METASTATIC CASTRATE RESISTANT PROSTATE CANCER: AN INTEGRATED APPROACH TO OPTIMIZE PATIENT THERAPY

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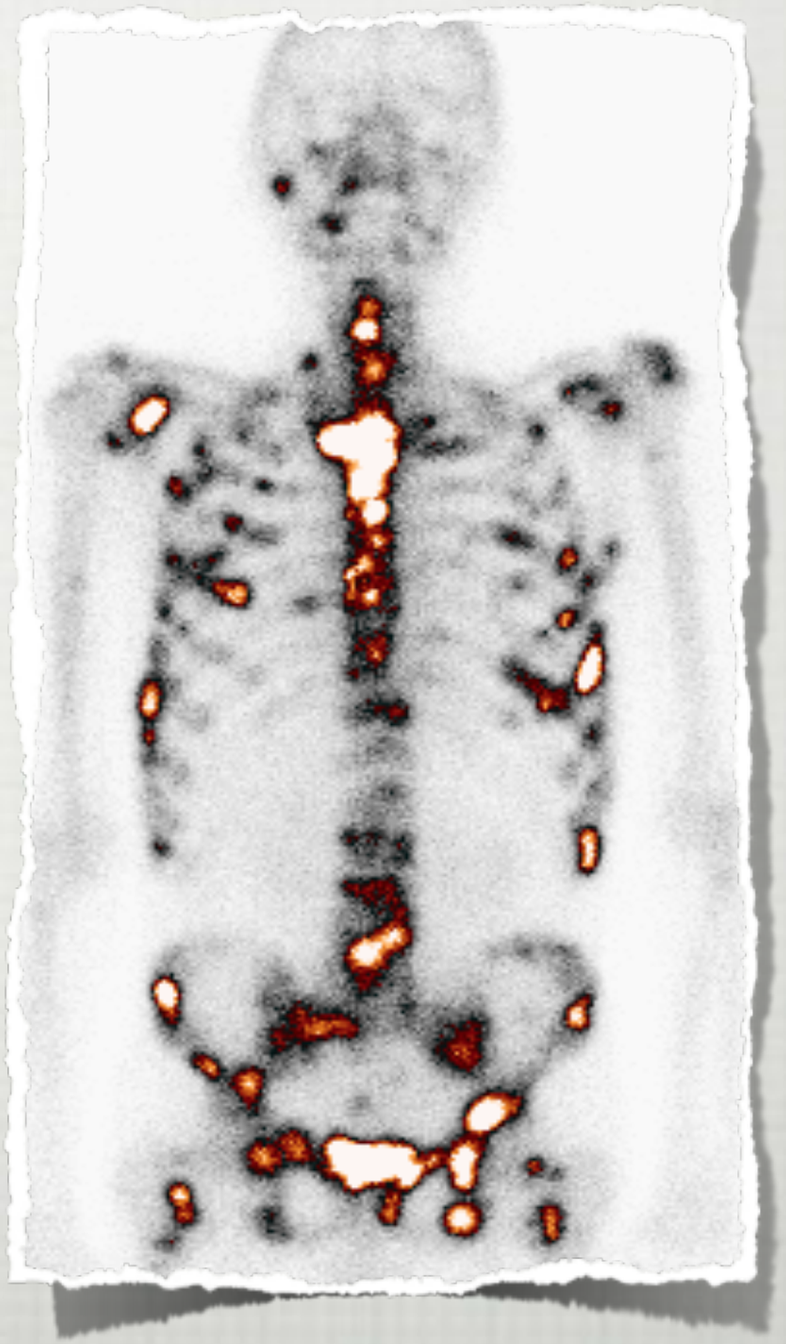
PARK, JULIO POW-SANG AND JAKE SCOTT

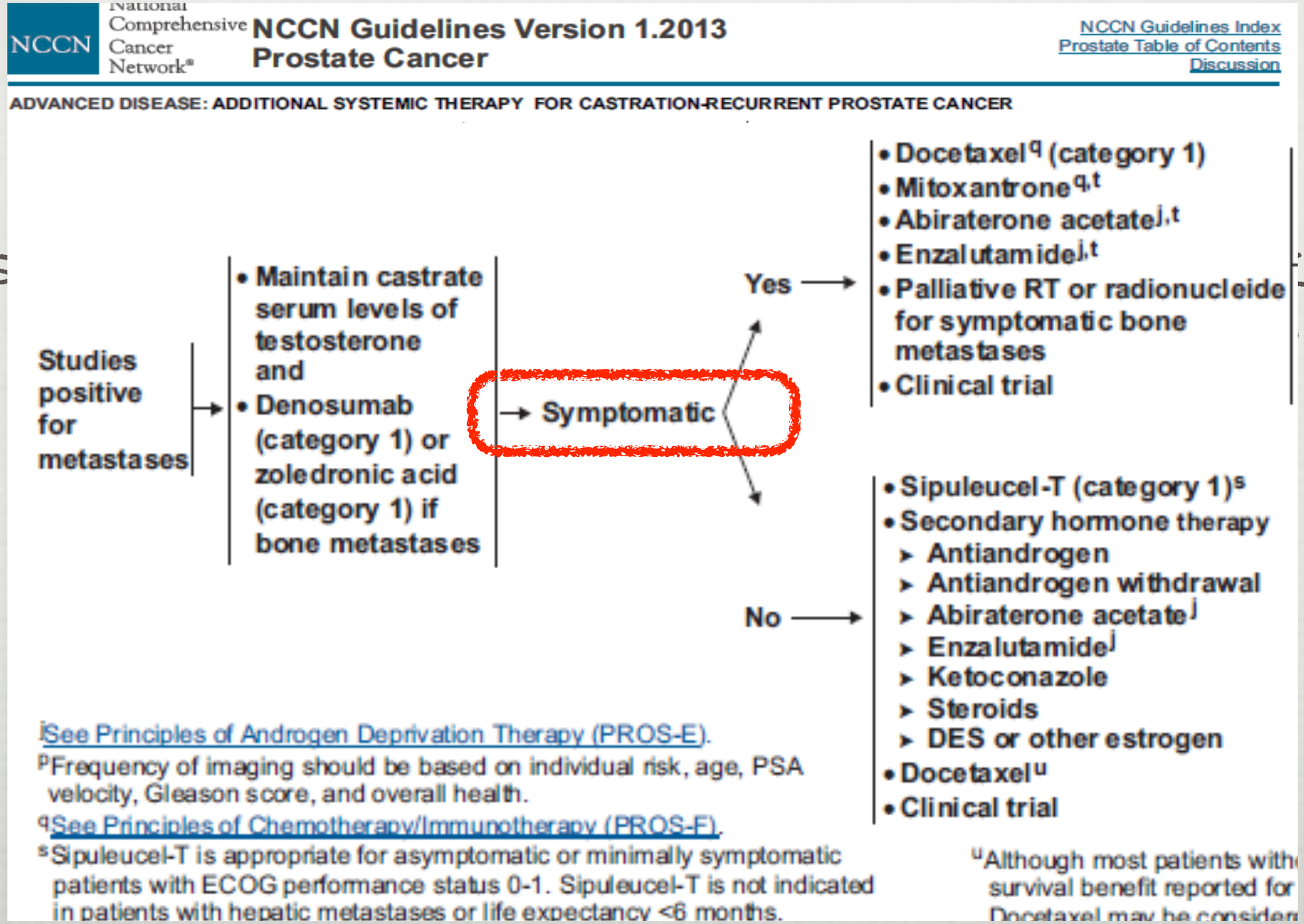
PROSTATE CANCER

- SINCE THE BEGINNING OF THIS MEETING, 232 MEN IN THE USA ALONE HAVE DIED FROM METASTATIC PROSTATE CANCER (WWW.CANCER.ORG)
- 90% OF MEN THAT DIE FROM PROSTATE CANCER WILL HAVE BONE METASTASIS
- INITIALLY, PROSTATE CANCER RESPONDS TO HORMONAL THERAPY; HOWEVER, RESISTANCE IS INEVITABLE
- R
- AND CURRENT THERAPIES ARE INEFFECTIVE

CASTRATE RESISTANT METASTATIC PROSTATE CANCER



TREATMENT STRATEGIES FOR CASTRATION RESISTANT PROSTATE CANCER @ MOFFITT

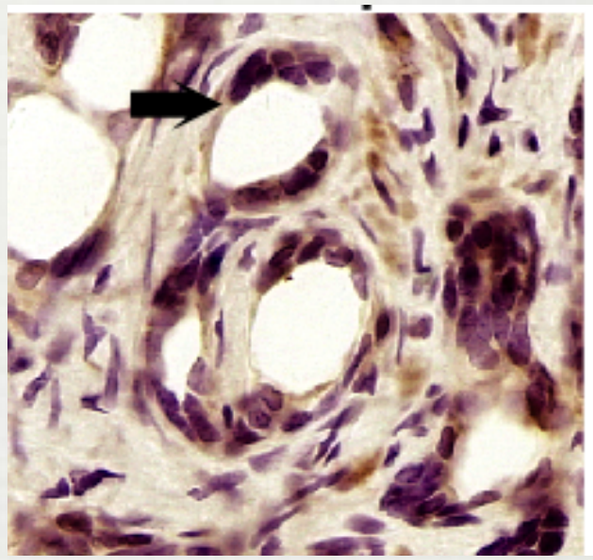


POTENTIAL TARGETED THERAPIES

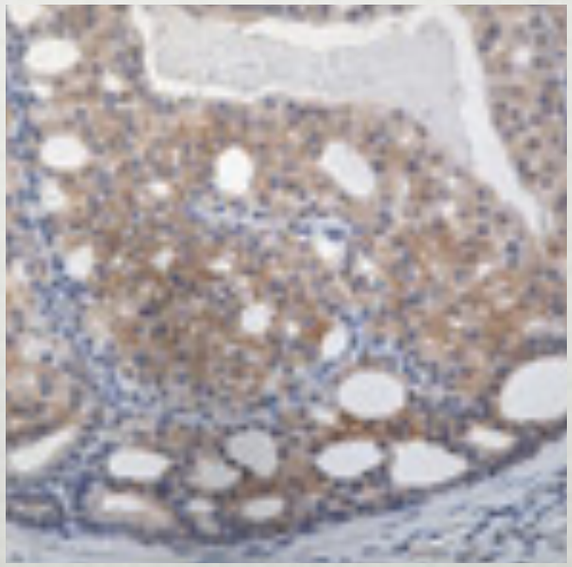
NOVEL THERAPIES

- ☐ BASED ON PATIENT'S CANCER PATHWAY ACTIVATION
- ☐ JAK/STAT PATHWAY
- ☐ AKT PATHWAY (LOSS OF PTEN)

STAT5



AKT



QUESTION?

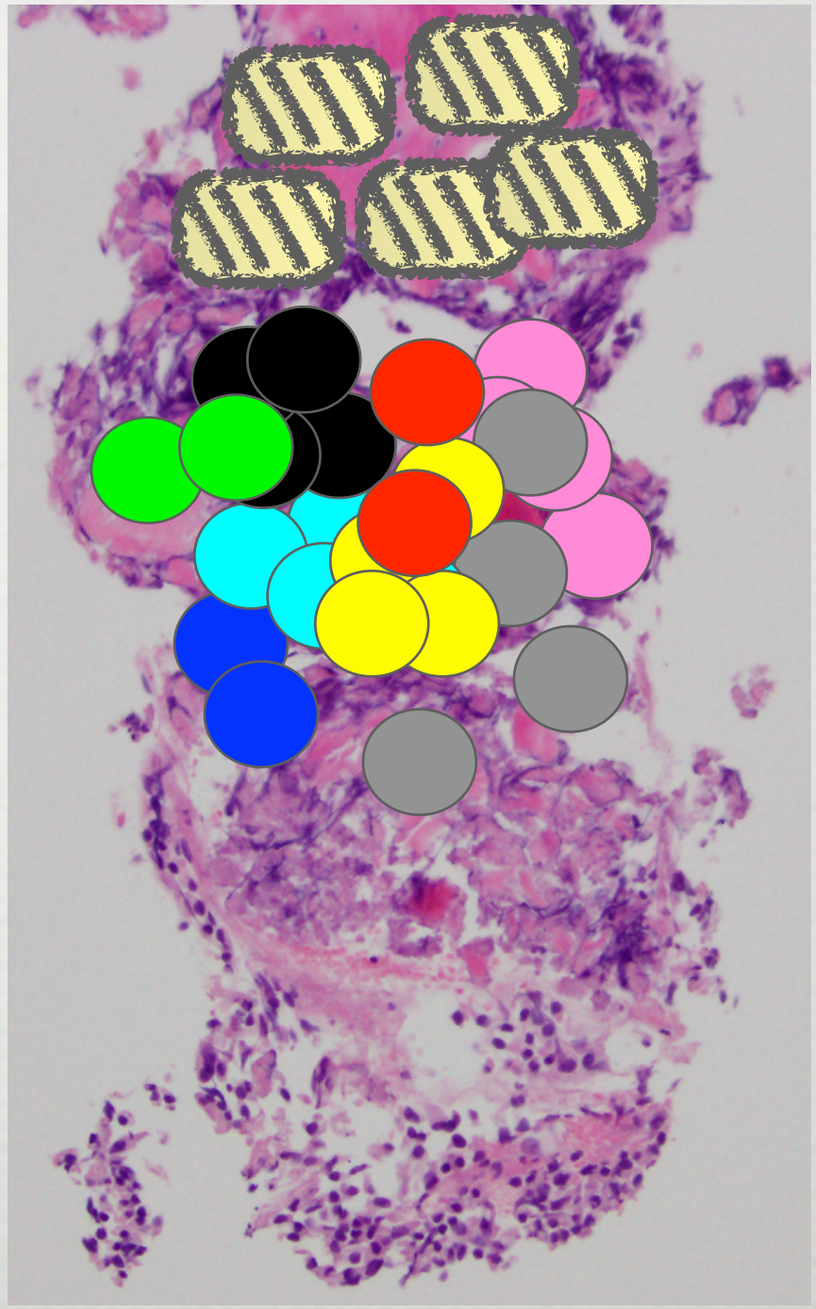
CAN WE OPTIMIZE THE USE OF CONVENTIONAL AND NOVEL TARGETED THERAPIES TO IMPROVE SURVIVAL OF PATIENTS WITH CASTRATE RESISTANT METASTATIC PROSTATE CANCER?

WE WILL USE AN INTEGRATED CLINICAL, BIOLOGICAL AND MATHEMATICAL MODELING APPROACH TO ADDRESS OUR QUESTION!

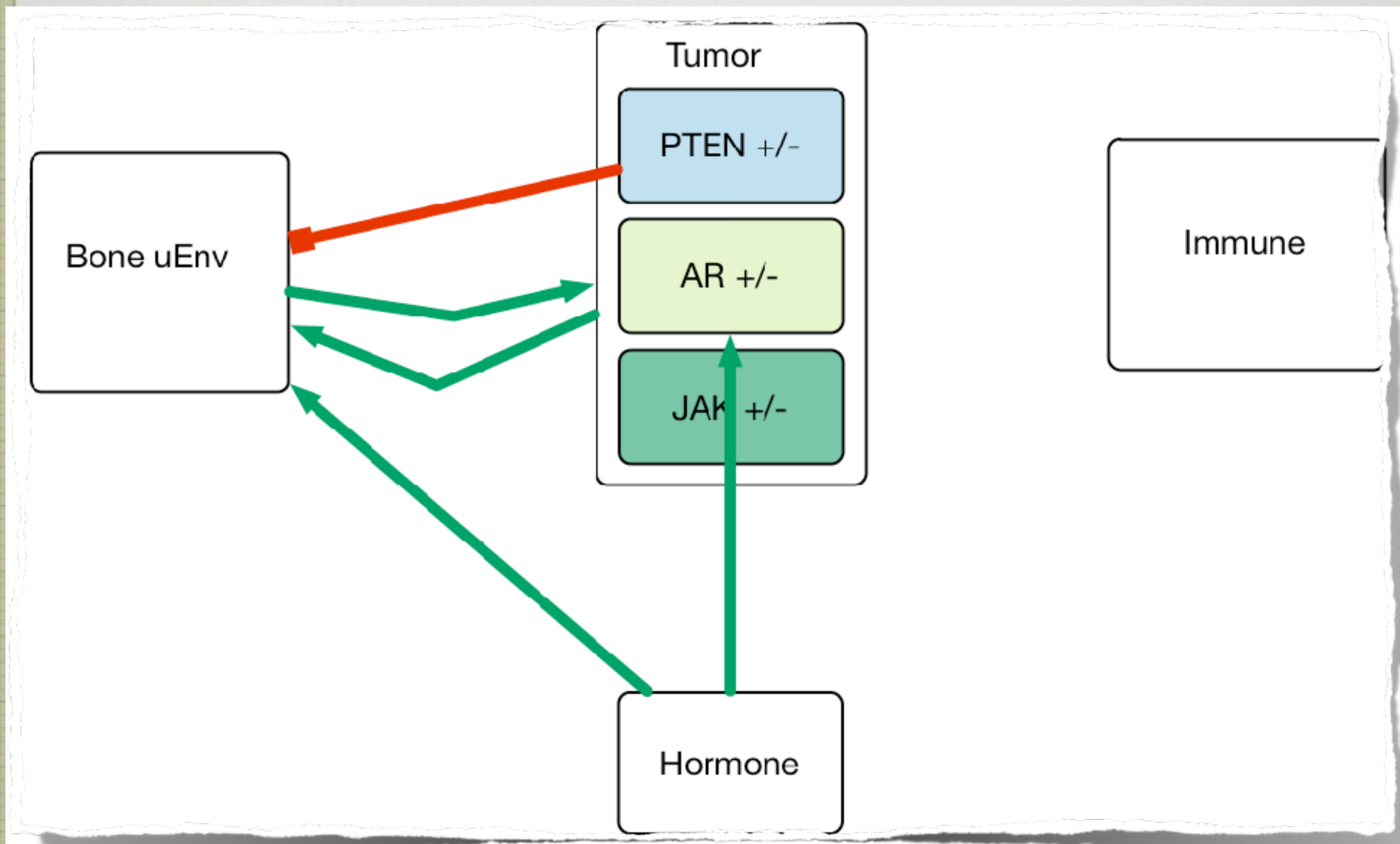
INDEX PATIENT-MR. SMITH: A MODEL CASE

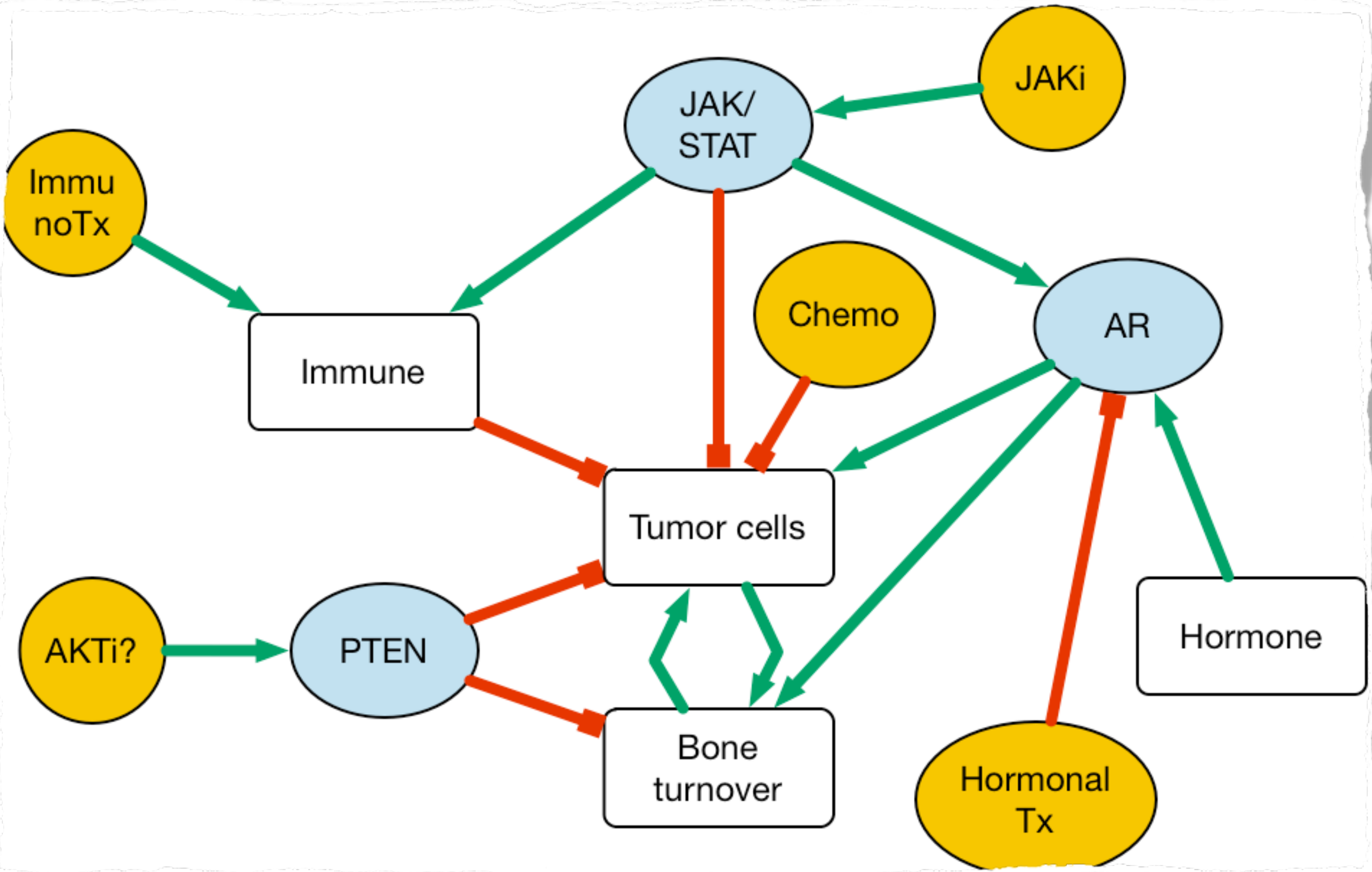
PCa	AR	JAK	AKT	
1	+	+	+	
2	+	+	-	
3	+	-	+	
4	+	-	-	
5	-	+	+	
6	-	+	-	
7	-	-	+	
8	-	-	-	

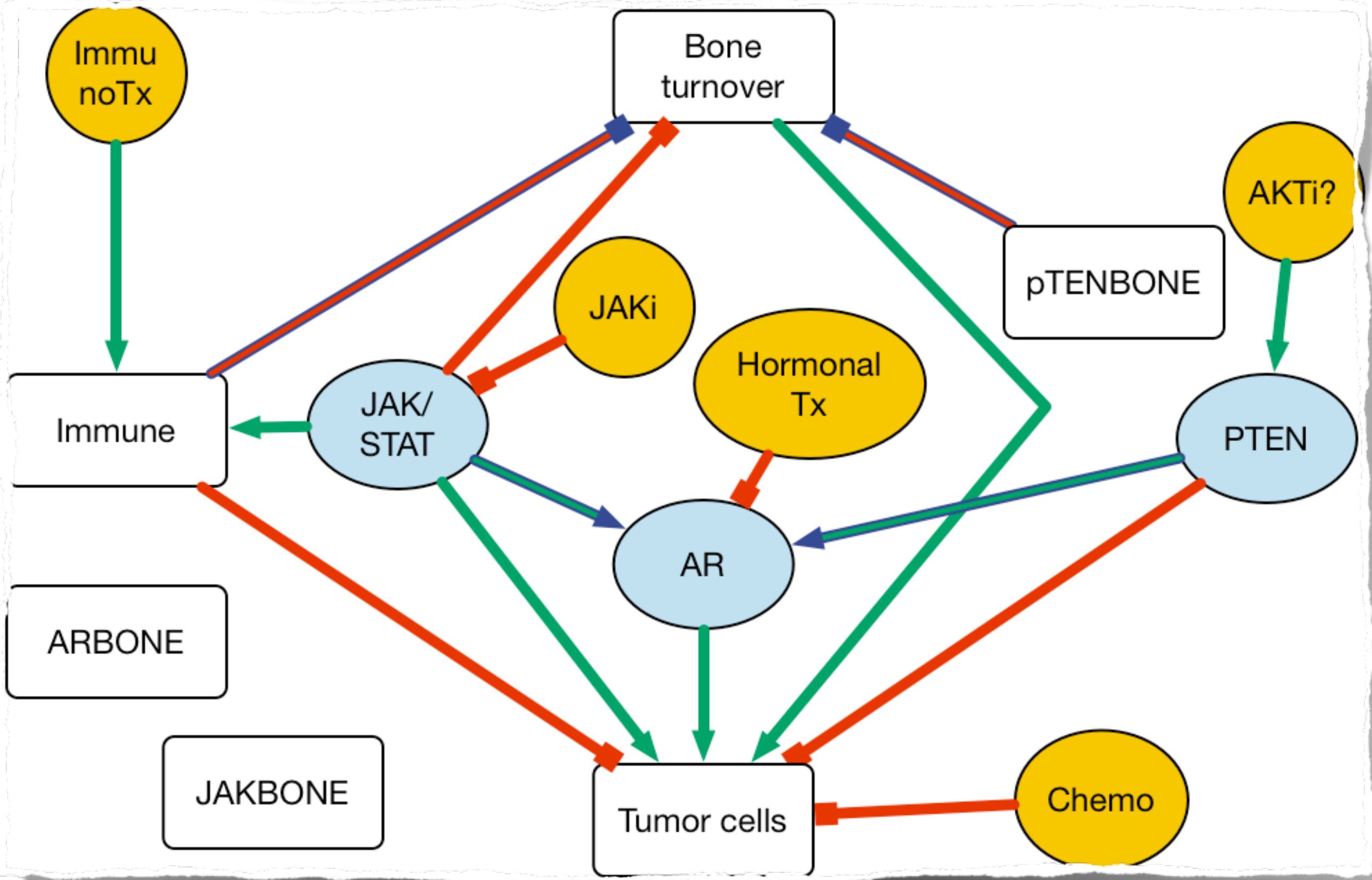
uENV	AR	JAK	AKT	
OCL/OBL	+/-	+/-	+/-	

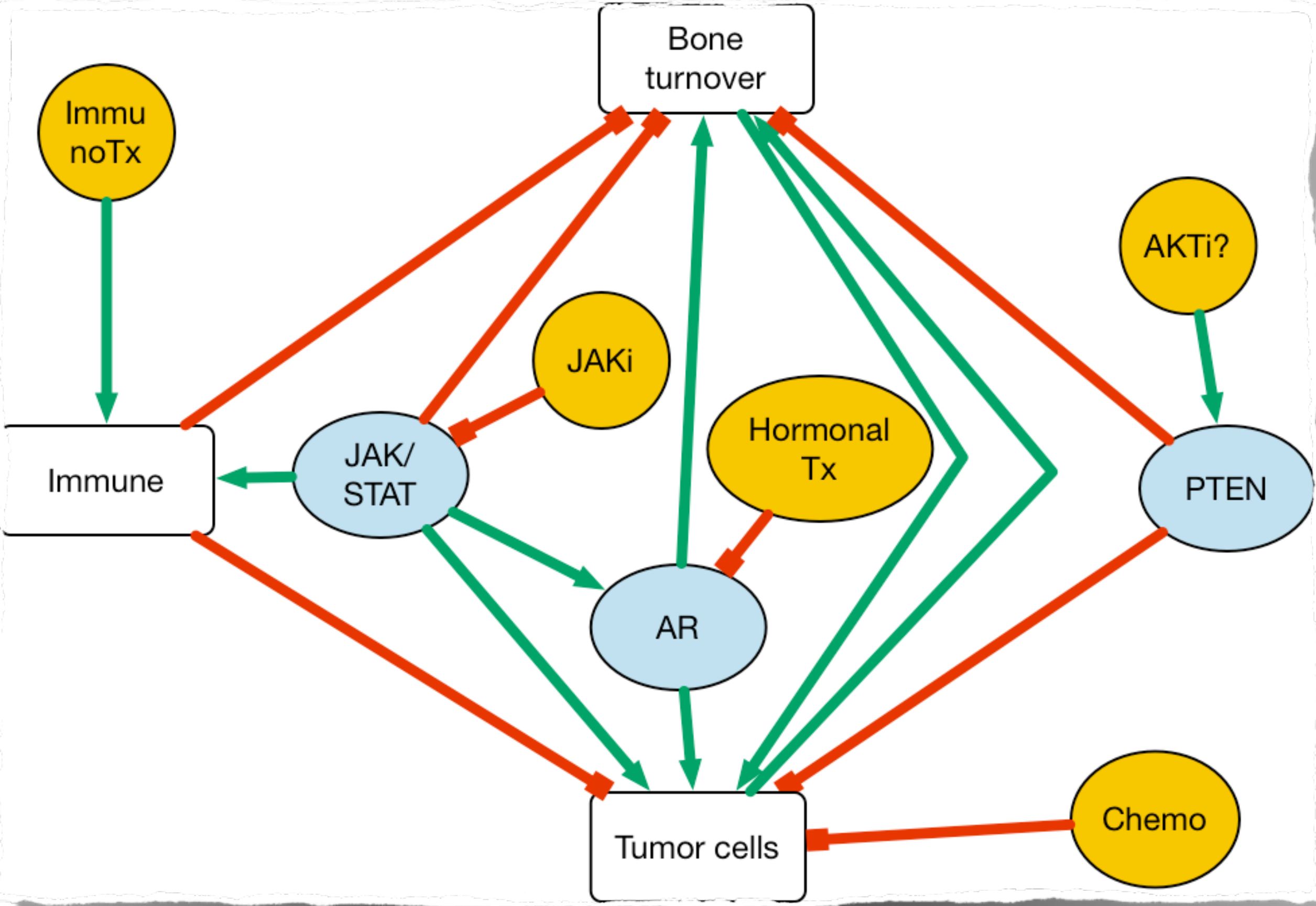


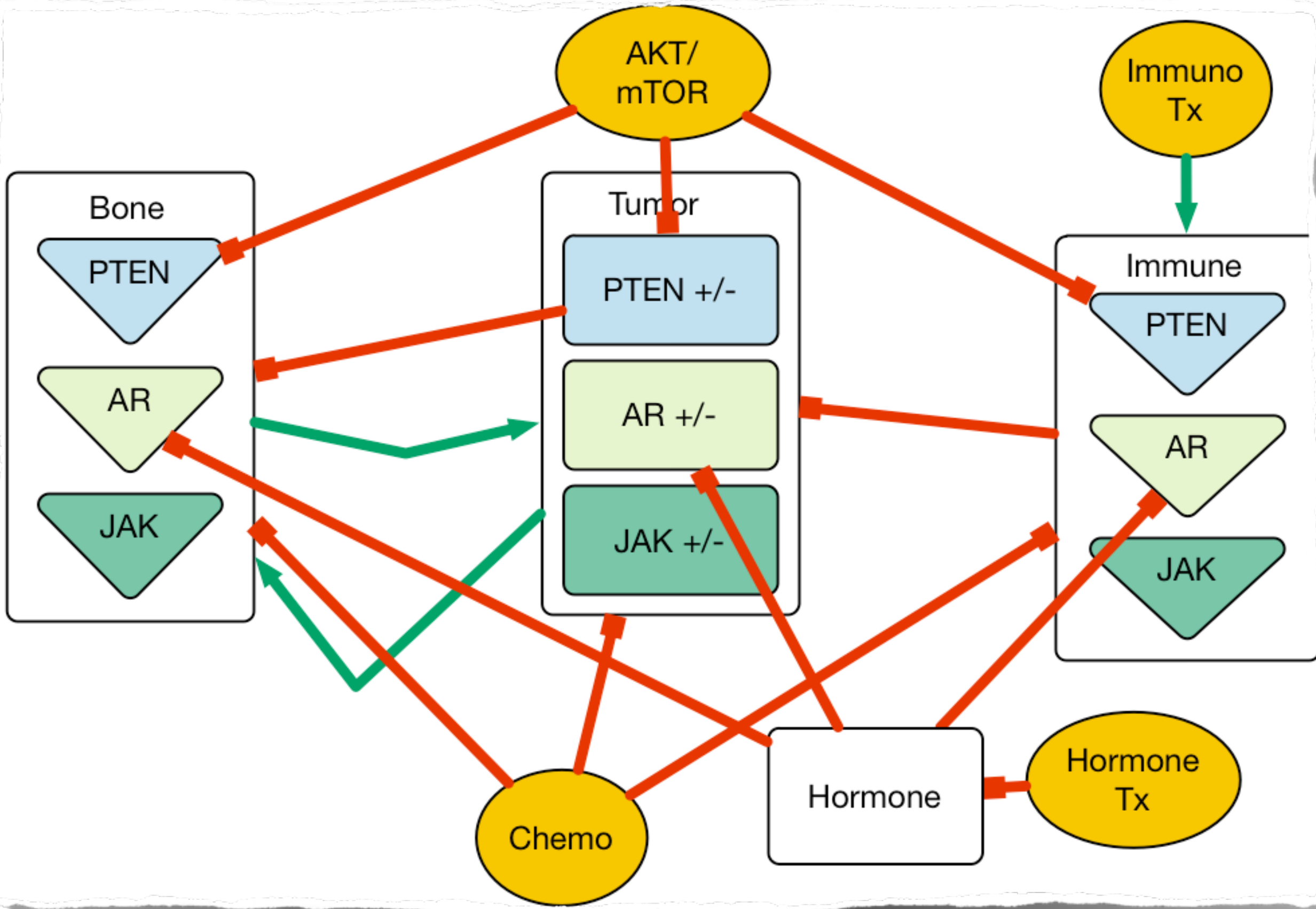
METASTATIC PROSTATE BONE BIOPSY FROM MOFFITT PATIENT, JAS DHILLON

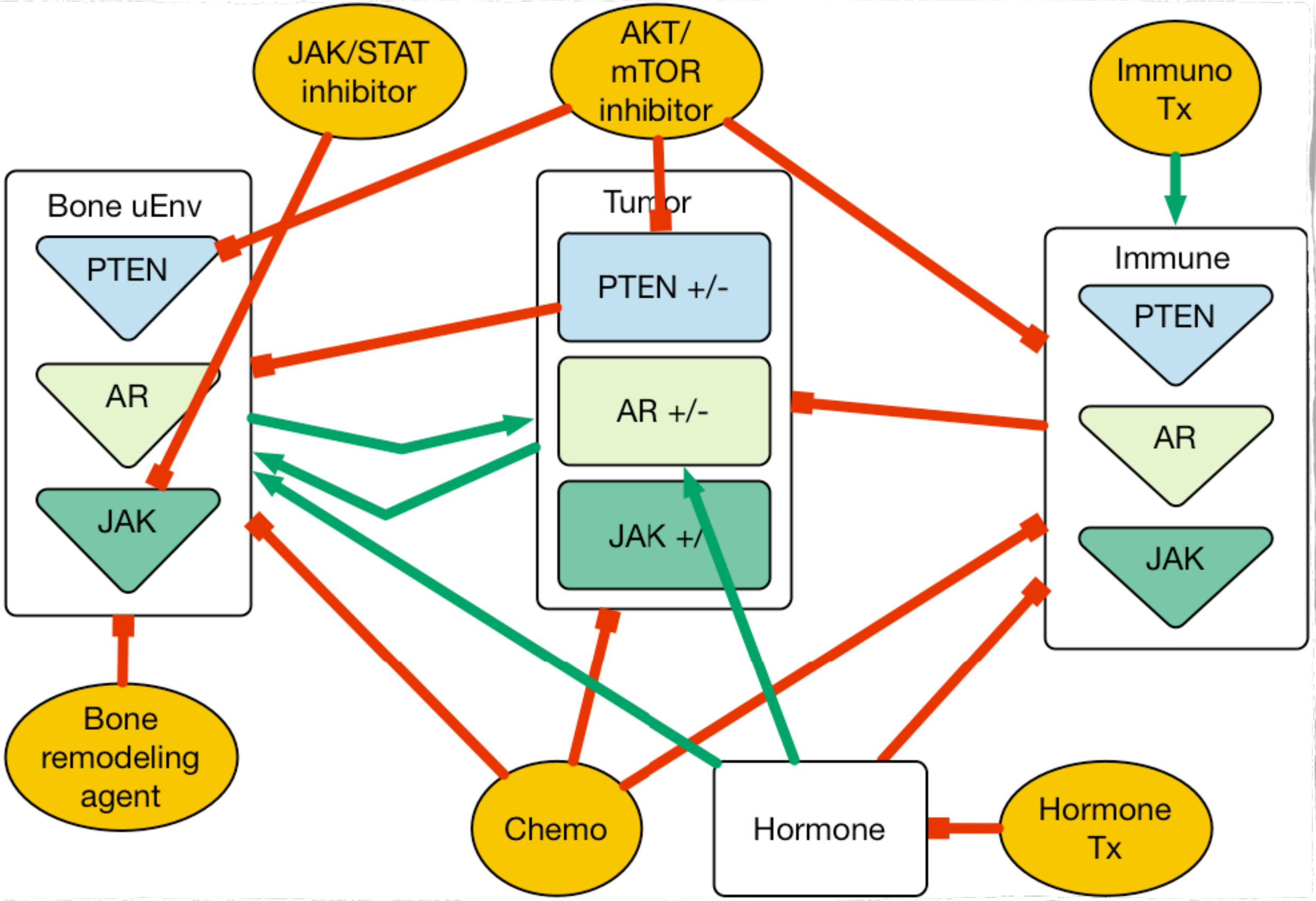

Tumor
PTEN +/-
AR +/-
JAK +/-
Bone uEnv
Immune
Hormone

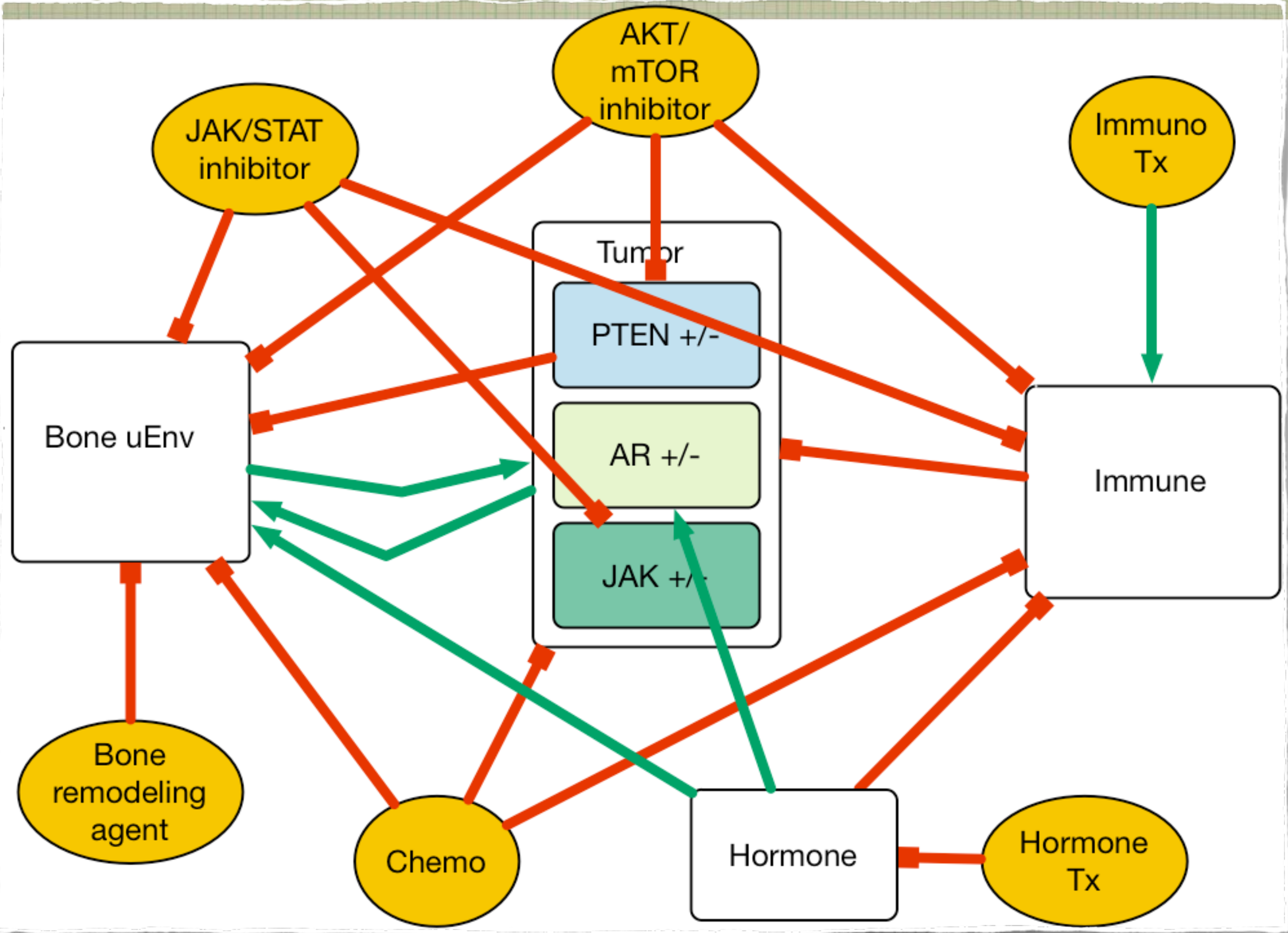

JAKi
JAK/
STAT
Immu
noTx
Immune
Chemo
AR
Tumor cells
AKTi?
PTEN
Hormone
Bone
turnover
Hormonal
Tx

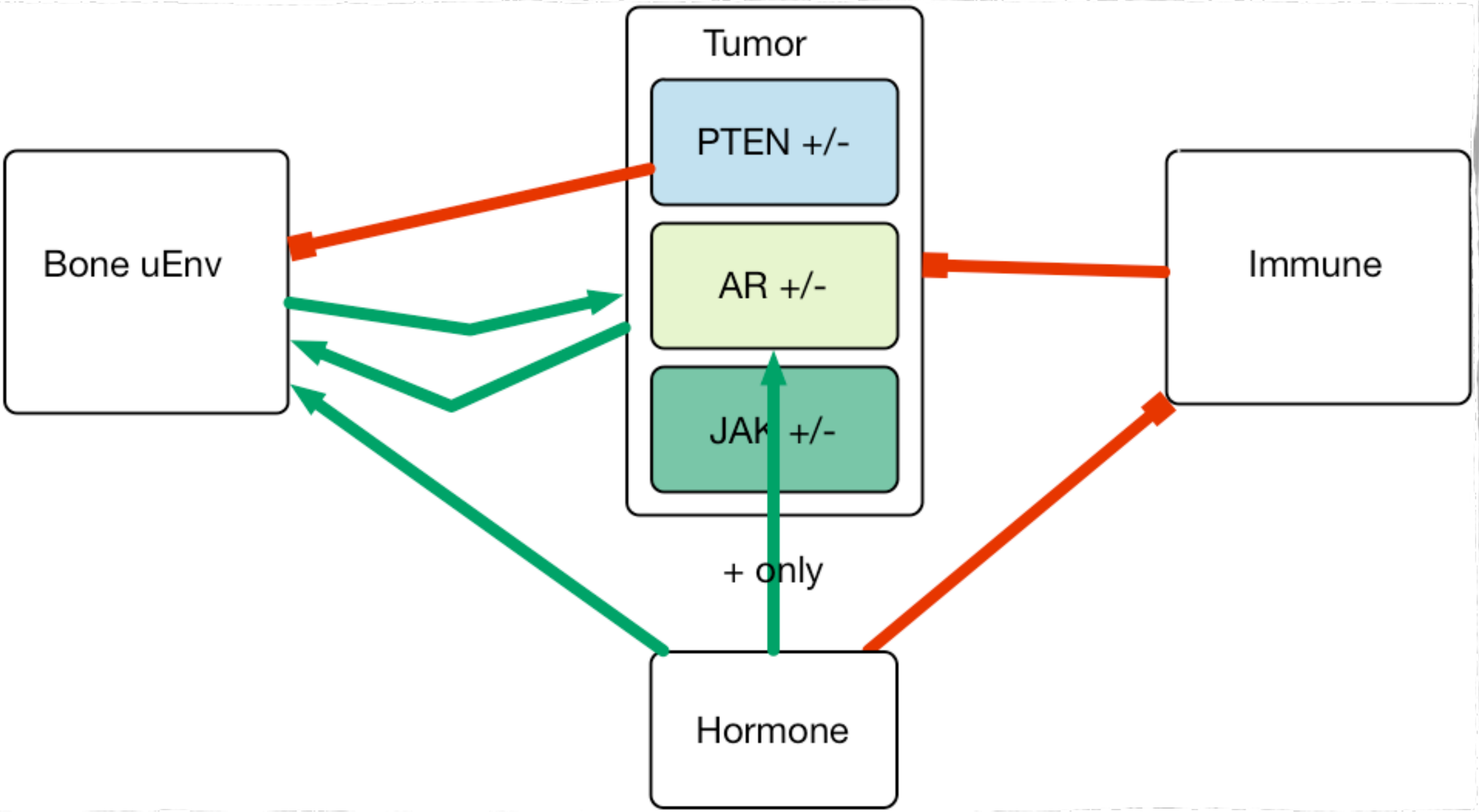

Immu
noTx
Bone
turnover
AKTi?
pTENBONE
JAKi
Hormonal
Tx
Immune
JAK/
STAT
PTEN
AR
ARBONE
JAKBONE
Tumor cells
Chemo

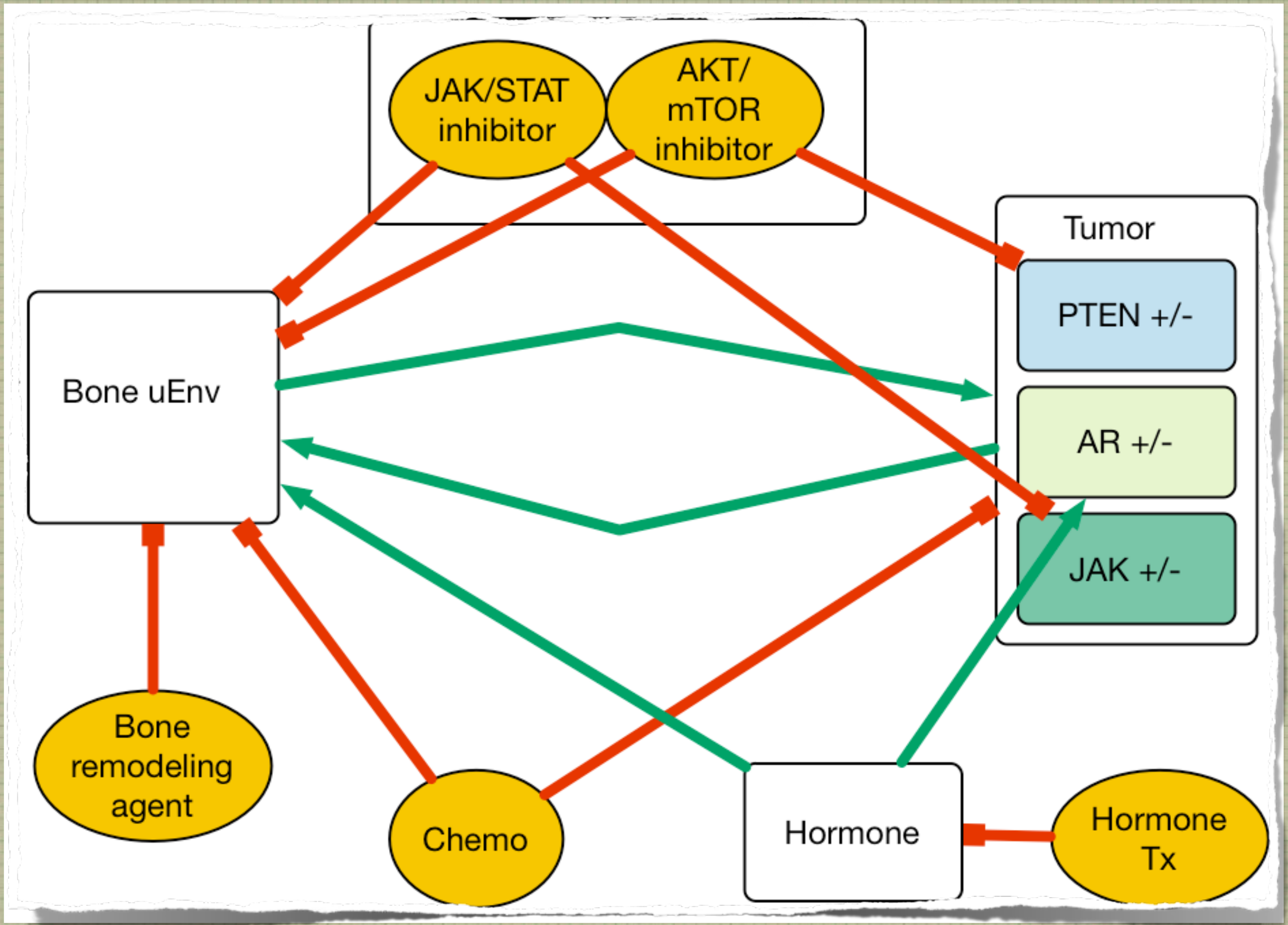

Bone turnover
Immu noTx
JAKi
AKTi?
Immune
JAK/ STAT
Hormonal Tx
PTEN
AR
Tumor cells
Chemo

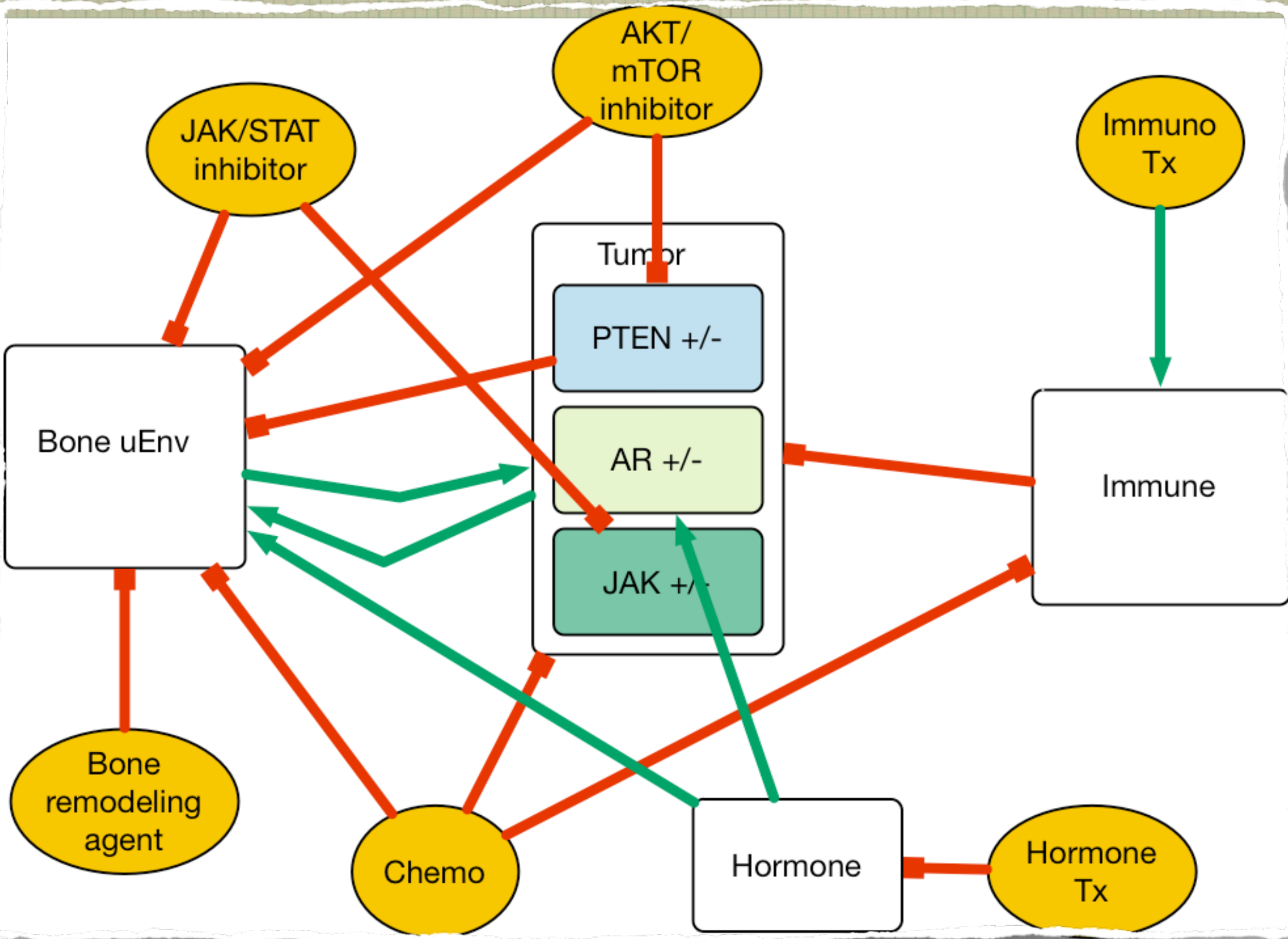

AKT/
mTOR
Immuno
Tx
Bone
PTEN
AR
JAK
Tumor
PTEN +/-
AR +/-
JAK +/-
Immune
PTEN
AR
JAK
Chemo
Hormone
Hormone
Tx


JAK/STAT inhibitor
AKT/ mTOR inhibitor
Immuno Tx
Bone uEnv
PTEN
AR
JAK
Tumor
PTEN +/-
AR +/-
JAK +/
Immune
PTEN
AR
JAK
Bone remodeling agent
Chemo
Hormone
Hormone Tx

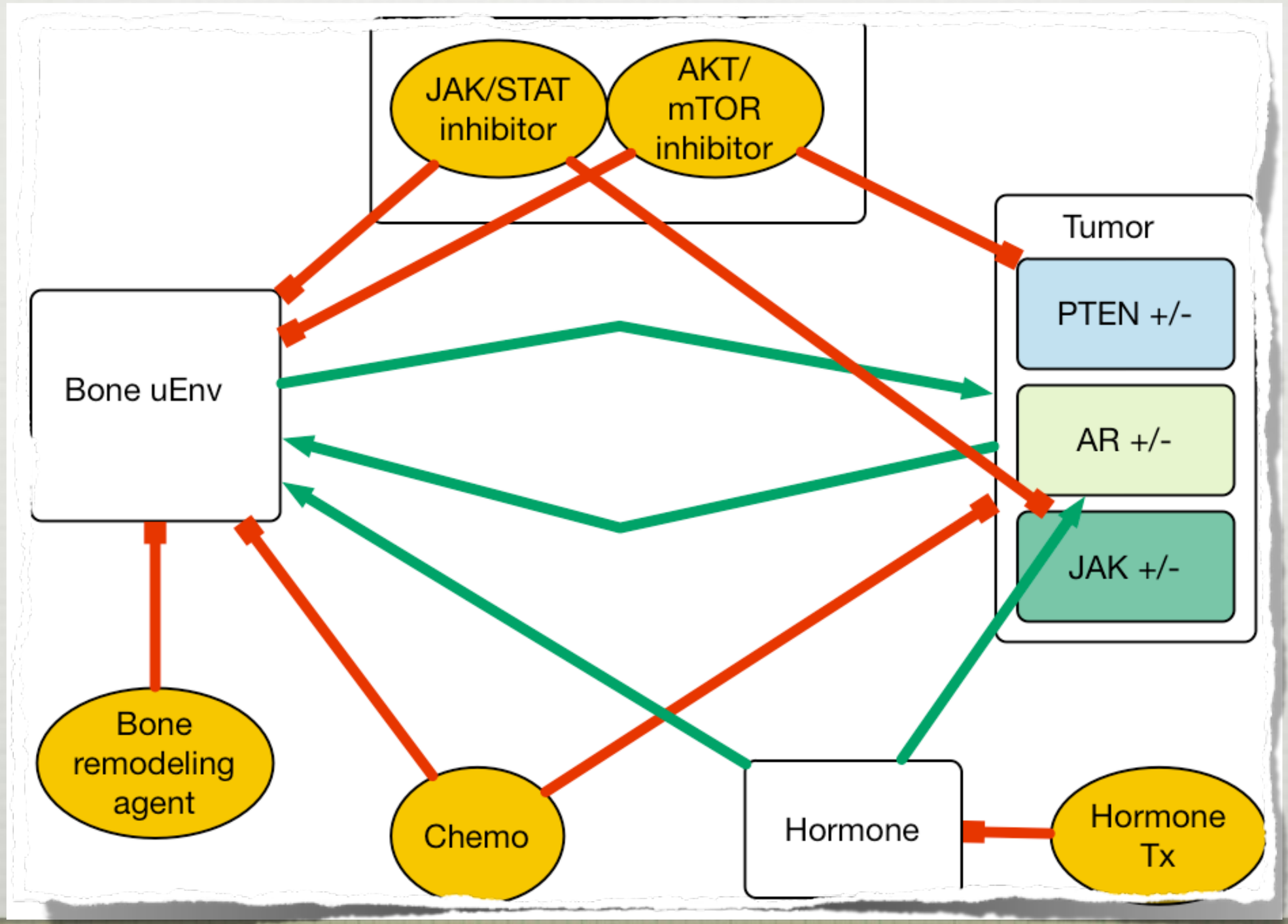

AKT/
mTOR
inhibitor
JAK/STAT
inhibitor
Immuno
Tx
Tumor
PTEN +/-
AR +/-
JAK +/-
Bone uEnv
Immune
Bone
remodeling
agent
Chemo
Hormone
Hormone
Tx


Tumor
PTEN +/-
AR +/-
JAK +/-
Bone uEnv
Immune
+ only
Hormone


JAK/STAT inhibitor
AKT/ mTOR inhibitor
Tumor
PTEN +/-
AR +/-
JAK +/-
Bone uEnv
Bone remodeling agent
Chemo
Hormone
Hormone Tx


AKT/
mTOR
inhibitor
JAK/STAT
inhibitor
Immuno
Tx
Tumor
PTEN +/-
AR +/-
JAK +/-
Bone uEnv
Immune
Bone
remodeling
agent
Chemo
Hormone
Hormone
Tx

FINAL WORKING MODEL



Model Implementation - 1st Order Linear Ordinary Differential Equations

$$\dot{T}_i = \Big(\overbrace{\alpha_i}^{\text{baseline proliferation}} + \overbrace{\beta_i B}^{\text{bone stimulation}} + \overbrace{\gamma_i J_i(1-J_x)}^{\text{JAK/STAT pathway}} + \overbrace{\rho_i P_i(1-P_x)}^{\text{AKT pathway}} + \overbrace{\sigma_i A_i H}^{\text{androgen stimulation}} - \overbrace{\eta_i C_x}^{\text{chemotherapy effect}} \Big) T_i$$

$$\dot{B} = \Big(\overbrace{-P_x\nu_p}^{\text{AKT inhibition}} - \overbrace{J_x\nu_J}^{\text{JAK/STAT inhibition}} - \overbrace{C_x\nu_C}^{\text{chemo effect}} - \overbrace{R_x\nu_R}^{\text{RANK-ligand}} + \overbrace{H}^{\text{androgen stimulation}} \Big) B + \overbrace{\sum_{i=1}^{8} T_i \quad \nu_T}^{\text{tumor cell stimulation}}$$

$$H = H_0 - H_x\eta$$

$$J_i, P_i, A_i = \begin{cases} 1 & \text{if mutation is present} \\ 0 & \text{otherwise} \end{cases} \qquad J_x, R_x, P_x, H_x, C_x = \begin{cases} 1 & \text{if treatment is applied} \\ 0 & \text{otherwise} \end{cases}$$

Parameterization...

al conditions (i.e. baselines):
- amount of bone (I know it's abstrac: - any parameters welcome) Human femur volume = 1x106 mm3, Bone= 0.14x106 mm3
- amount of immune cells (Tcells?)
- hormone (testosterone?)
- Tumor growth rate 6mm3 per day (PMID 15330153)

T times (either clinically relevant or proposed times based on studies of failure/success):
- Cx=chemo every 3 weeks for 12 weeks (based on scans and regression, continue until progression)
- Hx=hormonal AR directed therapy 12 weeks (based on scans.....if tumor regressing by scan, they stay on it)
- Ix=immuno 9 weeks with 3 courses
- Jx=JAK Jak2 inhibitor Daily treatment for 8 weeks (based on follow up and regression continue until progression)
- Px=AKT (PTEN loss) Oral daily for 8 weeks (based on scan and regression continue until progression)
- Rx=RANK Once overt mets detected by scan, Indefinite (always on)

Tx- independent:
- tumor stimulation of bone (i.e. rate of tumor increase per volume bone) 0.656um per day PMID: 3455637
- hormonal stimulation of immune (i.e rate of bone increase per mol hormone)
- hormonal stimulation of bone (i.e. rate of bone increase per mol hormone) 1.5x (0.656um per day)
- bone stimulation of tumor (i.e. rate of bone increase per tumor population) 3 fold increase in LnCAP growth in response to OB conditioned media over 5 days (Blaszczyk et al., Clin Can Res, 10, 2004
- tumor PTEN population inhibition of bone (i.e. rate of bone destruction per tumor PTENness)
- hormonal stimulation of the tumor: 7mm3 per day (PMID 15330153)

T x-dependent:

On Tumor Cells:
- rate of tumor decrease from Ix
- JAK/STAT Tumor death: 60% kill over one week at conc. (Dagvadorj A. et al. Clin Cancer Res. 2008). Agarwal et al., Carcinogenesis, 28, 2007
- AKT Tumor death: 80% kill over one week at conc. of (Dahlma KB, PLOS one 7(4) 2012), Agarwal et al., Carcinogenesis, 28, 2007)
- Abiraterone/ 50% kill rate over 4 weeks (mostaghel et al, Clin Can Res. 2011)
- rate of tumor decrease with Cx: with Cx 90% kill over 3 days of PC3 cells (Lee et al, Neoplasia, 6, 2004)
  In bone, Cx (Taxotere decreases tumor volume by 3% over 50 days)
- ?Rx: 12% decrease in tumor volume over time with zoledronate
- ?Rx plus Cx decreases in tumor volume over 20% decrease in tumor volume over time (Brubakker et al, 2006, BMC Cancer)

On immune:
- rate of immune decrease with Cx
- rate of immune decrease with Jx
- rate of immune decrease with Px
- rate of immune increase with Ix

On Bone:
- rate of bone decrease with Px: 60% reduction in mineralization over 10 days (Mukherjee and Rotwein, J. Cell Sci. 122, 2009
- ?rate of bone decrease with Jx: guess - 20% in 21 days - 80% increase in promoter activity in oble when stats are activated, time? (Gerland et Mol Cell Endo, 168, 2000)
- ?rate of bone decrease with Cx: 20% decrease in 21 days - guess
- Rate of bone decrease with Rx 50% decrease in bone apposition in mice, over 21 days (Kostenuik et al., JBMR, vol 24 2009)

On Hormone:
- depletion from residual hormone in castrate resistant men

ingle dose of abiraterone reduces systemic testosterone from 3.5nm/l to 0.7nm/l in over 7 days (80% reduction). (O'Donnell A et al. Br J Cancer, 2004)

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1	+	+	+	
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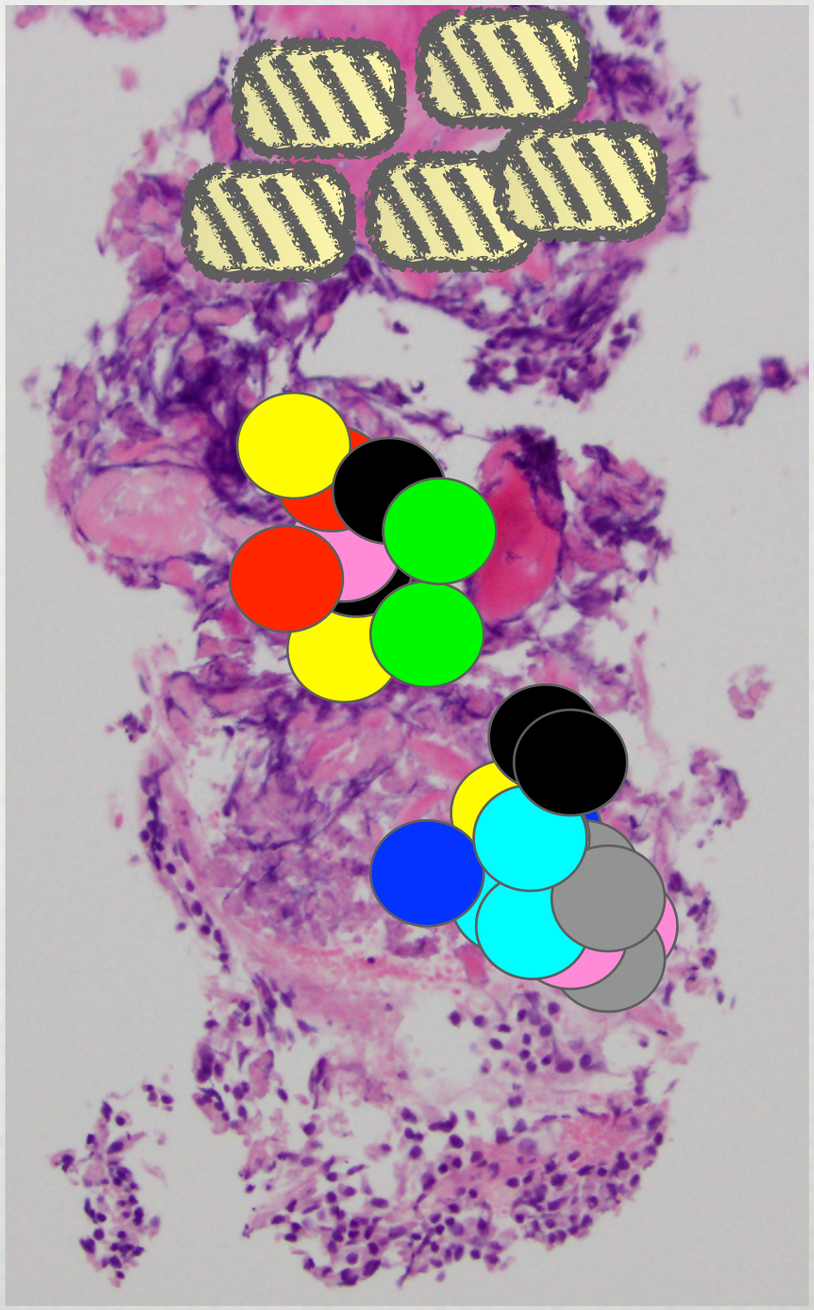
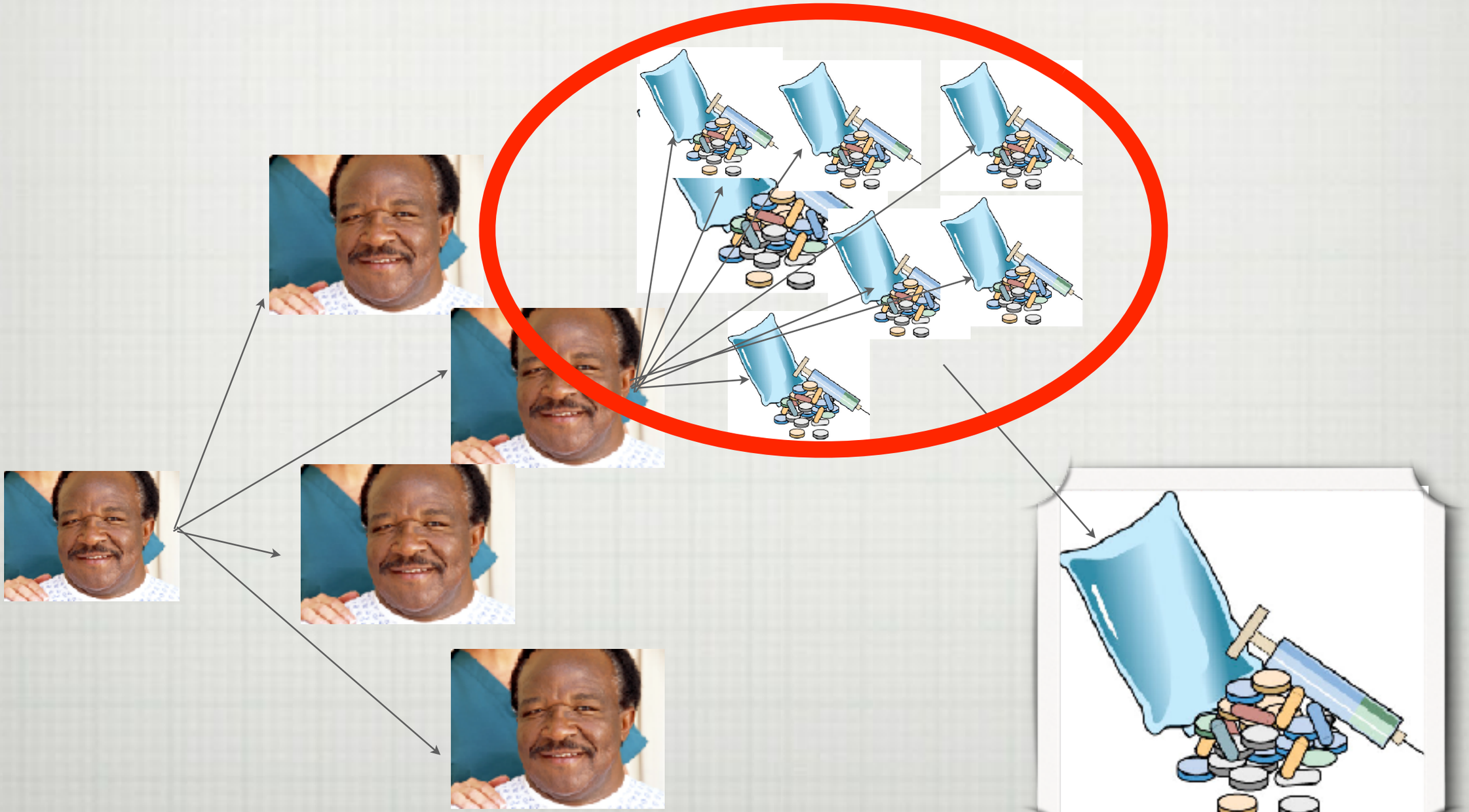
7	-	-	+	
8	-	-	-	

uENV	AR	JAK	AKT	
OCL/OBL	+/-	+/-	+/-	

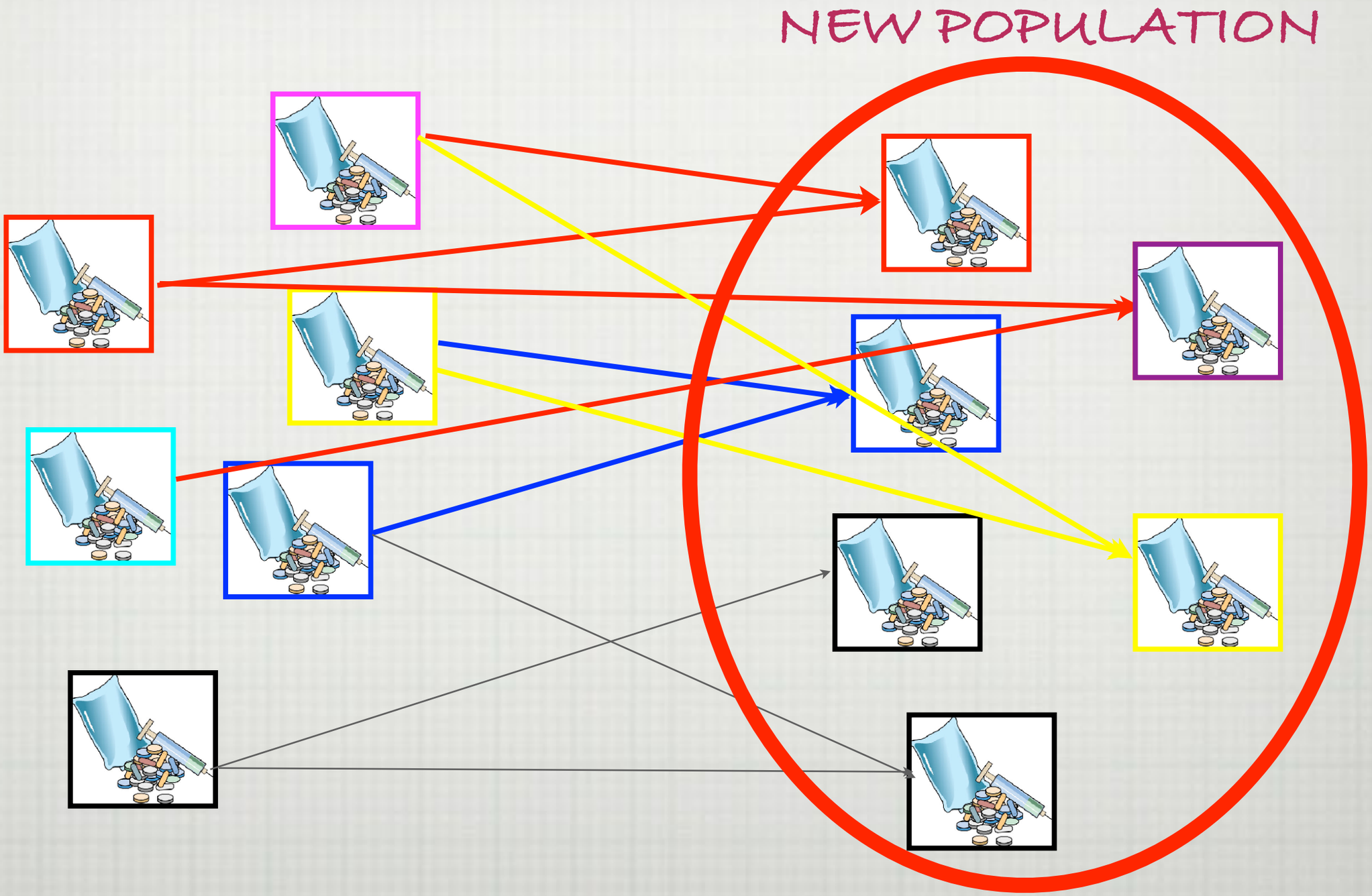


METASTATIC PROSTATE BONE BIOPSY FROM MOFFITT PATIENT, JAS DHILLON

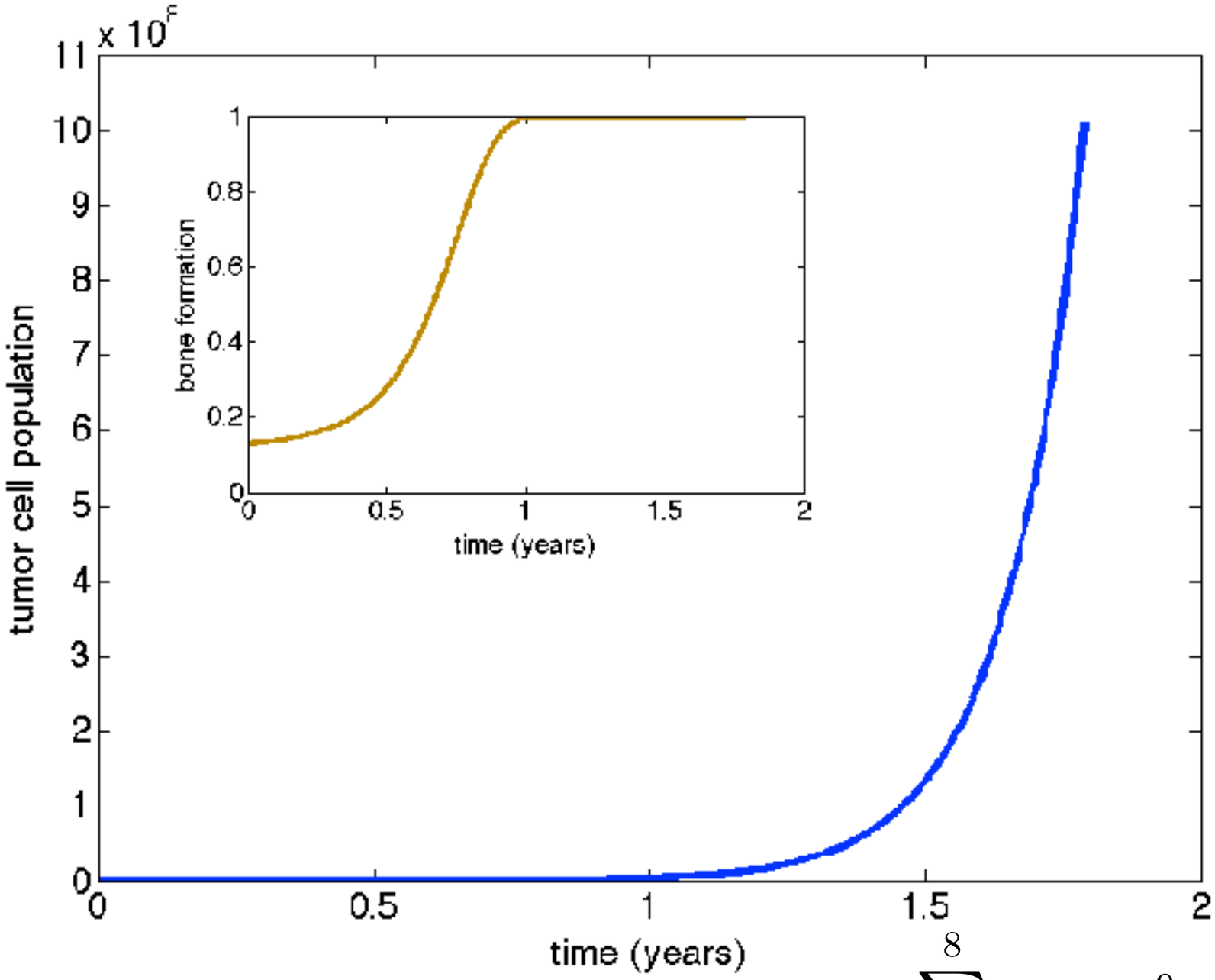
GENETIC ALGORITHM



GENETIC ALGORITHM



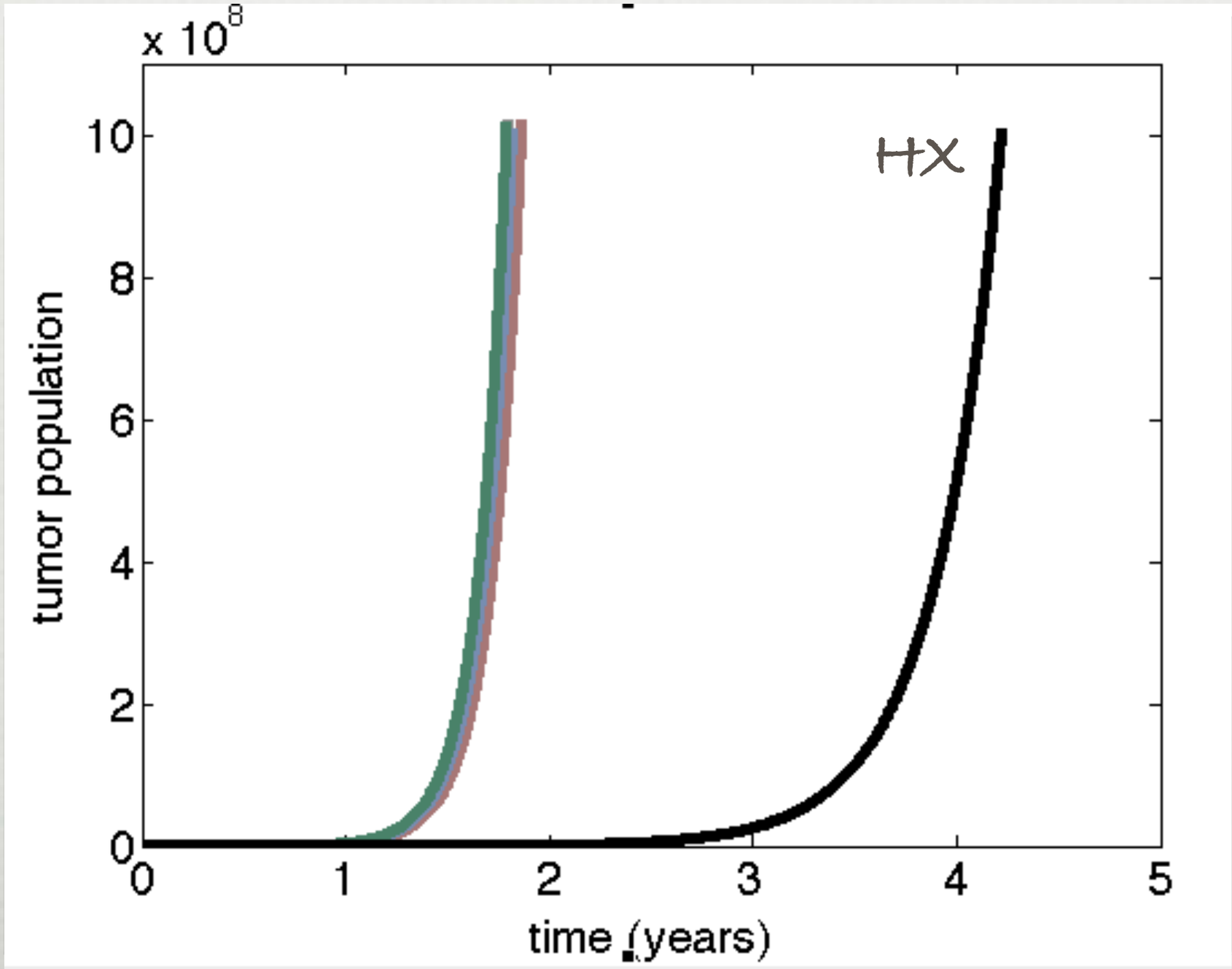
UNTREATED TUMOR GROWTH



$$\sum_{i=1}^{8} T_i = 10^9 \text{ tumor cells}$$

average size of detectable tumor ~ 10^7
~100 detectable tumors

RESULTS

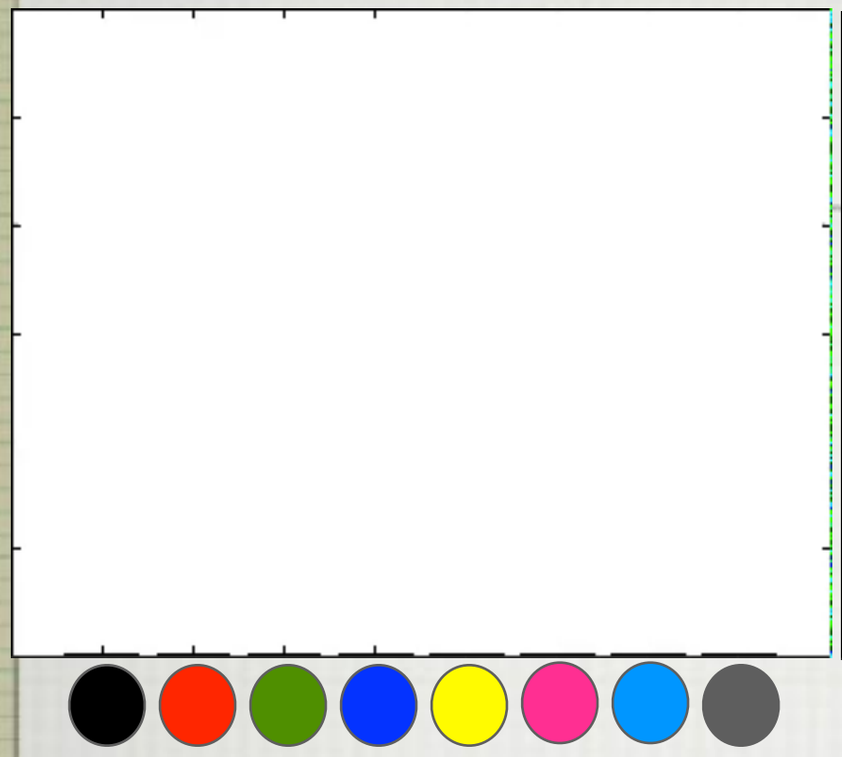


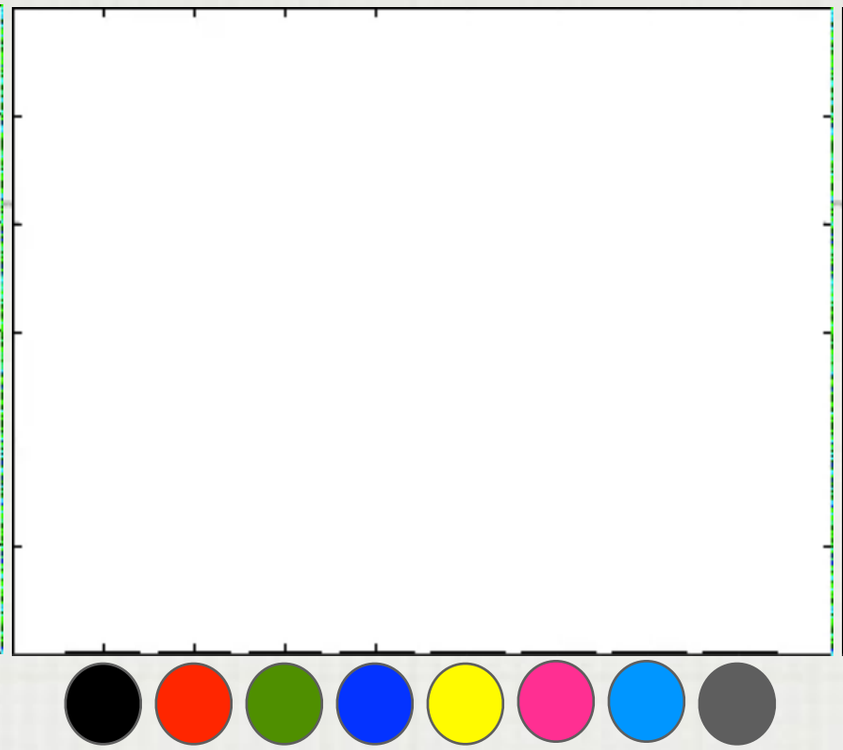
HORMONE

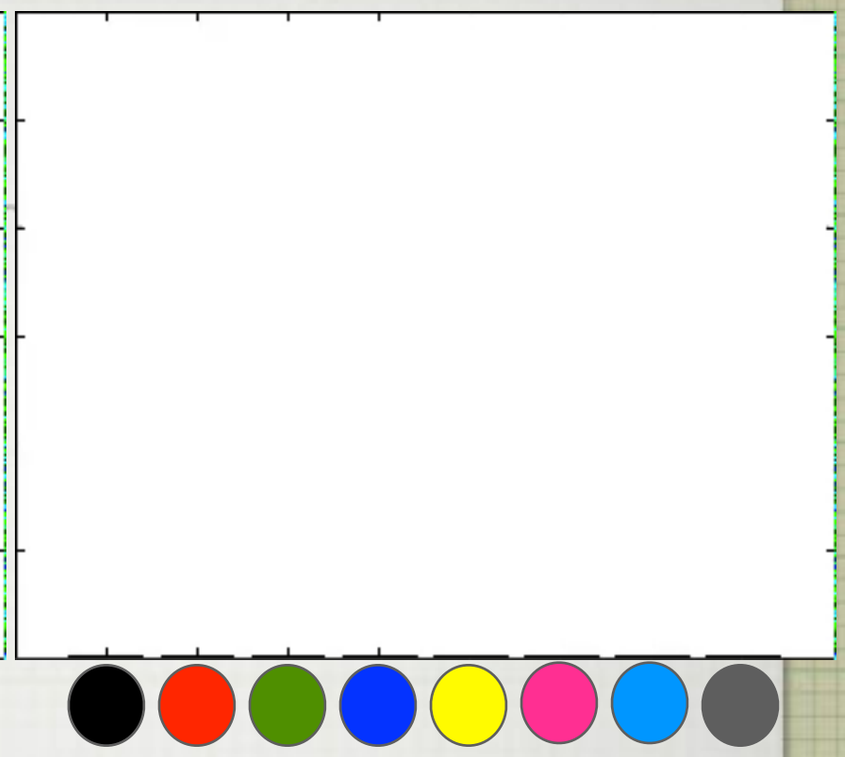
CHEMO

BONE TARGETED

CELL NUMBER



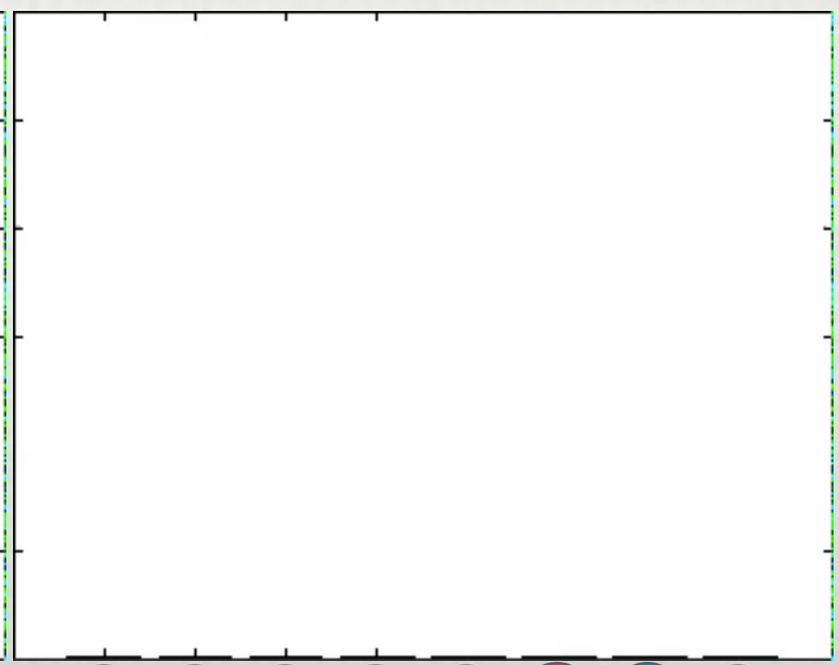




JAK/STAT

PTEN

CELL NUMBER

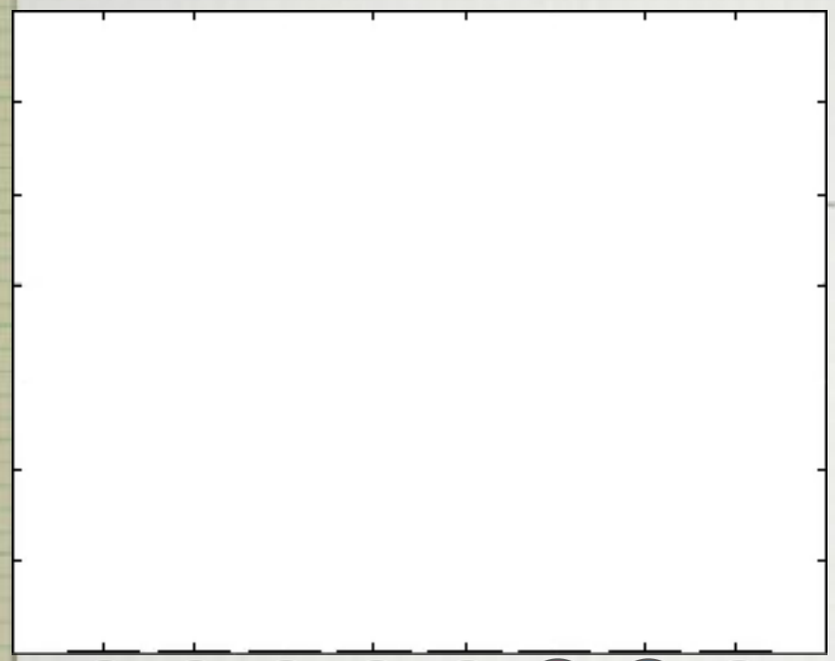


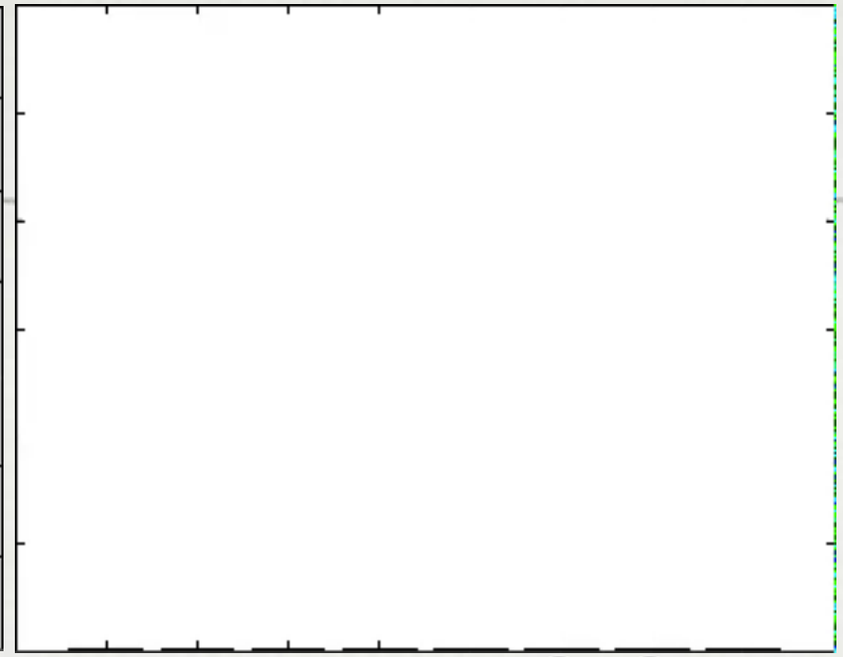
HORMONE

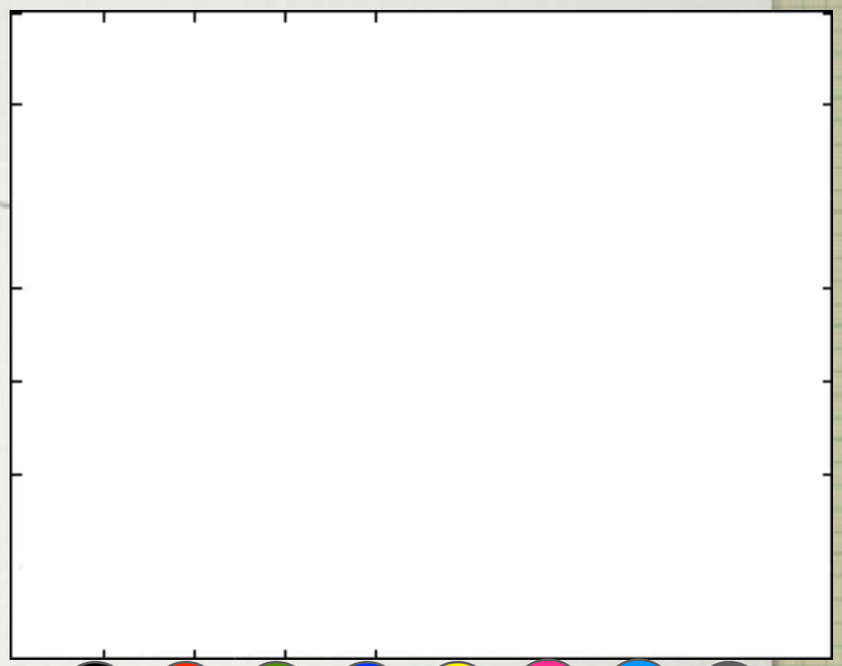
CHEMO

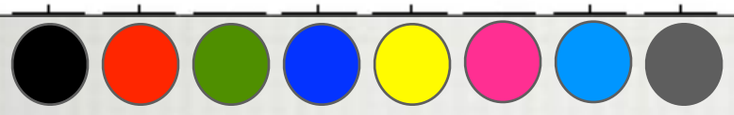
BONE TARGETED

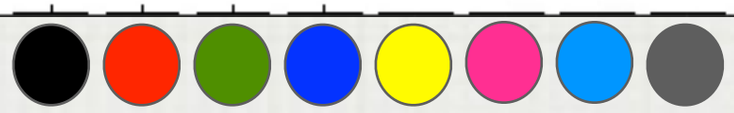
CELL NUMBER

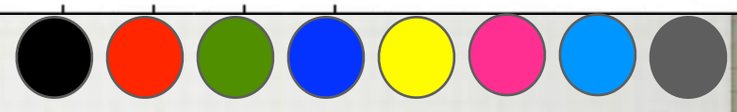








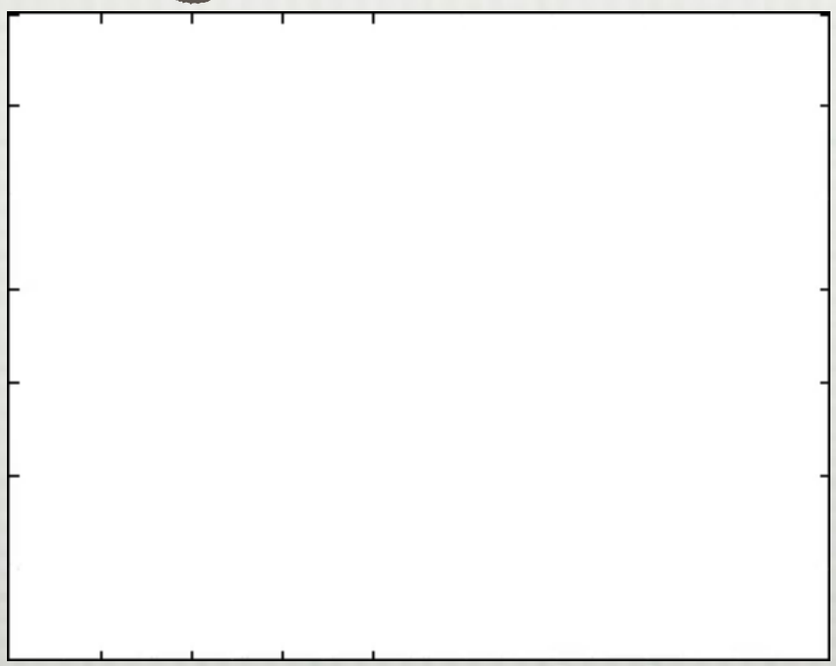


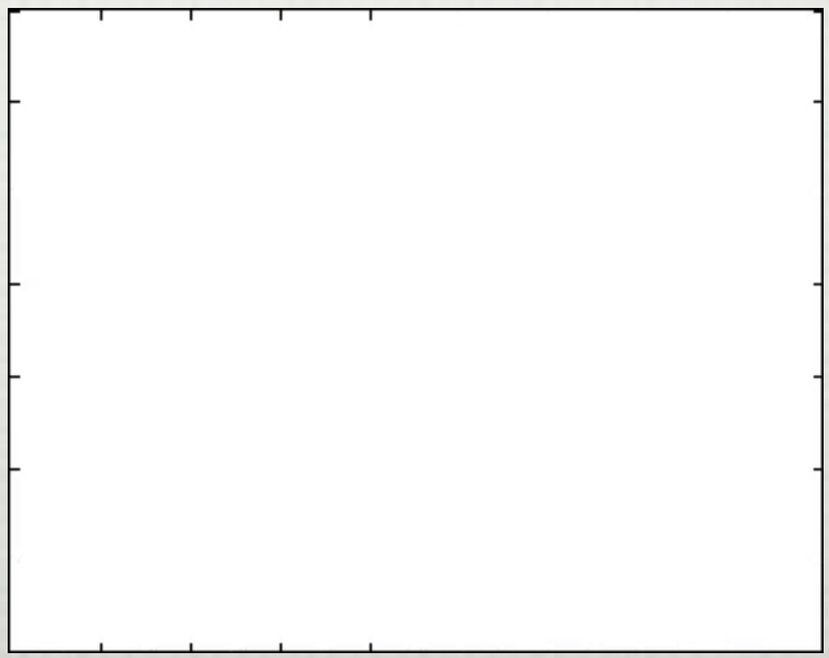


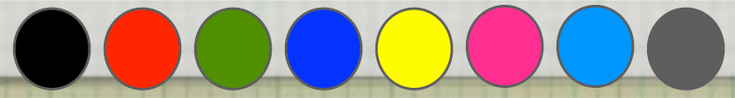
JAK/STAT

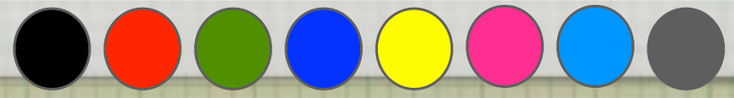
PTEN

CELL NUMBER









UNTREATED

SOC

CELL NUMBER

~2 YR OS

~6 YR OS

PREDICTED

PREDICTED

CELL NUMBER

~6 YR OS

~6 YR OS

CONCLUSIONS

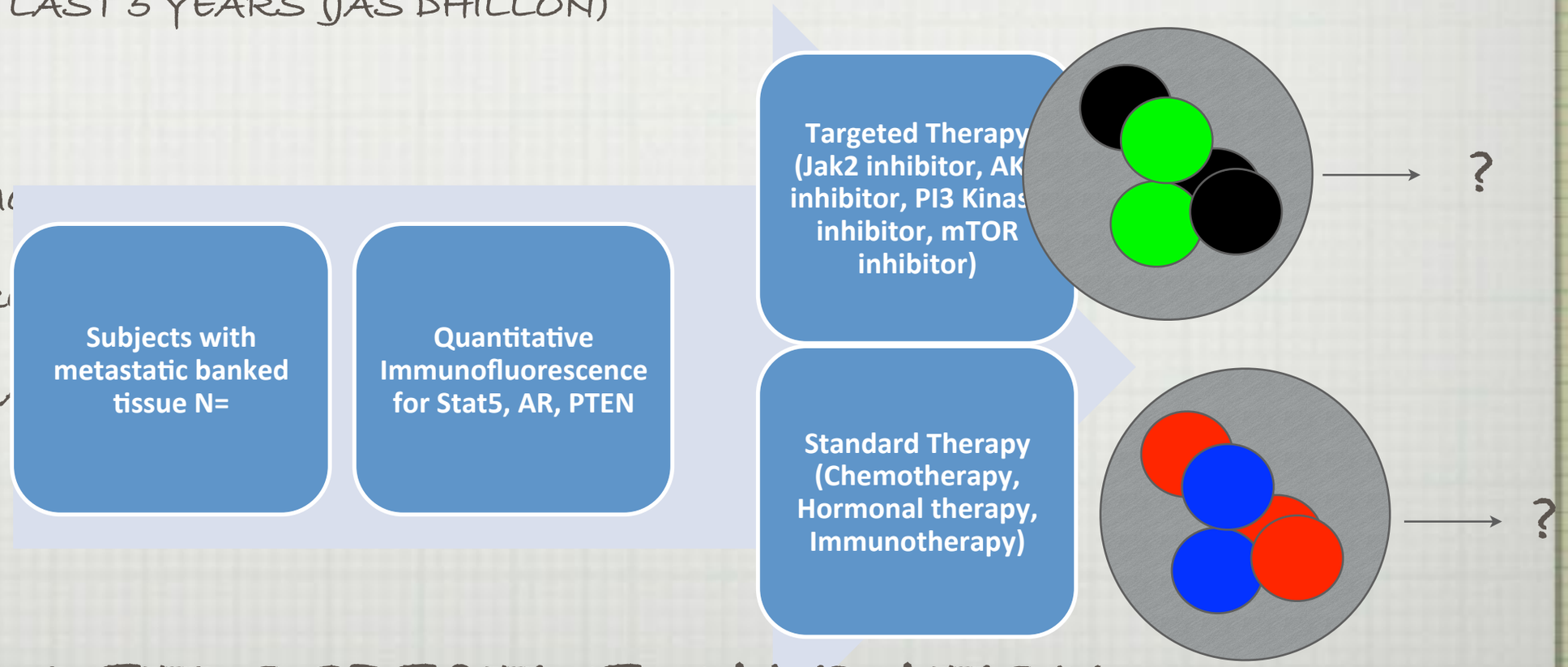
- ☐ PERSONALIZED THERAPY FOR "MR. SMITH" CAN BE TAILORED BASED ON THE EVOLVING MOLECULAR PROFILE OF FUTURE BIOPSY USING REAL-TIME DYNAMIC PREDICTIONS

- ☐ THE RESULTS OF THE MATHEMATICAL MODELING CONFIRMS STANDARD OF CARE IMPROVES OVERALL SURVIVAL

- ☐ OUR INTEGRATED APPROACH MAY OPTIMIZE CONVENTIONAL AND NOVEL THERAPEUTIC STRATEGIES

SHORT TERM IMPLICATIONS

- ☐ WILL ALLOW FOR AN IMMEDIATE RETROSPECTIVE STUDY OF MODEL IMPLICATIONS FOR OUR PROSTATE CANCER PATIENTS USING THE TCC DATABASE.
  - ☐ INTERROGATION OF THE TCC DATABASE = 50 PATIENTS WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER TISSUE SPECIMENS AVAILABLE FROM THE LAST 5 YEARS (JAS DHILLON)
- ☐ MODELING
  - ☐ INTRATUM
    - ☐ IN VITR
- ☐ IMMUNOTHER



SHORT TERM IMPLICATIONS

- ☐ PLATFORM FOR PROSTATE CANCER RESEARCH @ MOFFITT BY:

1) PROMOTING TEAM SCIENCE (CLINICAL/BIOLOGICAL/ MATHEMATICAL/STATISTICAL/EPIDEMIOLOGICAL)

2) ADDRESSING KNOWLEDGE GAPS IN CLINICAL CARE

3) UNDERSTANDING THE COMPLEXITIES OF CELLULAR AND MOLECULAR PATHWAYS AND THEIR INTERACTIONS

LONG TERM IMPLICATIONS

- ☐ RESEARCH IMPLICATIONS

  1) CLINICAL TRIAL DESIGN DRIVEN BY MATHEMATICAL MODELING

  2) EXTRAMURAL FUNDING TO SUPPORT PROSPECTIVE TRIALS

- ☐ CLINICAL IMPLIC

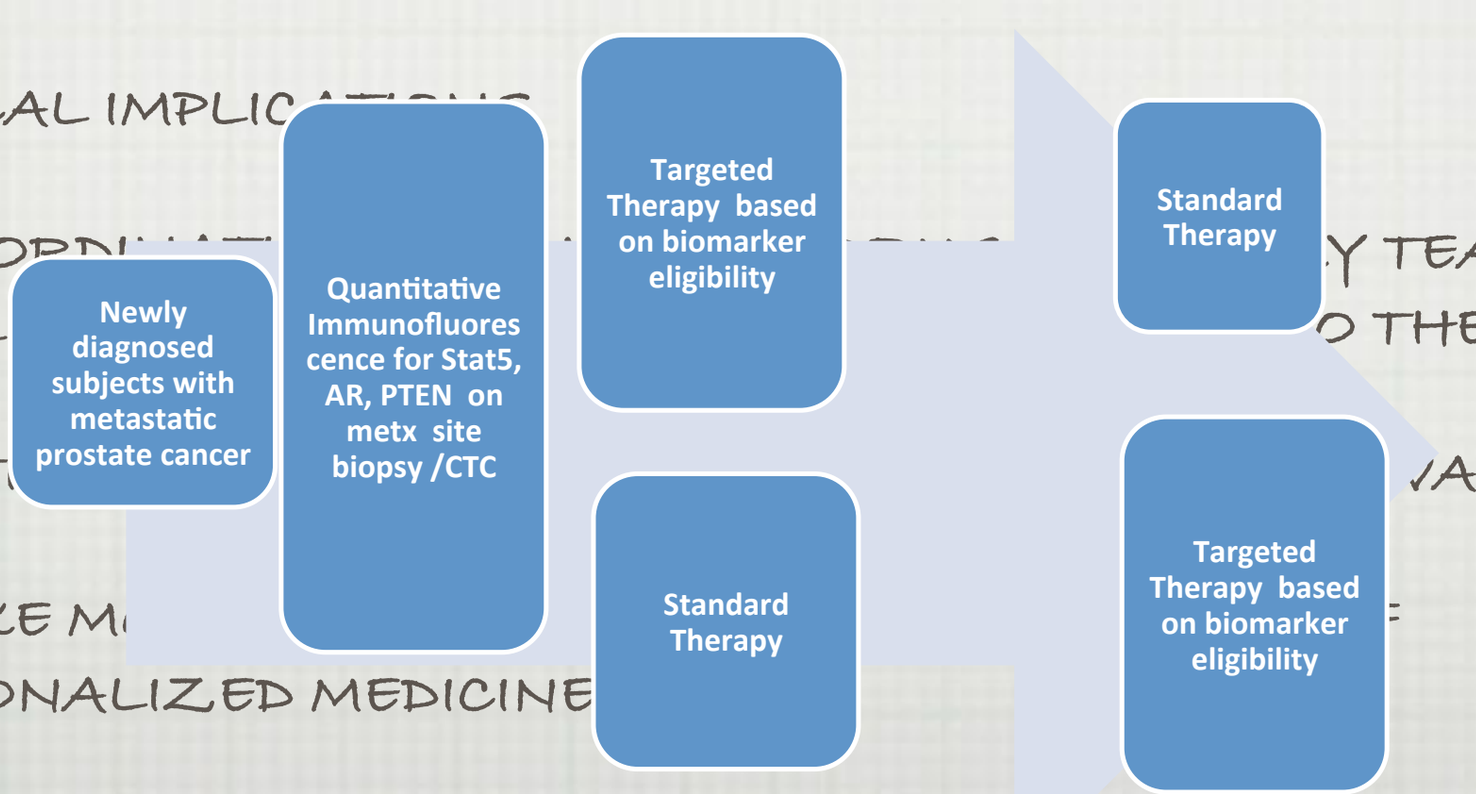
  1) CO-OR

  ACCEL

  2) OPT

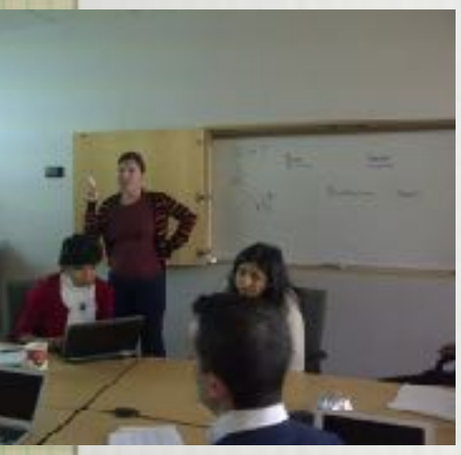
  3) MAKE M

  PERSONALIZED MEDICINE



BUDGET

Moffitt Cores		$	$Total
	AQUA	1000/patient n=20	20000
	TCC Service	Histo/Path	4000
	Statistics	$75/hour	3000
Supplies			
	Antibodies	250/antibody	3000
	Comp/Software		5000
	In Vitro Exp		5000
Personnel			
	IMO Post-Doc	% effort	10000
Total			50000








IMO FEEDBACK