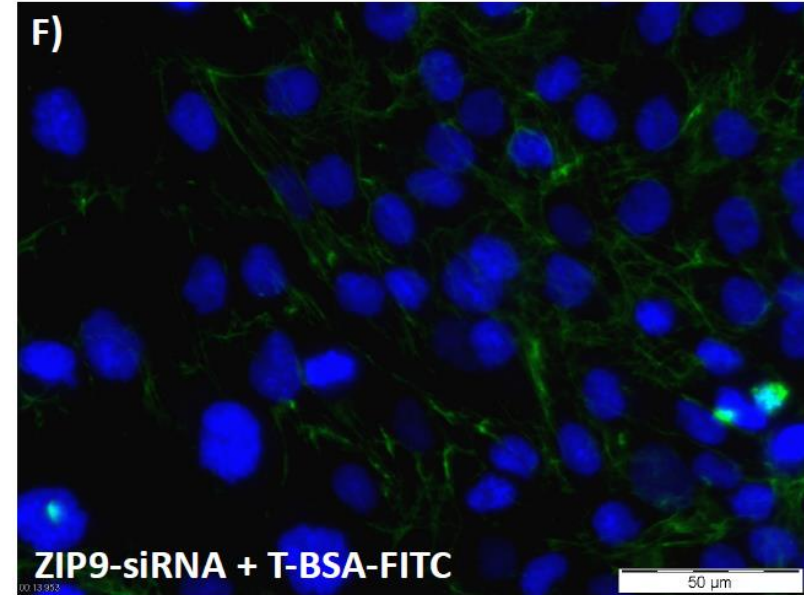
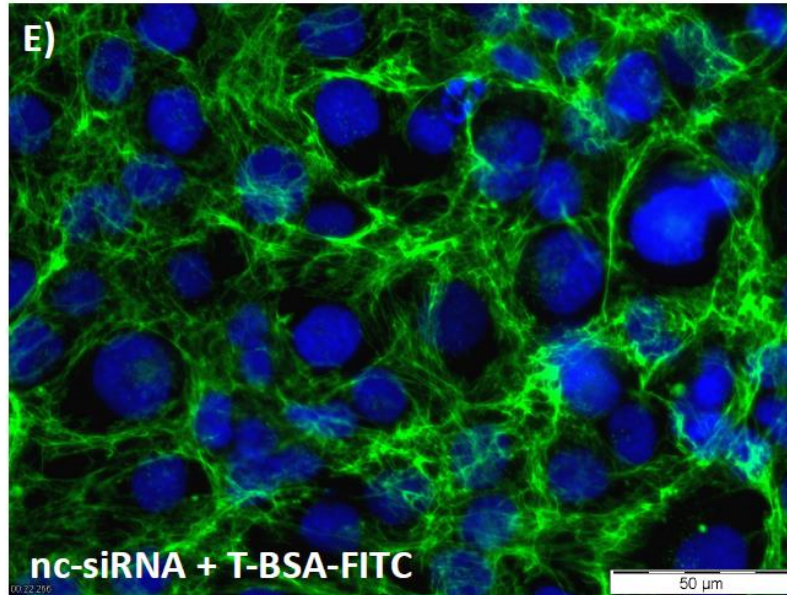




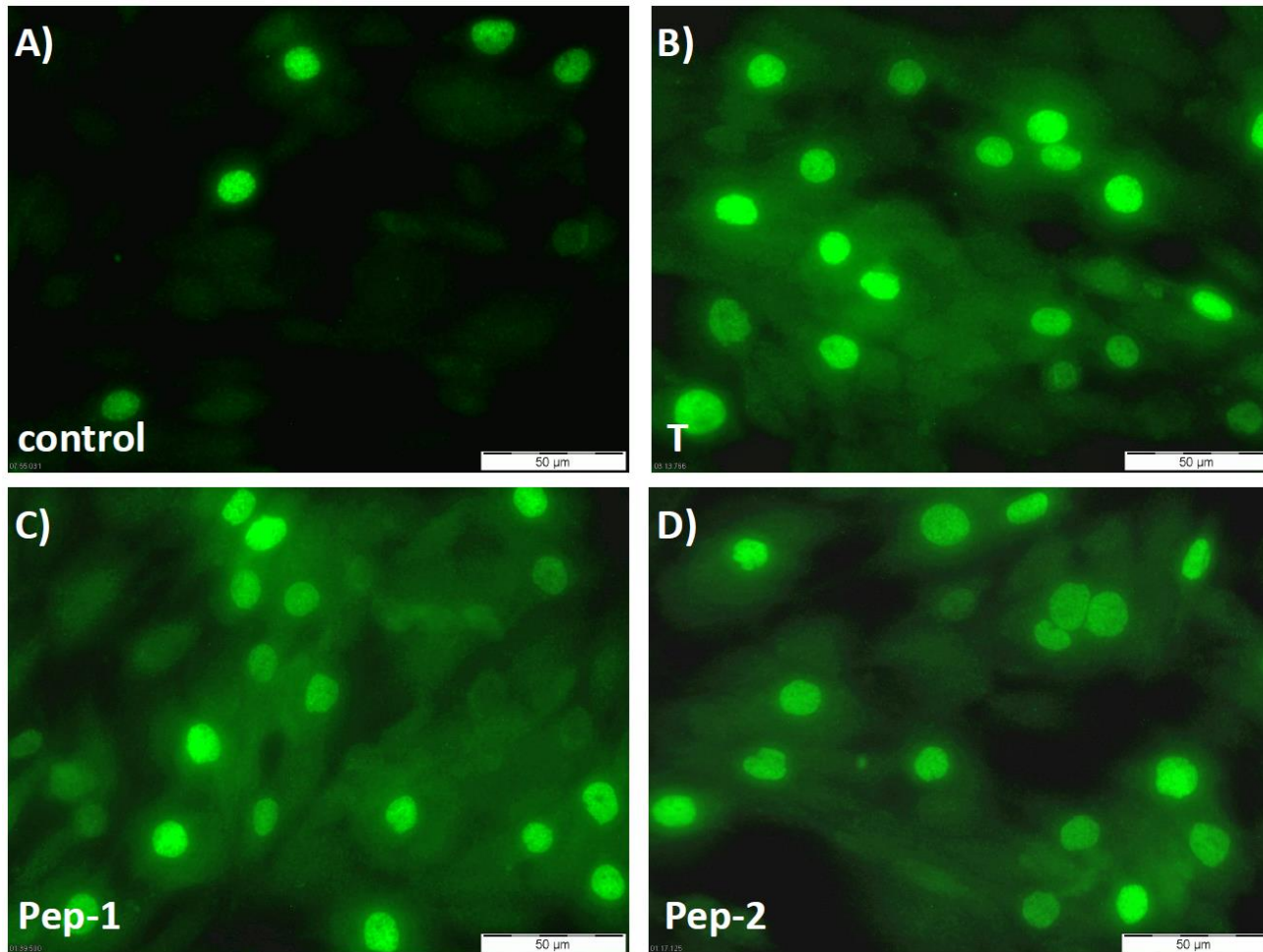
- Formation of skeletal muscular tissue
- Myoblasts fuse together to form myofibers
- Myogenin and FAK play a pivotal role



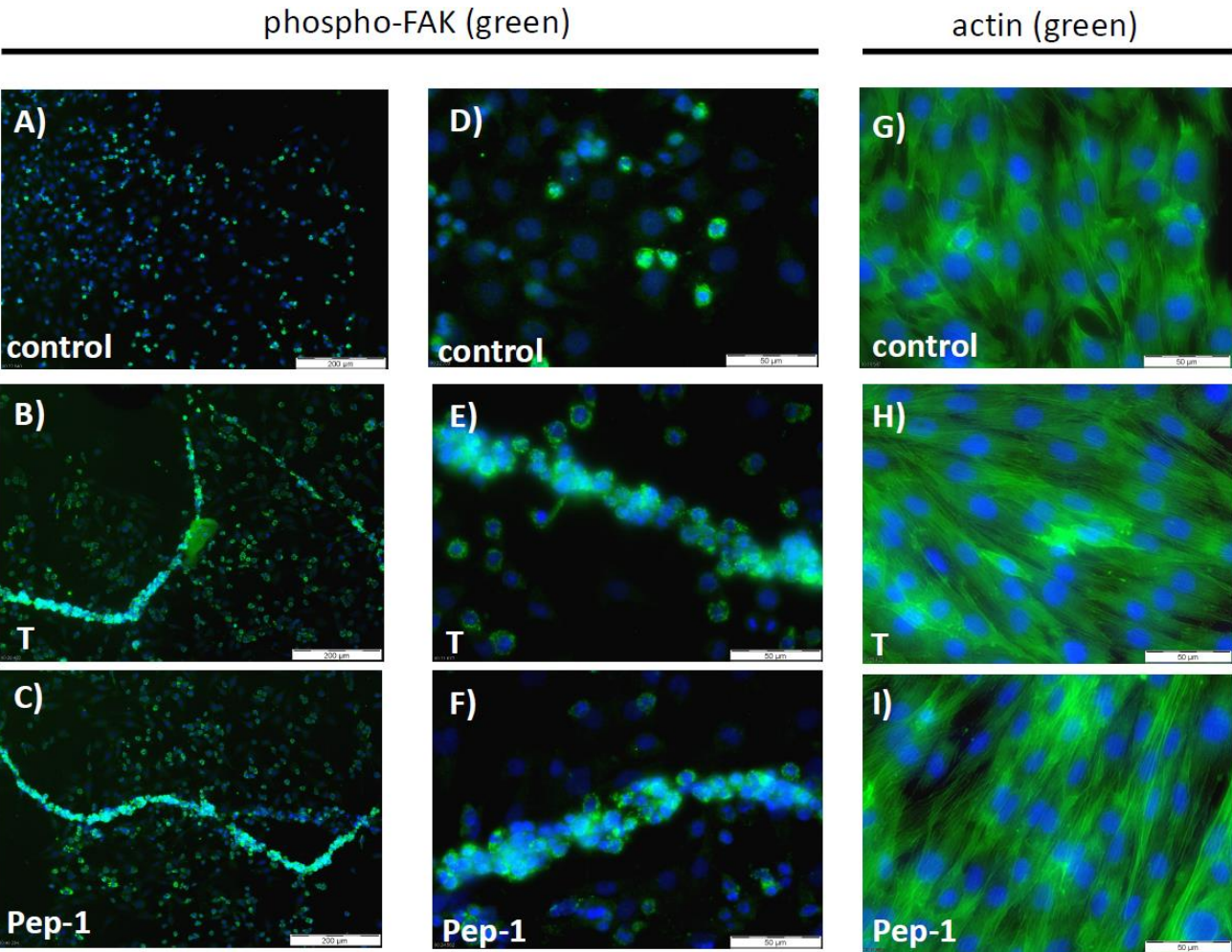


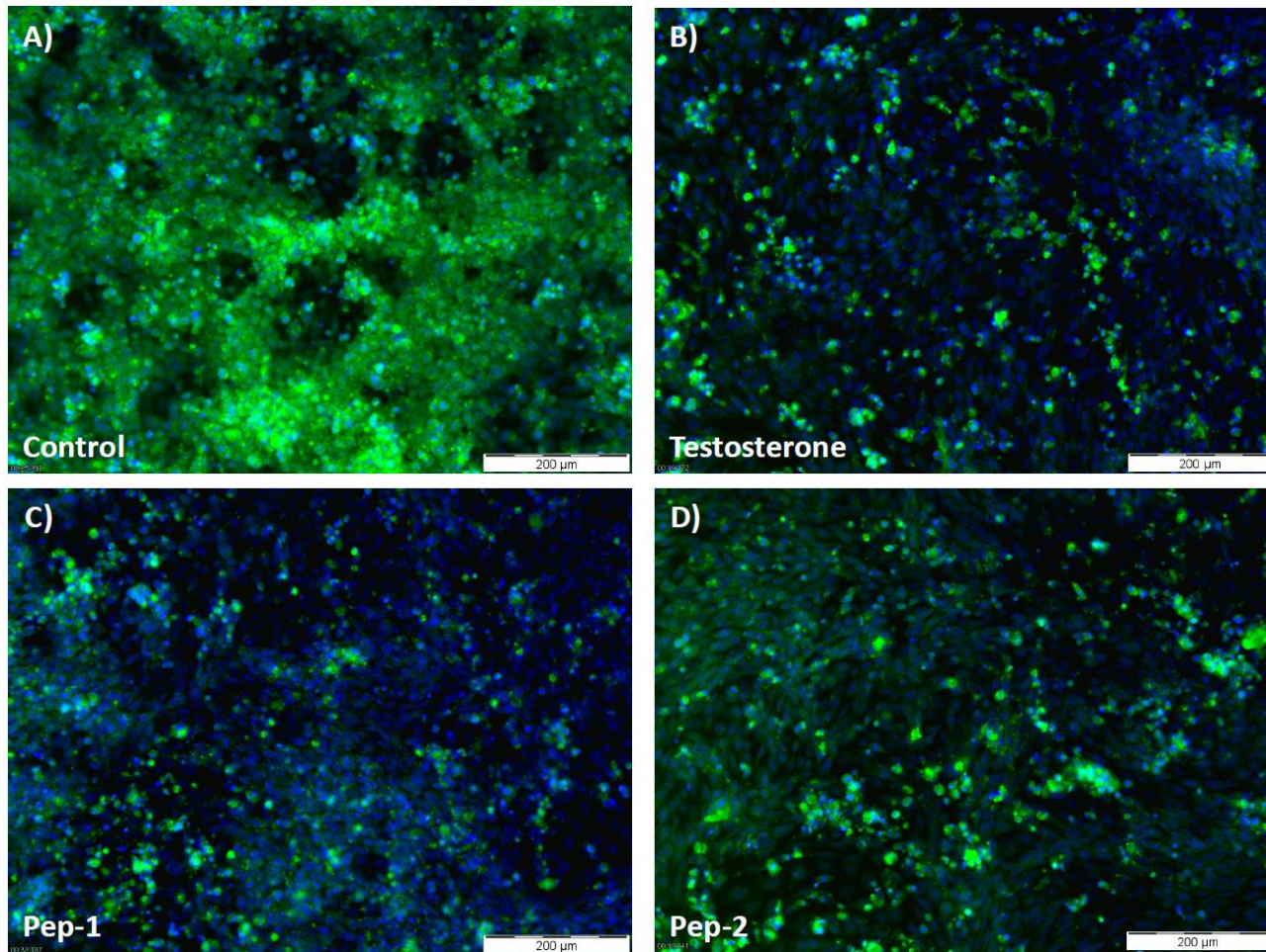


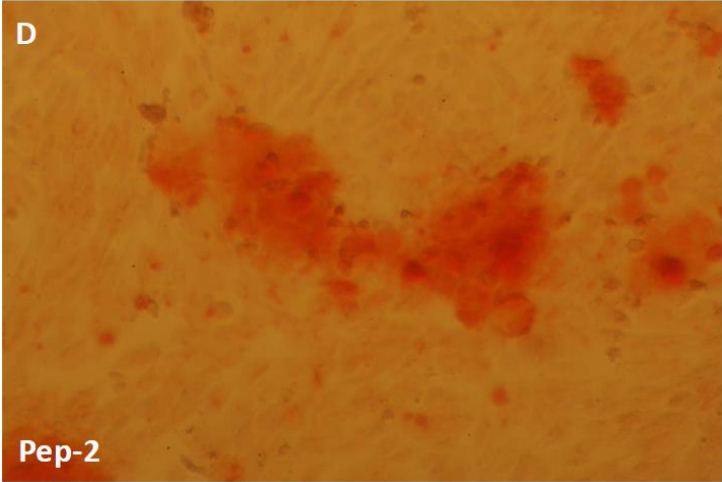
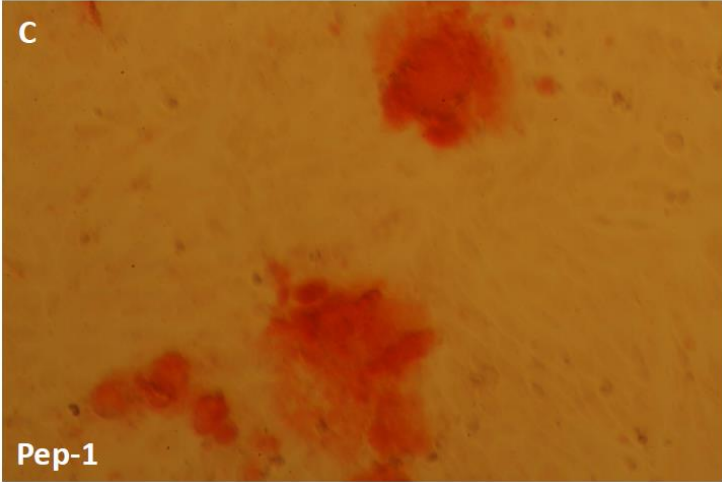
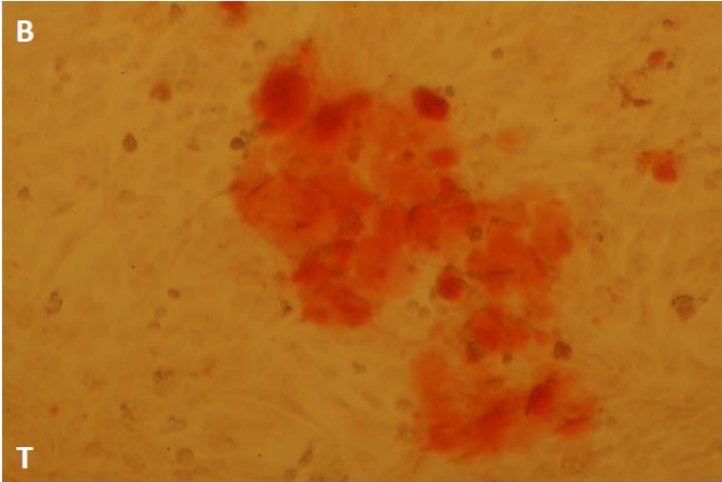
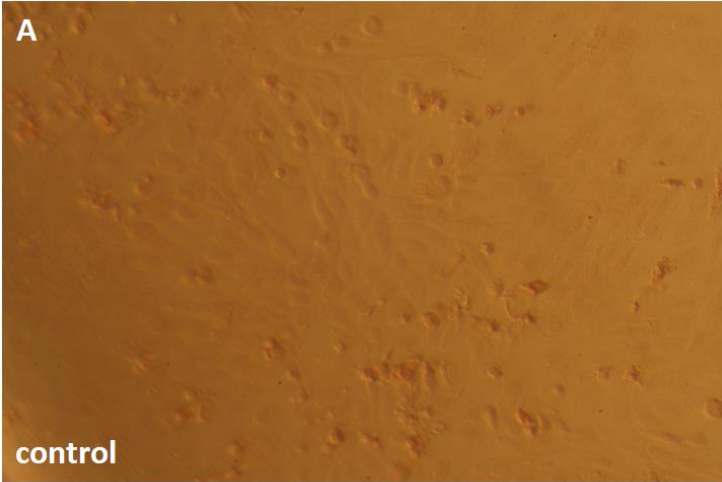
- No other membrane-bound protein capable of specifically binding testosterone exists besides ZIP9
- Peptides displace T-BSA-FITC from the extracellular binding-pocket

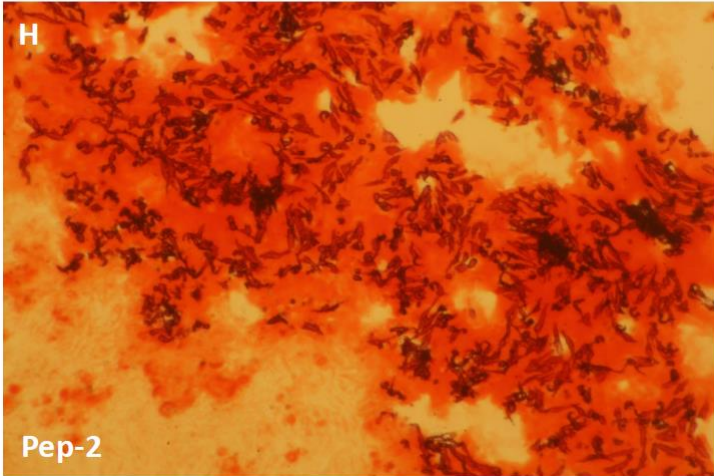
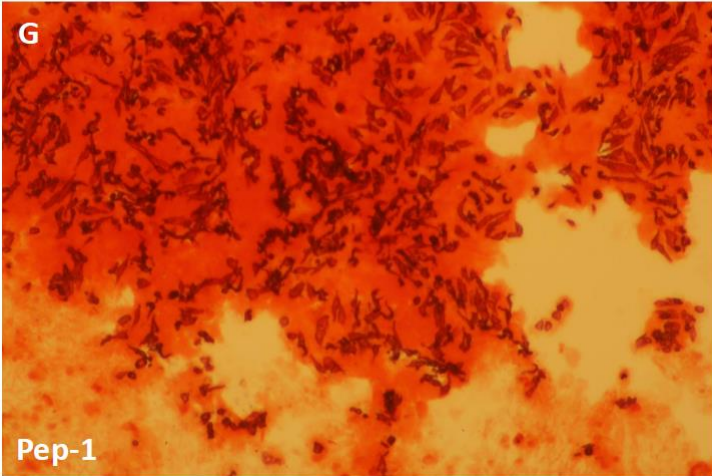
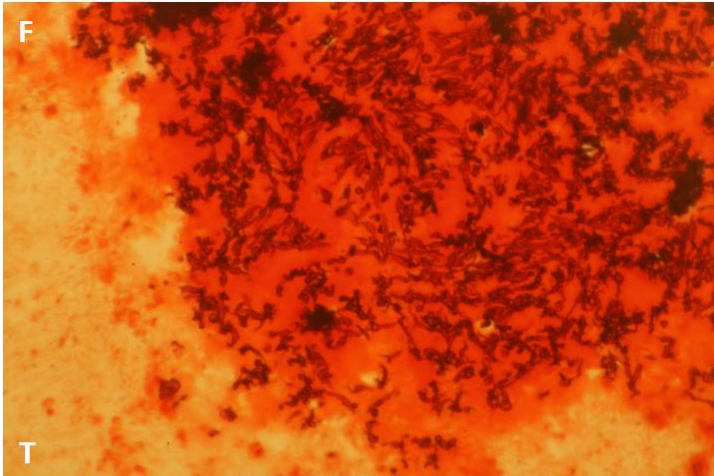
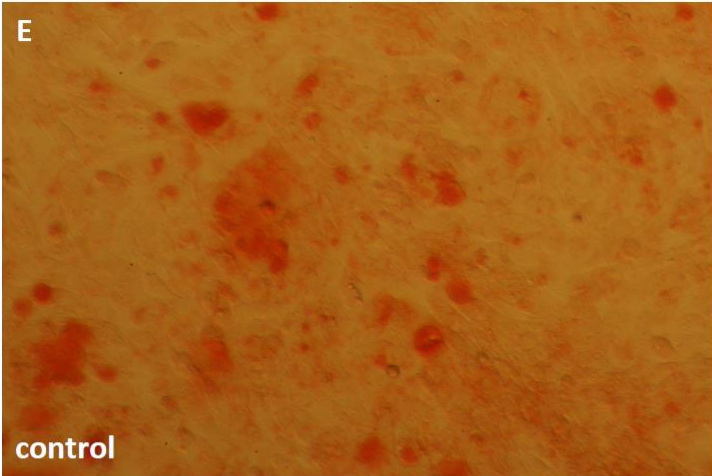


Stimulation of FAK Phosphorylation and Myotube Formation





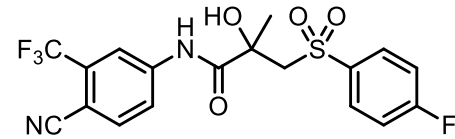




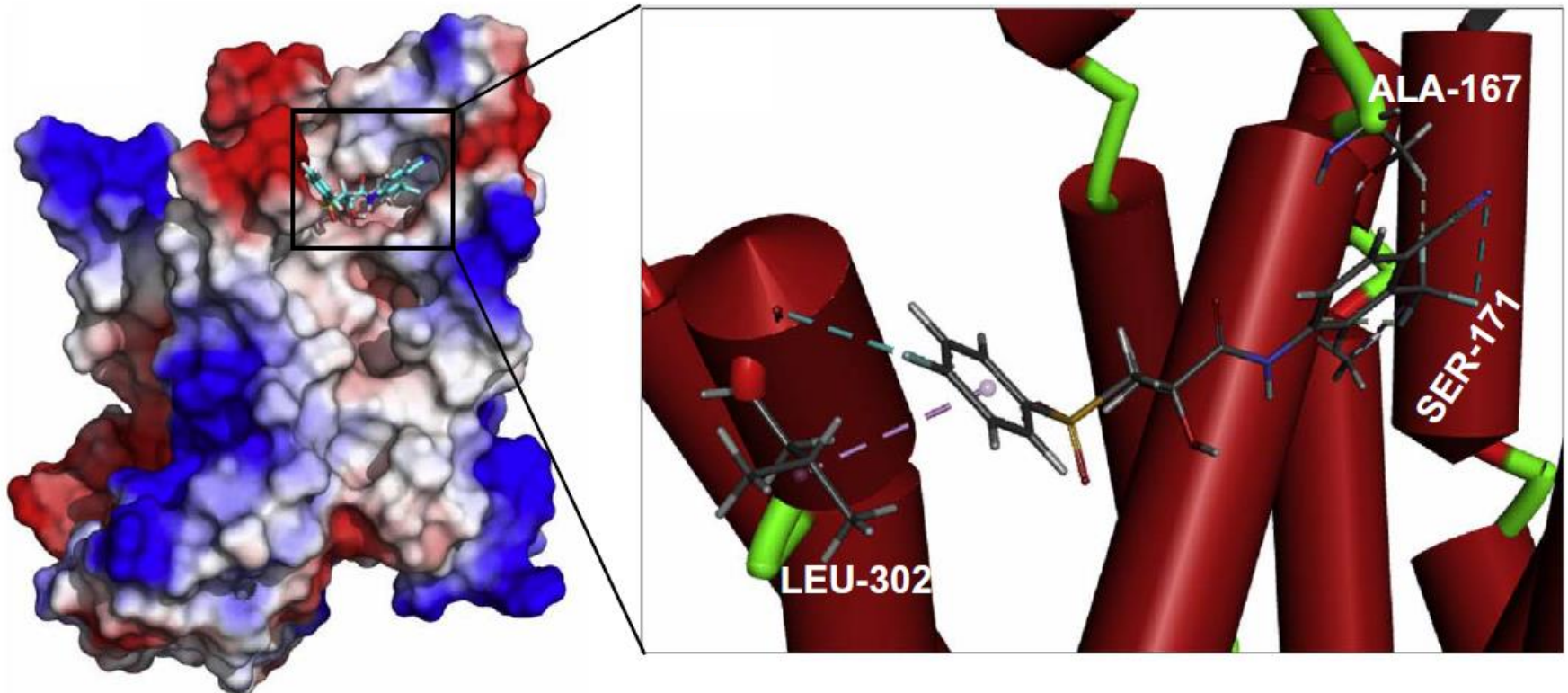
The Antiandrogen Bicalutamide



- Significant clinic impact
- Severe side-effects
- Accommodates same binding pocket as testosterone



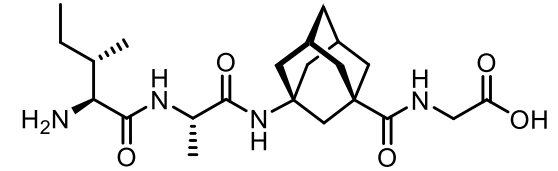
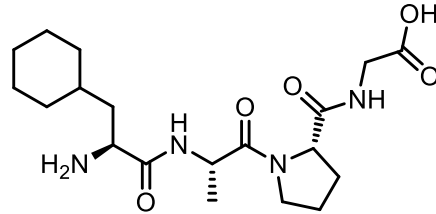
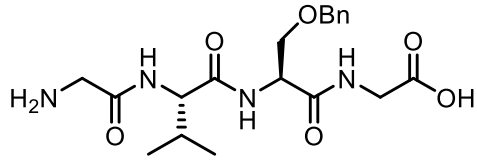
1.3 billion US\$ world wide sales in 2007
13.4 billion as of the end of 2018



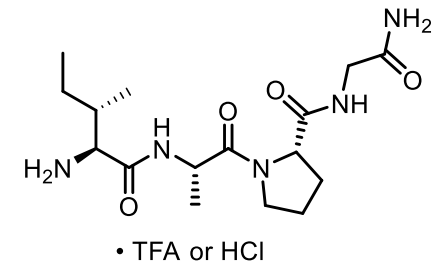
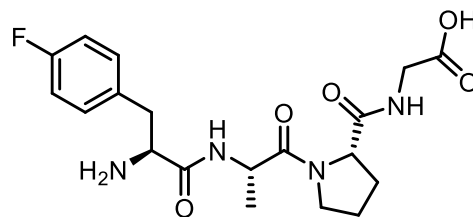
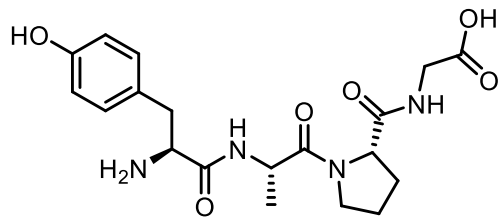
Design of Potential Antiandrogenic Peptides

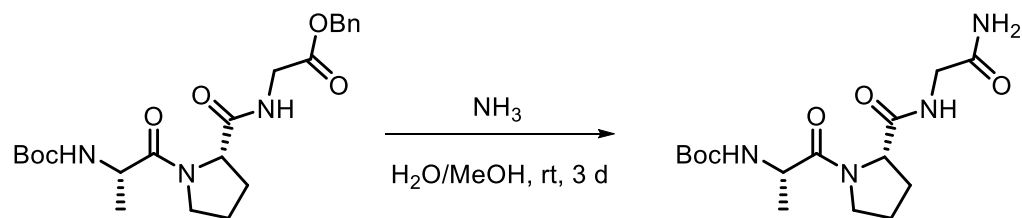
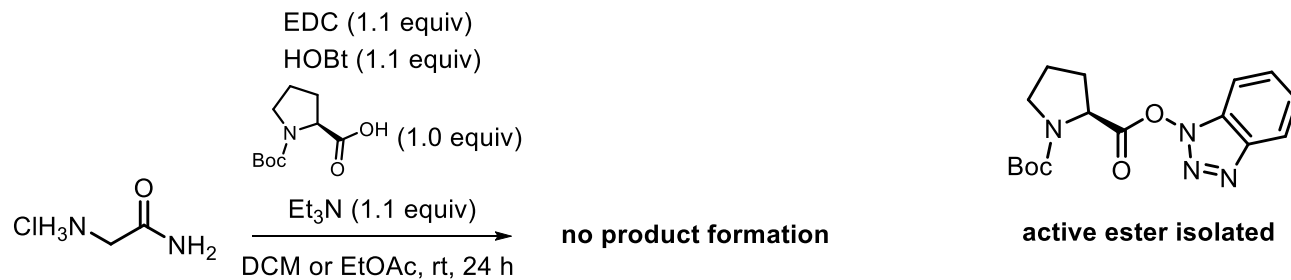


More hydrophobic side-chains



Further modifications







- Tested peptides stimulate formation of myotubes and mineralization in Saos-2 cells
- Classical nuclear AR is not required
- Testing of novel peptides
- Determination of binding constants
- Expression of blood-testis barrier in Sertoli cells
- Replacement for testosterone in treatment of osteoporosis
- Effect on osteoblasts and osteoclasts

Acknowledgement



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