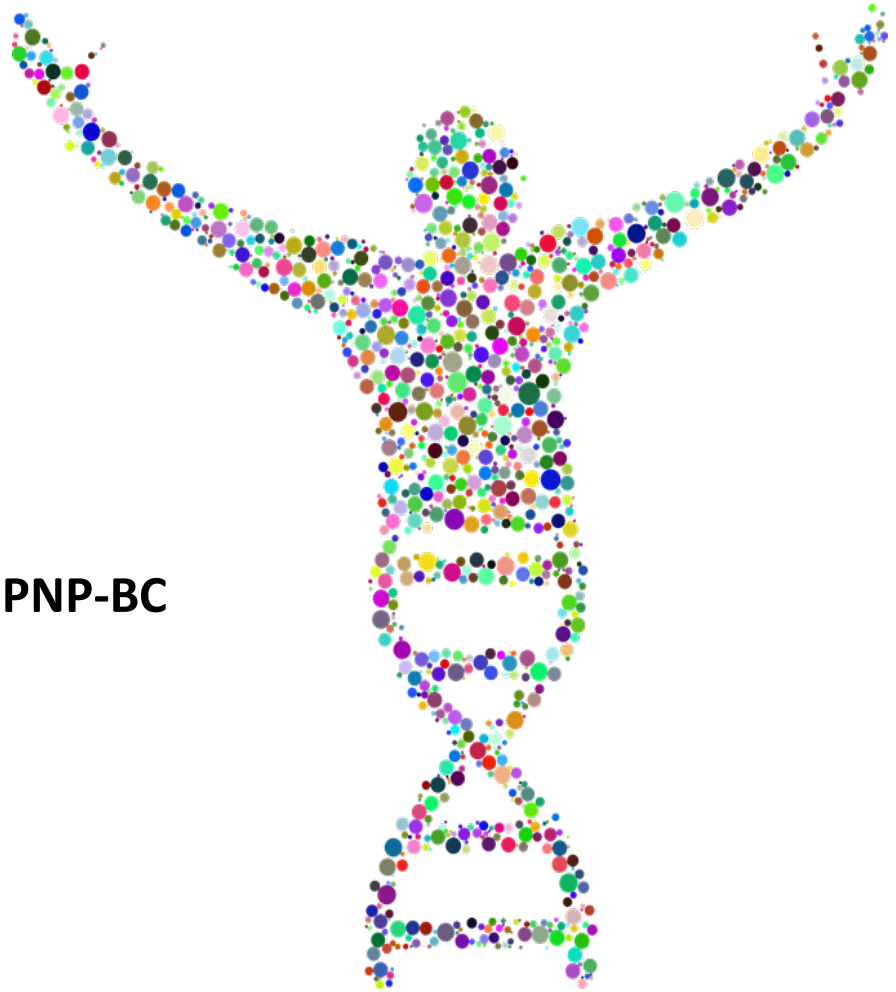
MARY CROWLEY CANCER RESEARCH
HOPE LIVES HERE



Metastatic Prostate Cancer Clinical Research Trials

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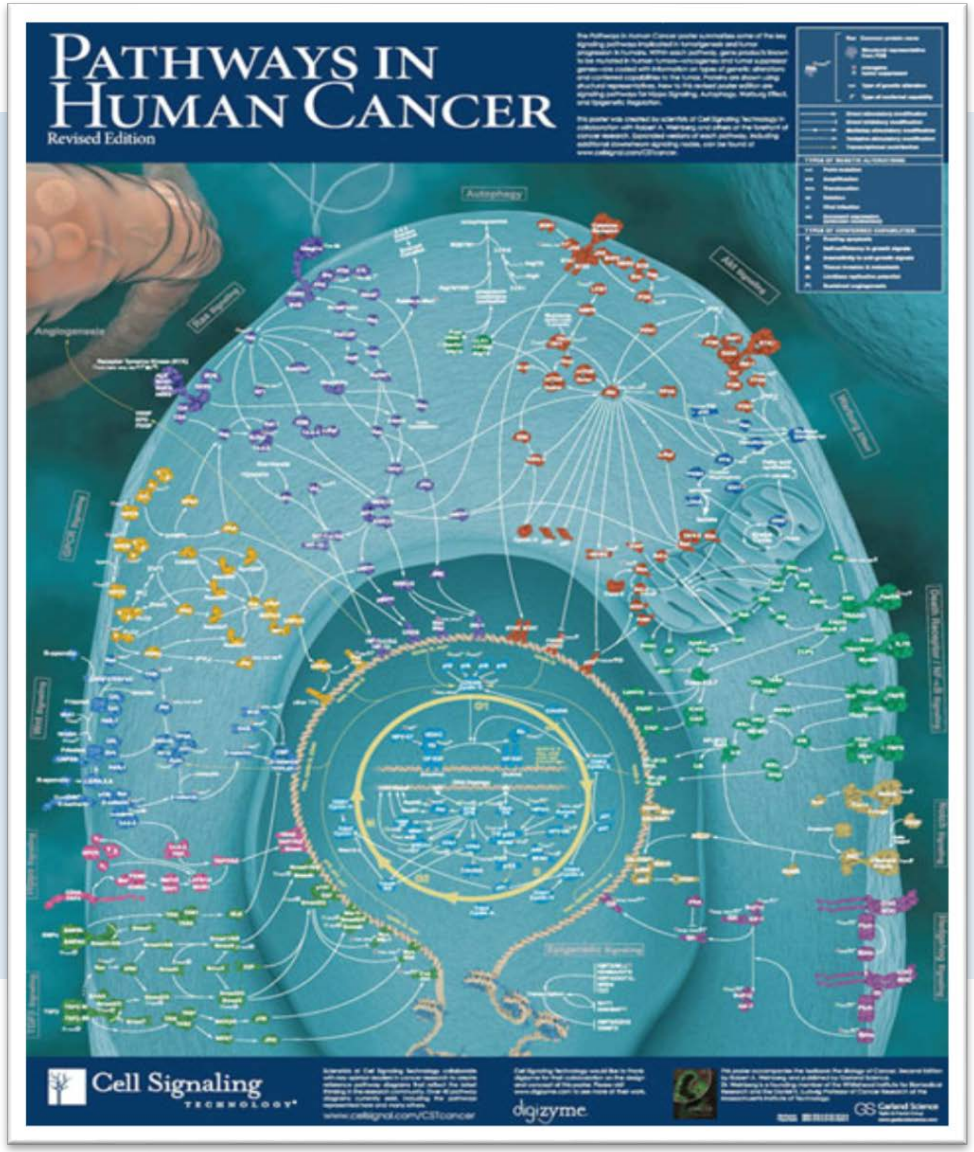
Mary Crowley Cancer Research
July 09, 2020

The Mary Crowley **MISSON**

To bring hope to cancer patients through innovative clinical trials while advancing treatment for patients in the future.

Hope Lives Here



OVERVIEW

1. Understand and define the different stages of drug development.
2. Prostate cancer Epidemiology and treatment history
3. Limitation of current prostate cancer treatment
4. Open clinical trials at Mary Crowley Cancer Research

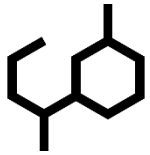
DRUG DISCOVERY Process

Target Selection

- Cellular & Genetic Targets
- Genomics
- Proteomics
- Bioinformatics

Lead Discovery

- Synthesis & Isolation
- Combinatorial Chemistry
- Assay Development
- High-throughput screening



Medicinal Chemistry

- Library Development
- Structure Activity Studies
- In Silico Screening
- Chemical Synthesis

In Vitro Studies

- Drug Affinity & Selectivity
- Cellular Disease Models
- Mechanism of Action
- Lead Candidate Refinement

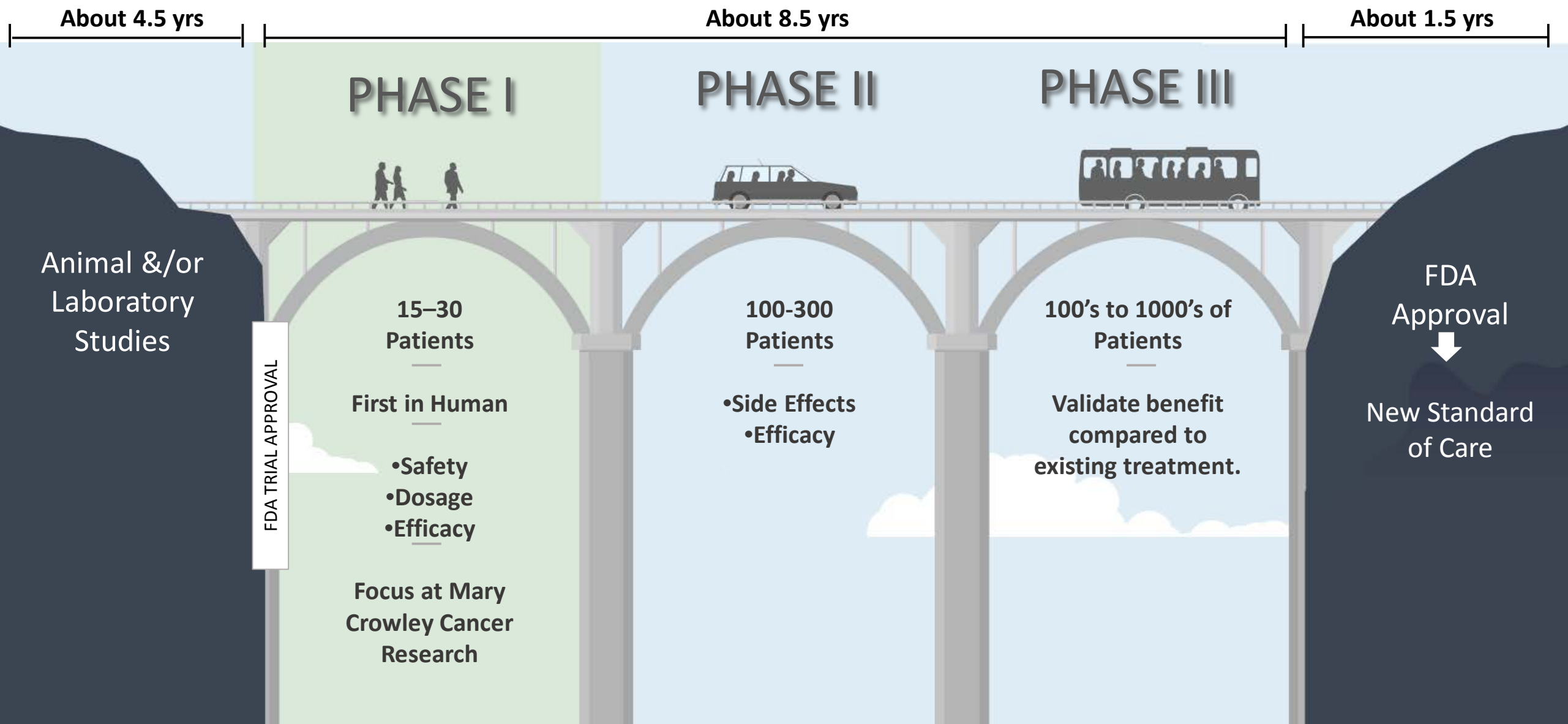
In Vivo Studies

- Animal Models of Disease States
- Behavioral Studies
- Functional Imaging
- Ex vivo Studies

Clinical Trial

- Phase 1-3
- NDA
- Phase 4

DRUG DEVELOPMENT: Clinical Trial Stages



PROSTATE CANCER Epidemiology

Prostate cancer is the most common non-cutaneous malignancy in men.

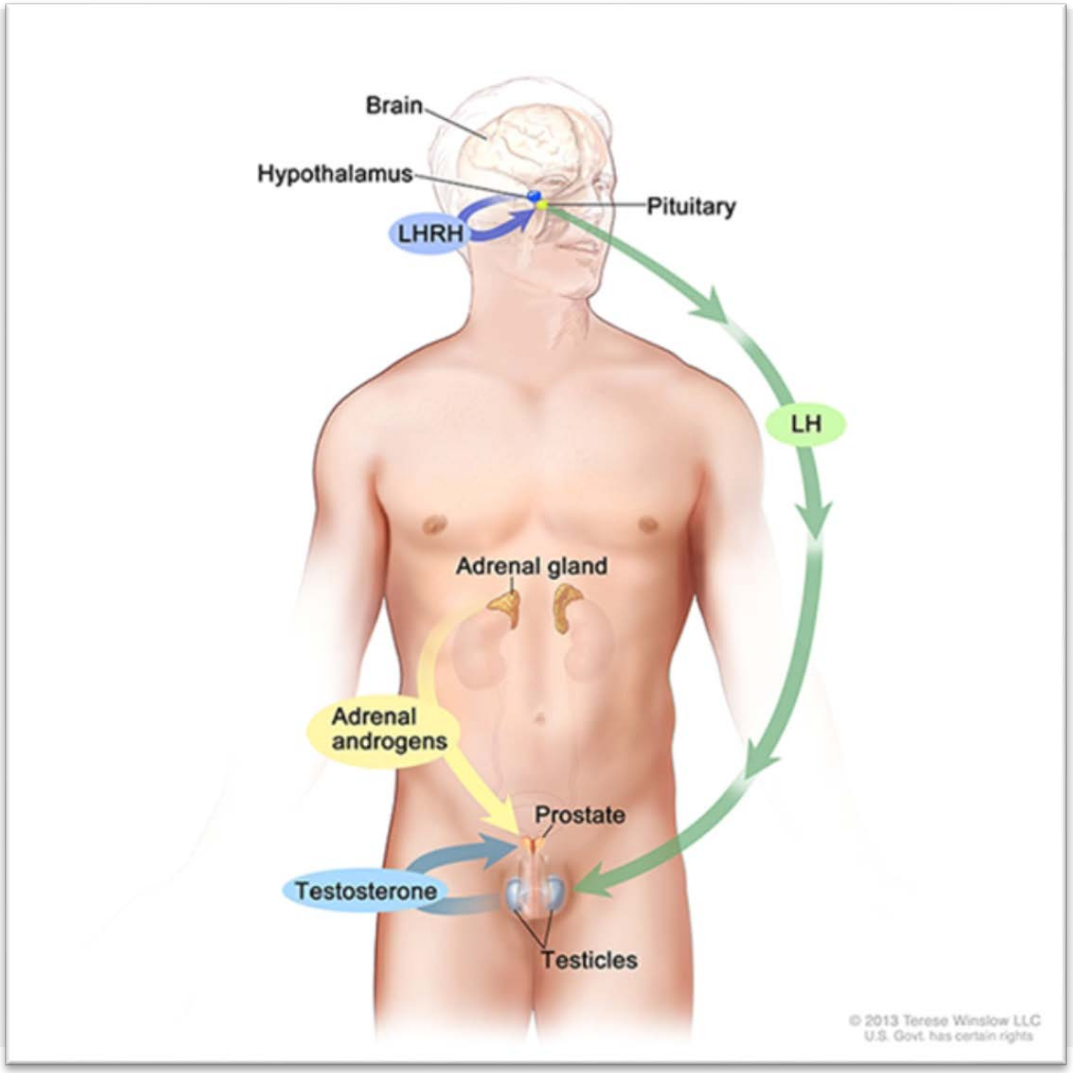
It is the 2nd most common cause of cancer-related mortality in men just behind lung cancer worldwide and in the USA.

Prostate cancer is responsible for approximately 13% of all cancer death worldwide.

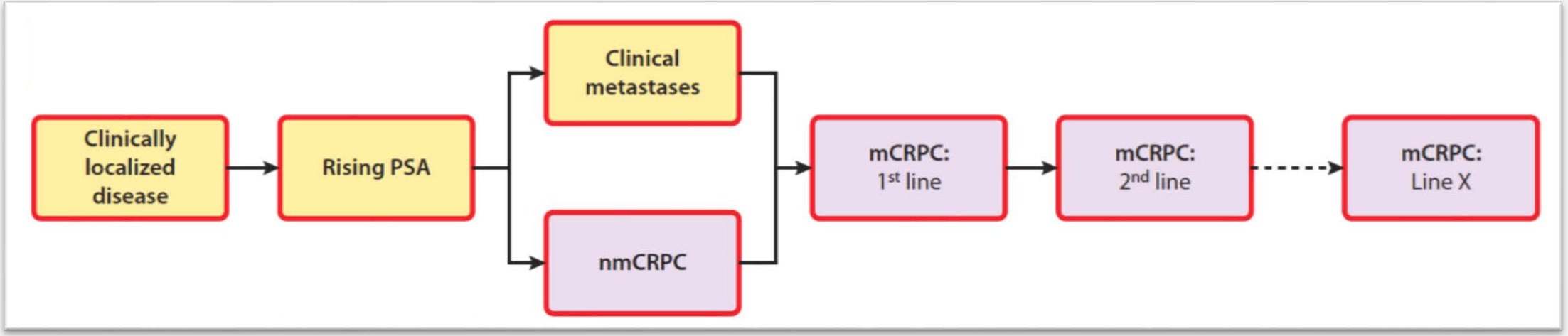
HISTORY OF TREATMENT for Prostate Cancer

- In the 1940s Huggins demonstrates prostate cancer regression with hormonal suppression
  - Androgen deprivation therapy becomes the gold standard for treating metastatic prostate cancer

    - LHRH agonists
    - Androgen receptor blockers
    - Androgen synthesis inhibitors
    - Chemotherapy
    - Parp inhibitor
    - Immunotherapy

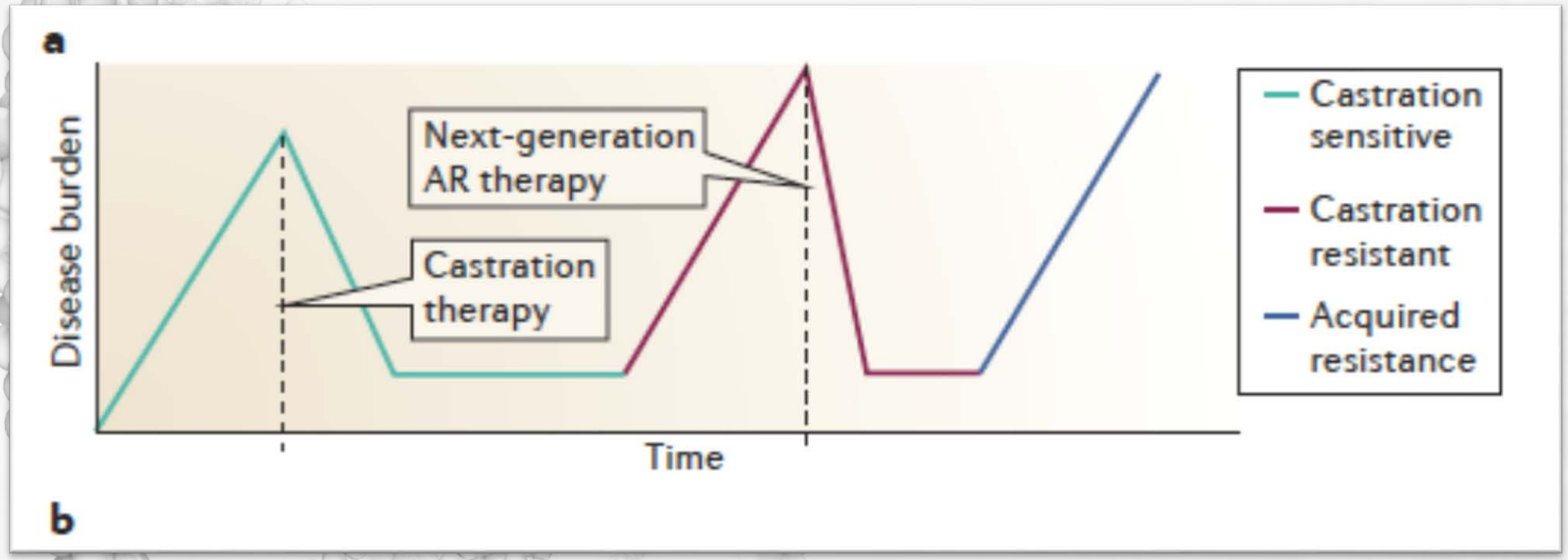


HISTORY OF TREATMENT for Prostate Cancer



Teo, Kantoff, et al. *Ann Rev Med* 2019; 70:479

Resistance to Androgen Deprivation Therapy



Watson, Arora, and Sawyers. *Nature Reviews Cancer* 2015; 15:701

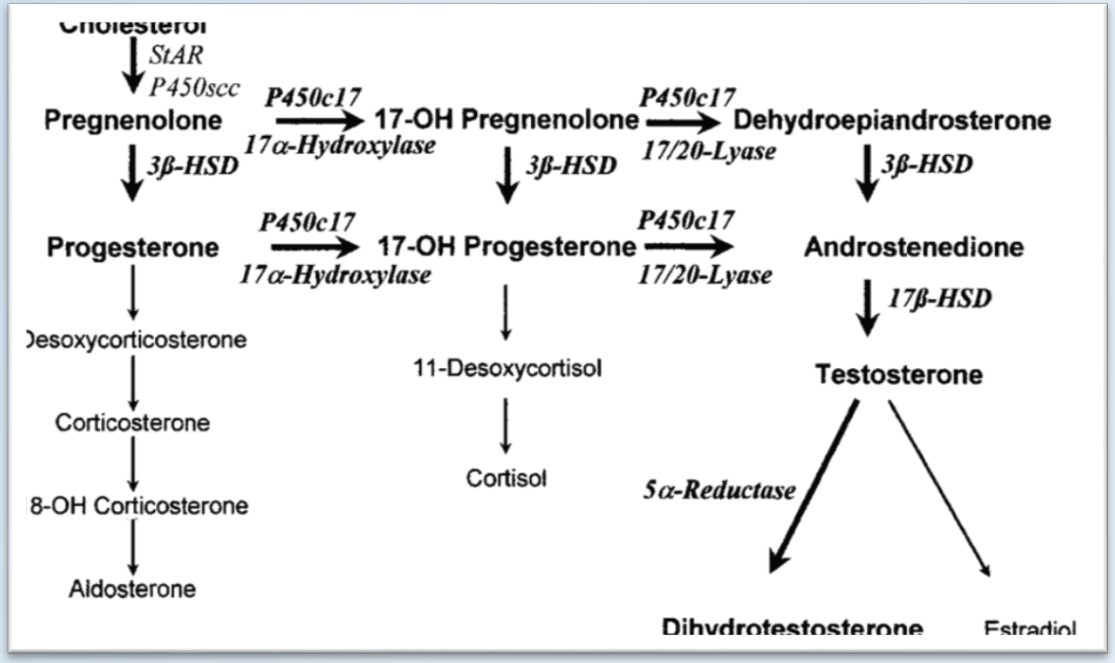
MCRPC Clinical Metastatic Trials at MARY CROWLEY

Standard Eligibility CRITERIA

- Advanced prostate cancer that has progressed on either enzalutamide or abiraterone + prednisone.
- Tumor measurable by PCWG3 criteria with bone scan and CT or MRI.
- Castrate level serum testosterone.
- Has had orchiectomy or is continuing treatment with GnRH analog or antagonist.
- Standard criteria regarding results of lab tests for bone marrow, kidney, and liver function.

MCCR 19-16

A Phase I/II Dose-Escalation and Efficacy Study of LAE001/Prednisone Plus Afuresertib in Patients with Metastatic Castration-resistant Prostate Cancer Following Standard of Care Treatment.

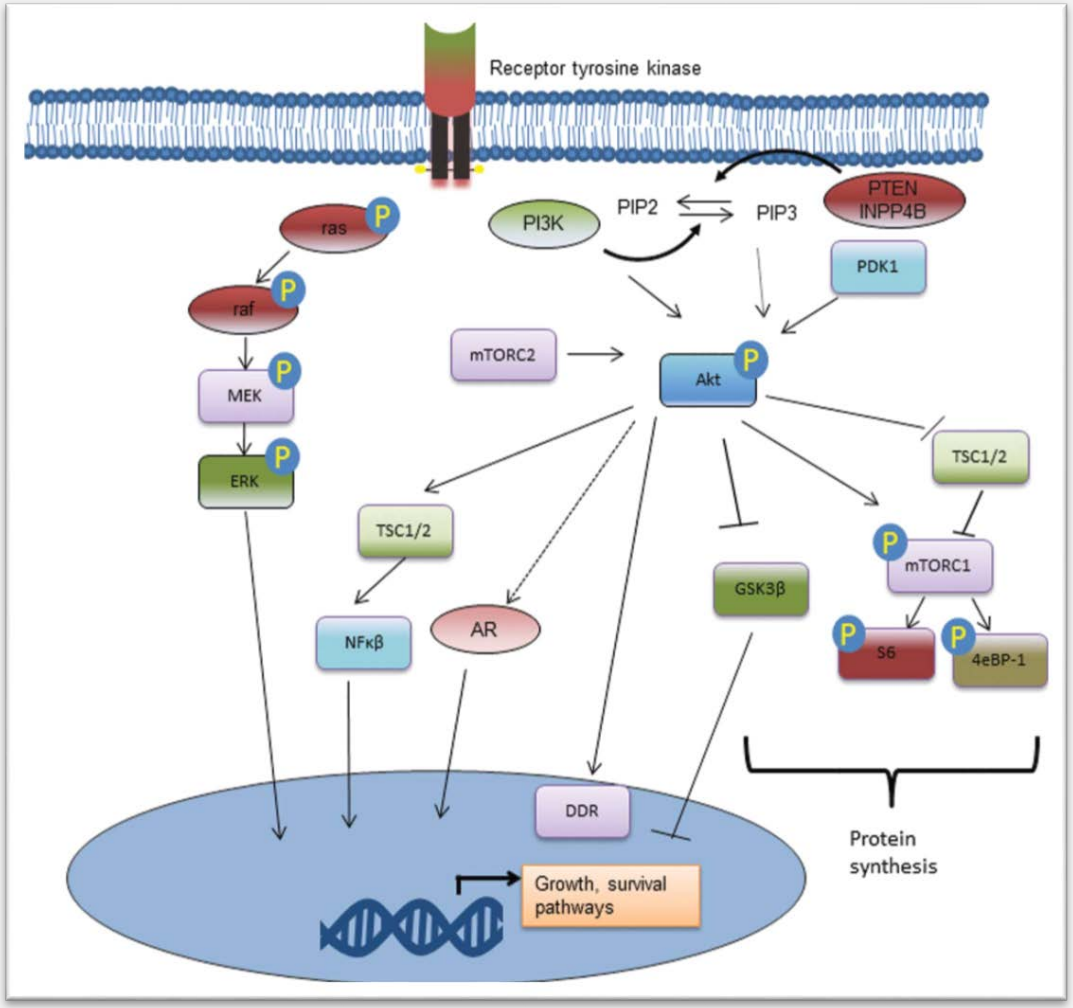


Androgen SYNTHESIS

Abiraterone is an FDA approved CYP17 inhibitor that improves OS in CRPC.

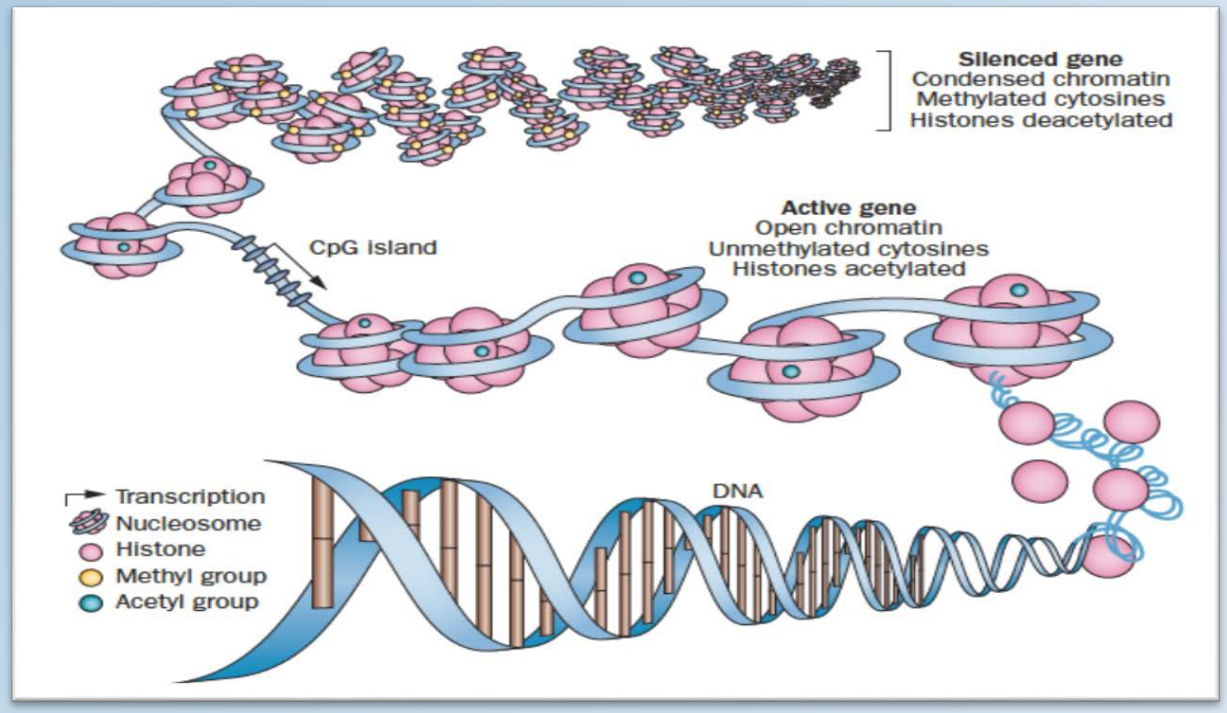
LAE001 is an oral novel nonsteroidal, reversible, CYP17 and CYP11B2 inhibitor (may decrease MC excess toxicities of Abiraterone (htn, hypokalemia)); has been used in phase I/II trials by Novartis; 28% men with CRPC had >50% PSA response.

AKT PATHWAY



- The PTEN tumor suppressor is lost in >50% of CRPC leading to upregulation of AKT
- PTEN loss leads to development of prostate cancer in mice
- PTEN loss portends worse prognosis in humans
- Afuresertib (LAE002) is an oral AKT inhibitor; has been used in 3 phase I/II trials in other malignancies

MCCR 19-30



A phase 1B/2 open-label study evaluating tazemetostat in combination with enzalutamide or abiraterone/prednisone in chemotherapy naïve subjects with metastatic castration resistant prostate cancer.

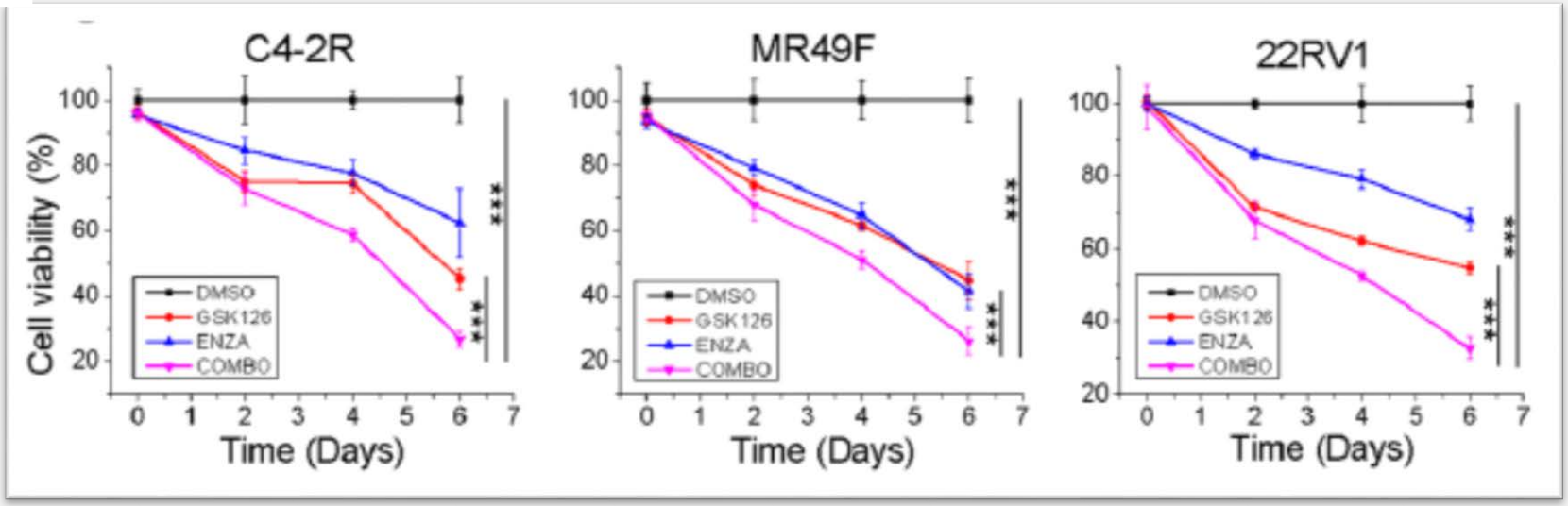
Azad, Baylin, et al. *Nature Reviews Clinical Oncology* 2013; 10:256

MCCR 19-30 Tazemetostat

- Tazemetostat is able to inhibit the activity of wild type EZH2 and EZH2 with activating mutations Y641, A677, and A687.
- The drug is orally administered and has a highest concentration peak at 1 to 2 hours and a elimination half time of 3 to 5 hours.

MCCR 19-30 EZH2 Inhibitor + Enzalutamide

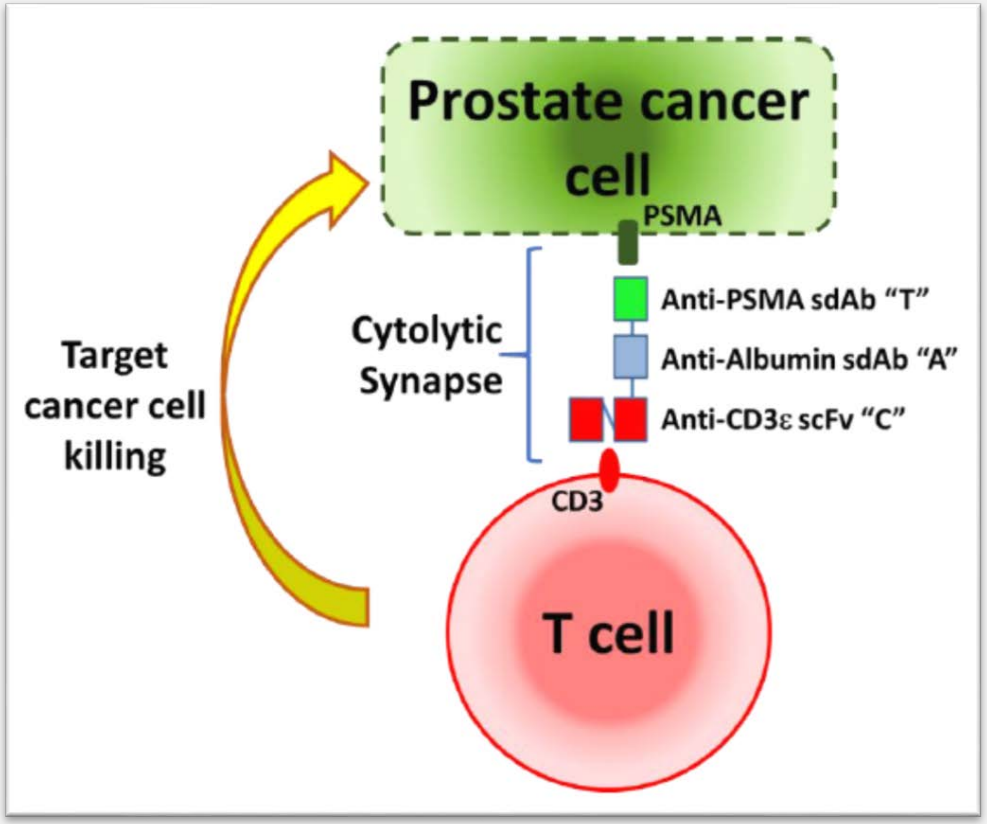
Prostate cancer cell lines treated with a small molecule EZH2 inhibitor and enzalutamide.



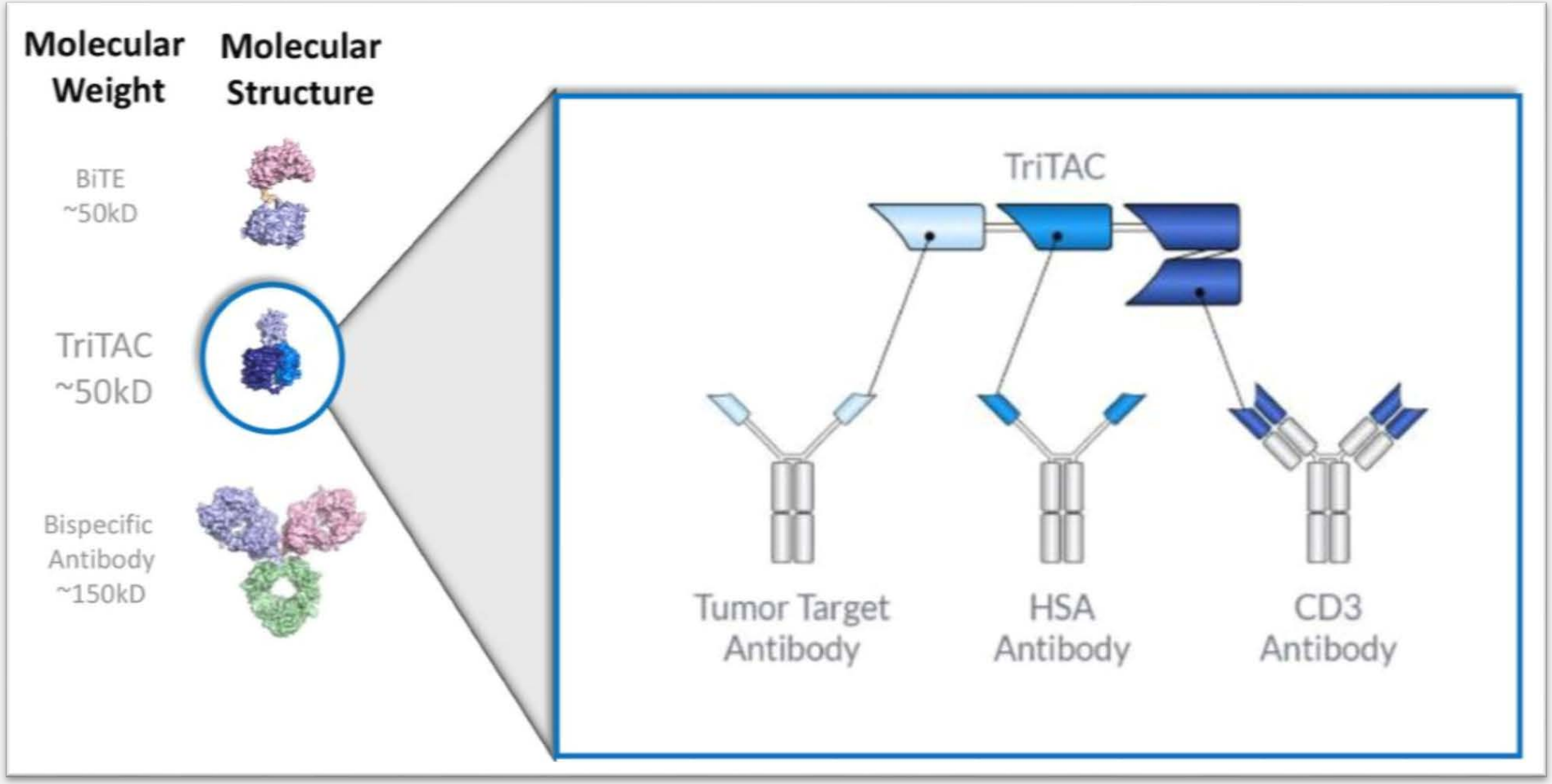
Bai, Lui, et al. *J Biological Chemistry 2019*; 294(25):9911

MCCR 19-32 Metastatic Castrate Resistant Prostate Cancer

A phase 1 open-label, multicenter, dose escalation and dose expansion study of the safety, tolerability, and pharmacokinetics of HPN424 in patients with advanced prostate cancer refractory to androgen therapy.



HPN 424 Tri-specific T-cell Activating Construct (TriTAC)



Get in TOUCH

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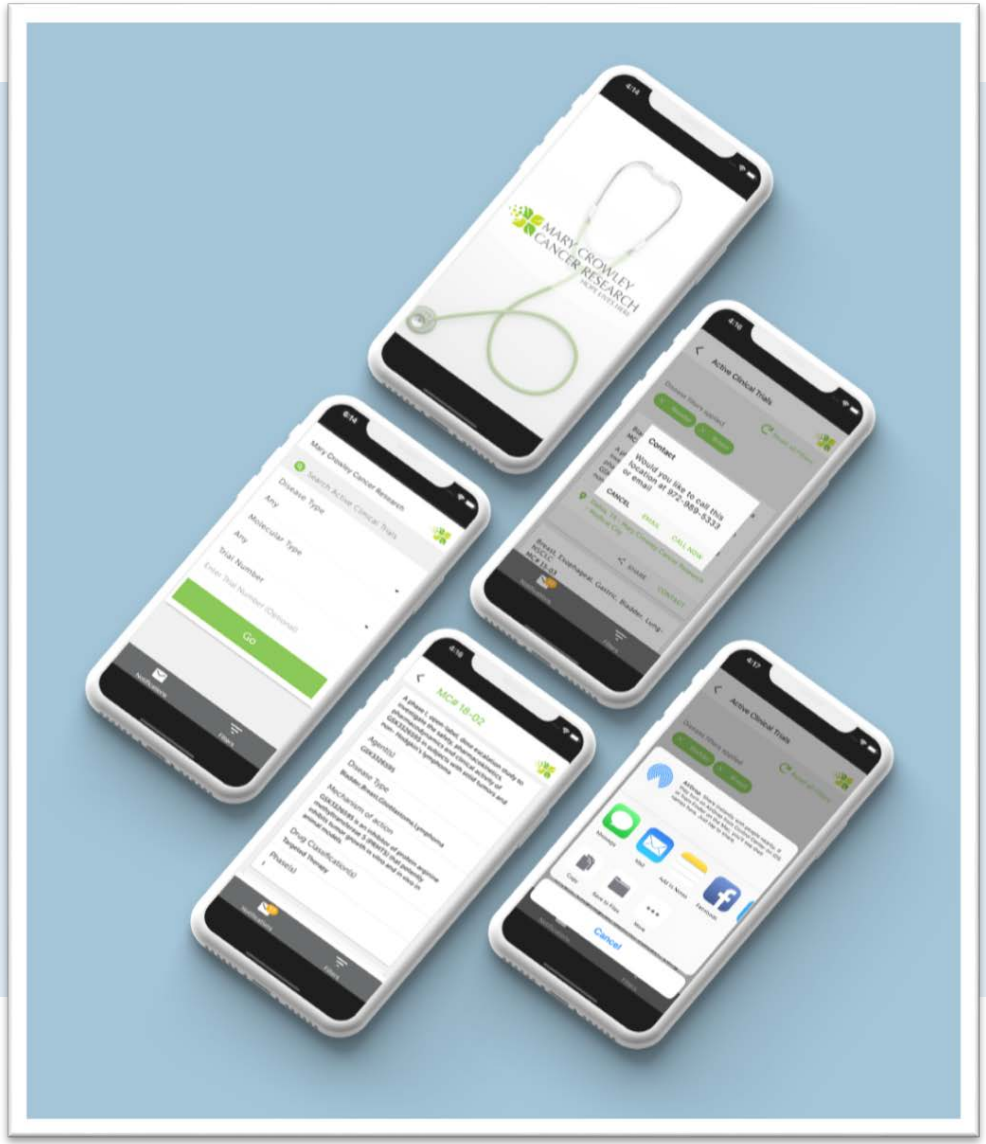
Find our Clinical Trials App for free in Apple and Google App Stores



THANK YOU

Patients

A special thanks to all patients who participate in clinical trials. It is because of them that others will live.

Thank you to my team!