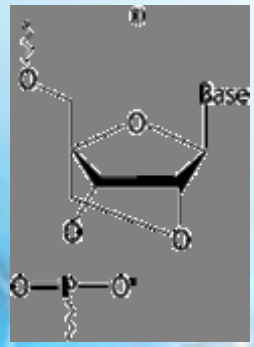

Targeting The Stress-Induced Cytoprotective Chaperone, Clusterin, to Overcome Treatment Resistance in Advanced Prostate Cancer

THE PROSTATE CENTRE
AT VANCOUVER GENERAL HOSPITAL

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Director, The Prostate Centre at VGH

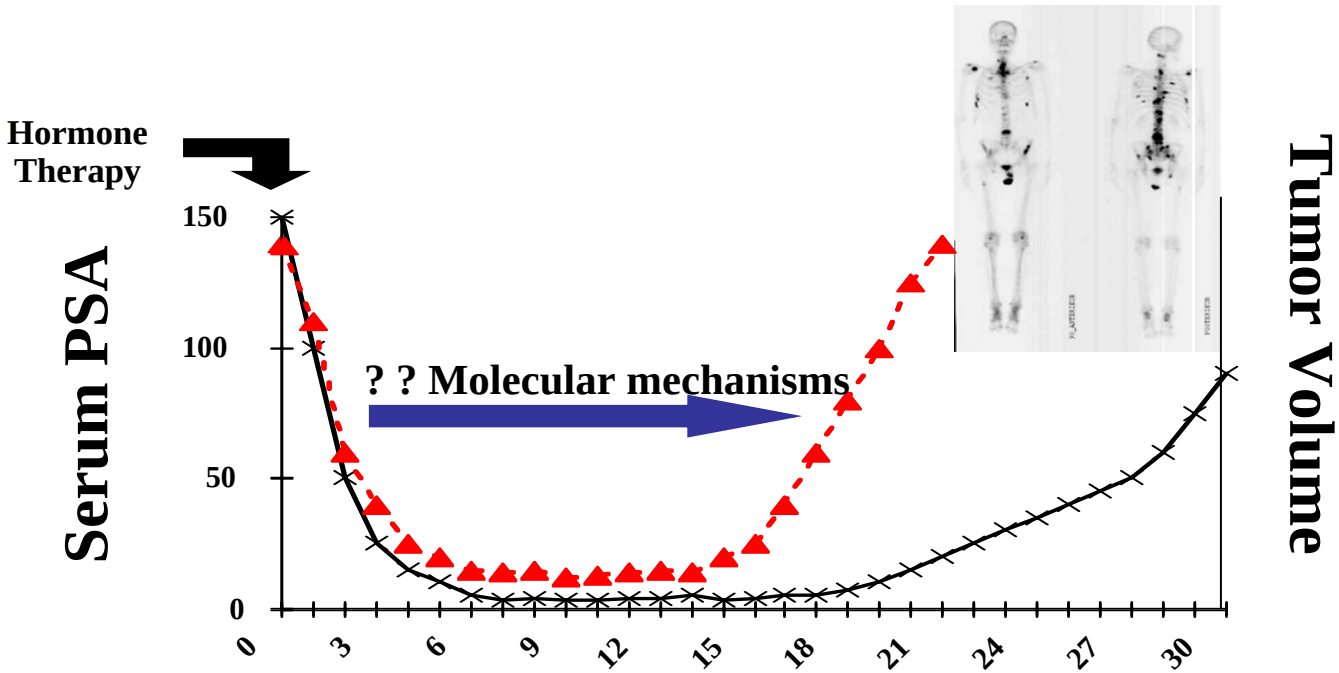
Disclosure of Conflicts of Interest

Patent - OGX-011

Founder - OncoGenex Technologies
Consultant - CSO, OncoGenex Technologies

Castration Resistance and Prostate Cancer

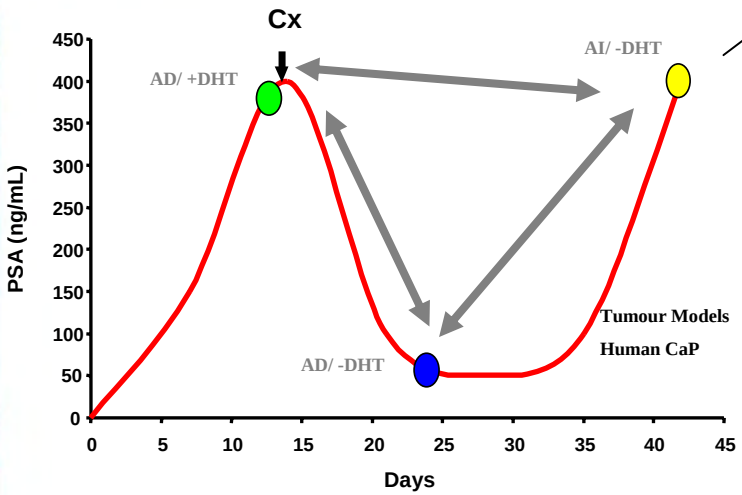
1. **Androgen receptor (AR) related**
   - **Overamplification (hypersensitive)**
   - **Mutations (promiscuous)**
   - **cross-talk - TK, PKA, AKT, STAT3 (phosphorylation, co-regulators)**
2. **Adaptation**
   - **Up-regulation of survival genes (Bcl-2, clusterin, Hsp27, YB-1)**
   - **Increased alternative GF pathways (her2/neu; IGF-1/IGFBP2&5; IL-6/STAT3)**



High-Throughput Bioprofiling of Hormone-Treated Prostate Cancers to Identify Stress-Induced Targets

Hypothesis:

➢Treatment-induced changes in gene expression after hormone therapy render cells resistant to castration- and chemo-therapy.



Tissue Bank:

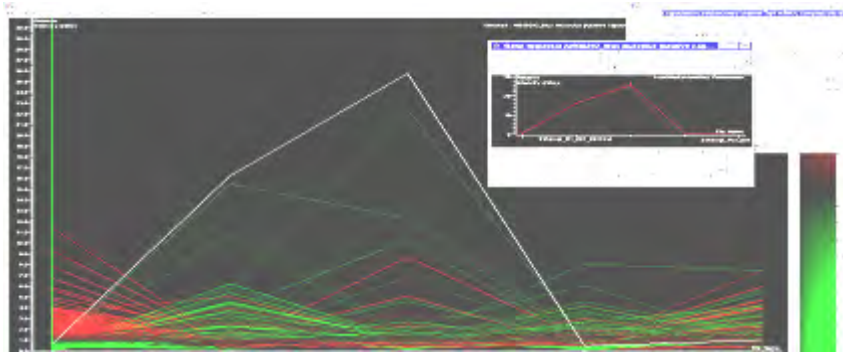
-Xenografts

-Post-NHT-treated human CaP

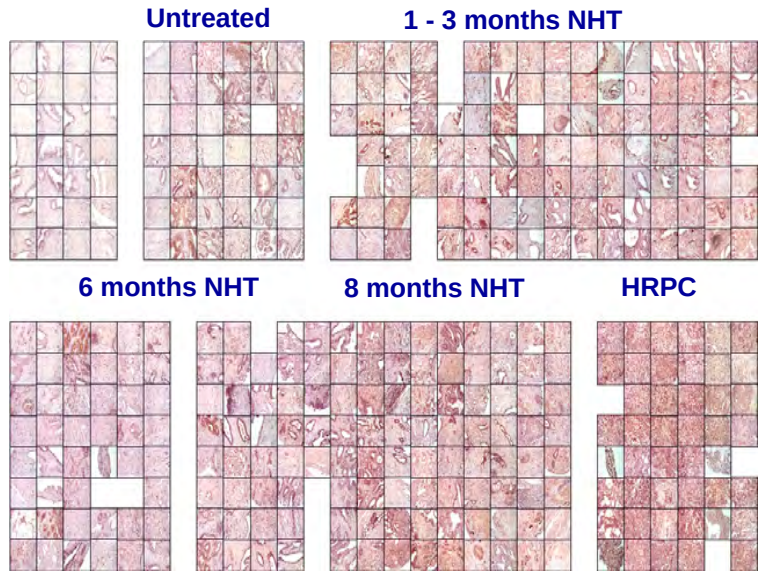
-pre-surgery NHT + Taxotere RP specimens

-rapid autopsy HRPC specimens

Gene expression profiling for Target I.D.

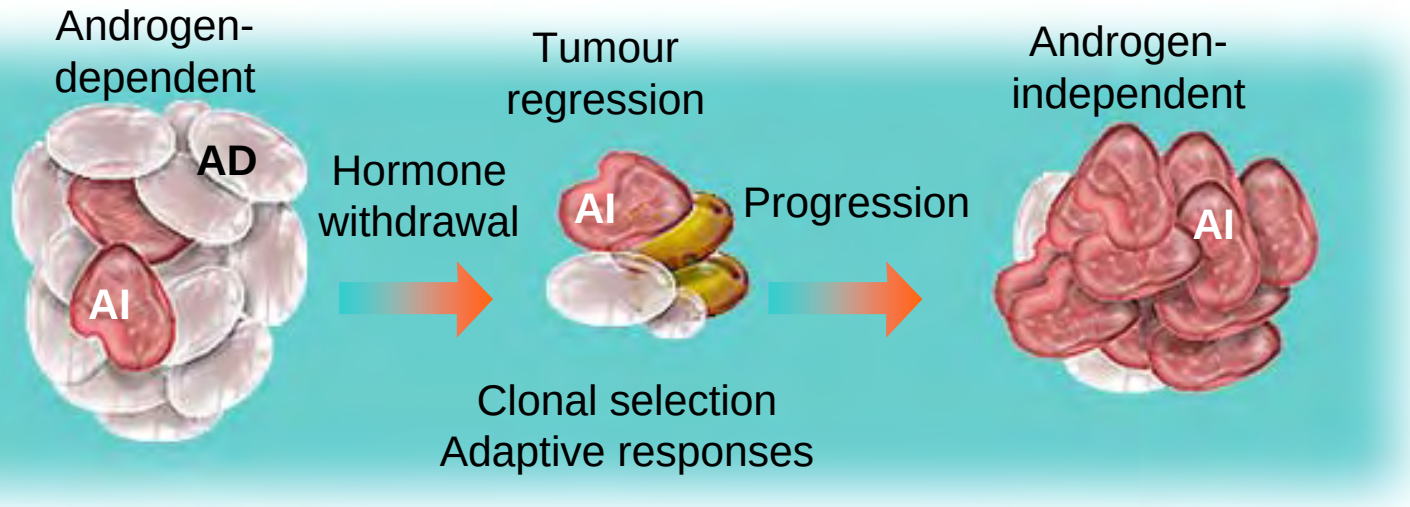


TMA profiling for Target Validation



Post-Hormone-Treated TMA

Changes in Gene Expression After Castration and During AI Progression



++ PSA
- Bcl-2
- EGFR
- clusterin
- IGFBP 2&5
- TGFβ
++IGFBP 3 & 4
-YB-1
++survivin
-Hsp27
+ PKC-α

↓

- PSA
++ Bcl-2
++Bclx-L
- EGFR
+++ clusterin
++++IGFBP 5
IGFBP 3 & 4
+c-*myc*
+YB-1
-survivin
+Hsp27
+ PKC-α

++ PSA
++ Bcl-2
++Bclx-L
+ EGFR
+++ clusterin
++ IGFBP 2
++ IGFBP 5
++YB-1
++ survivin
+++Hsp27

THE PROSTATE CENTRE
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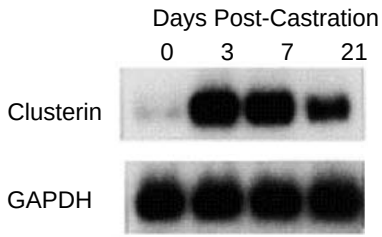
Therapeutic Stress Increases Clusterin Levels in CaP Tumor Models and Human Tissues

Transcriptionally activated by

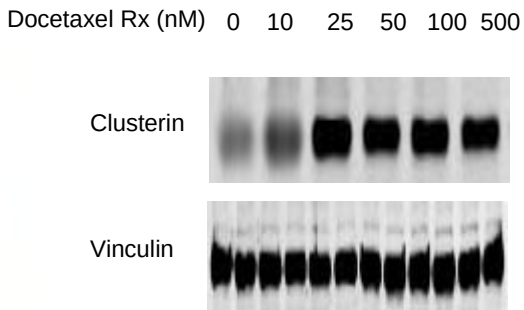
- Hormone withdrawal (*a.k.a. TRPM-2*)
- Chemotherapies
- Radiotherapy
- Targeted therapies (Herceptin, Velcade, OGX-225, etc)

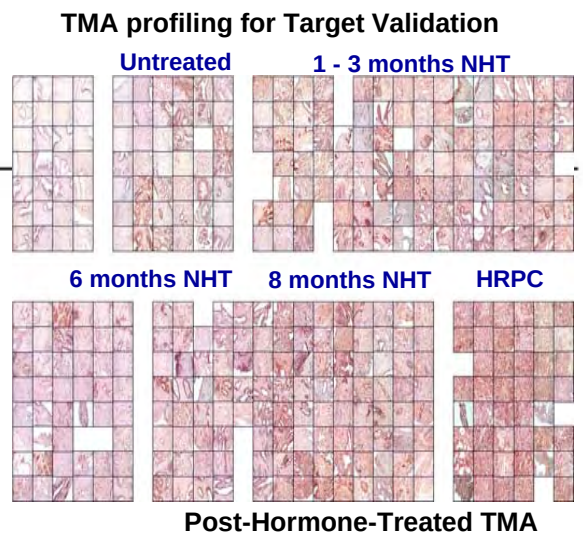
Androgen Ablation in Shionogi Tumors

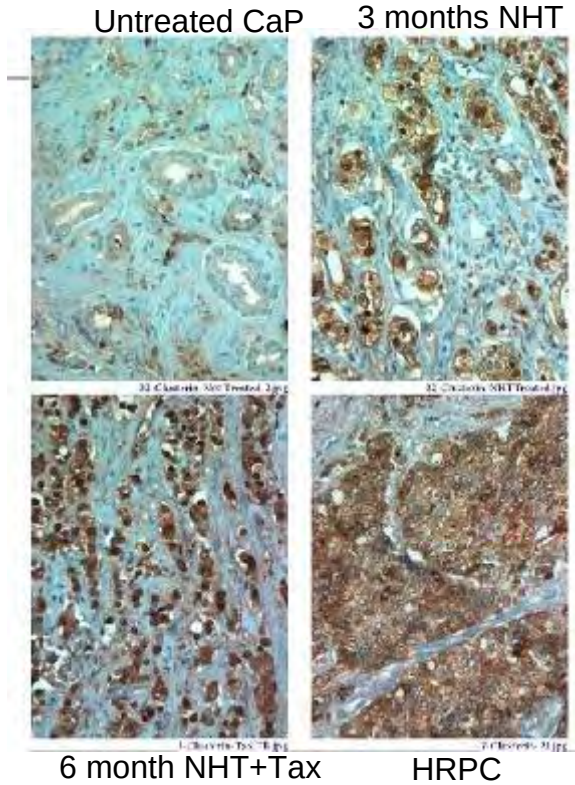


Cancer Research 60; 170, 2000

Docetaxel Rx in PC-3

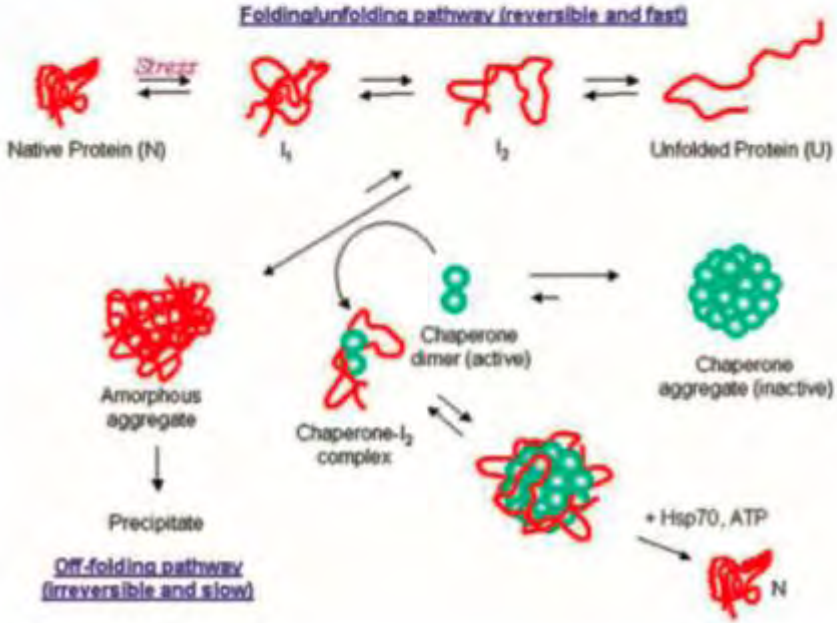






SCLU-2: Stress-induced Cytoprotective Chaperone

1. Transcriptionally activated by HSF-1, repressed by p53
    a. Increased by diverse array of therapeutic triggers (HT, CT, RT, velcade, herceptin)
    b. Increased by cell survival factors like androgen, IGF-1
2. Intrinsically disordered and flexible protein
3. Potent inhibitors of aggregation of client proteins under stress conditions
4. Often associated with neurodegenerative diseases and cancer
5. Interact with and inhibit activated Bax; enhances NF-kB transcriptional activity



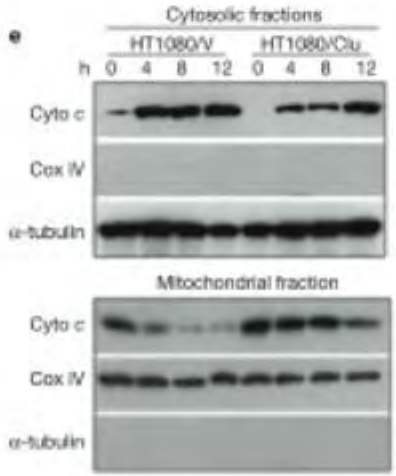
Clusterin: Cytoprotective Mechanisms

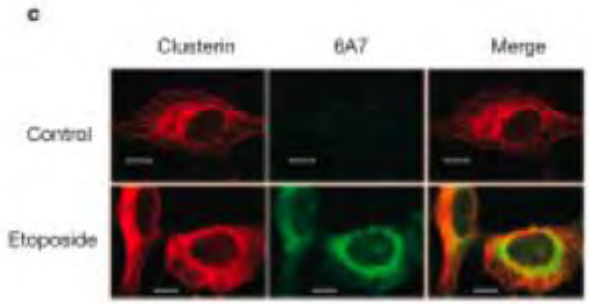
LETTERS

nature
cell biology

Clusterin inhibits apoptosis by interacting with activated Bax

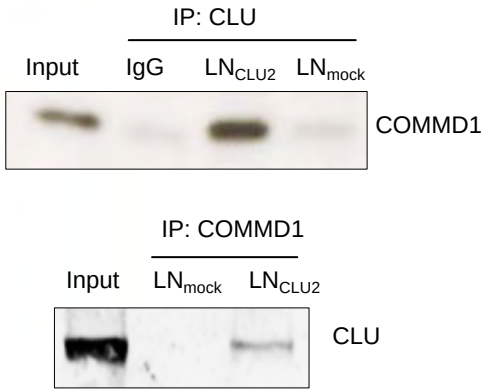
Honglai Zhang[1], Jin Koo Kim[1], Chris A. Edwards[2], Zhaohui Xu[3], Russell Taichman[4] and Cun-Yu Wang[1,5]

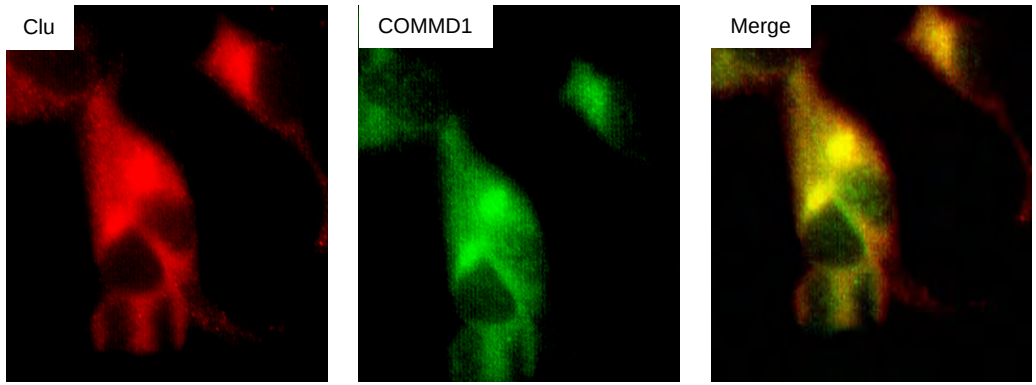




sCLU-2 is a COMMD1 and ubiquitin binding partner in cancer cells

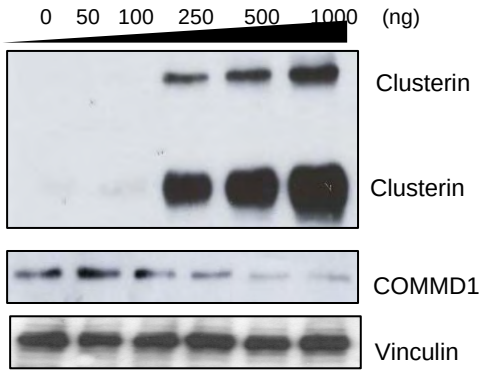
1. sClu-2 and COMMD1 co-localize in cytoplasm with a juxtanuclear aggregation



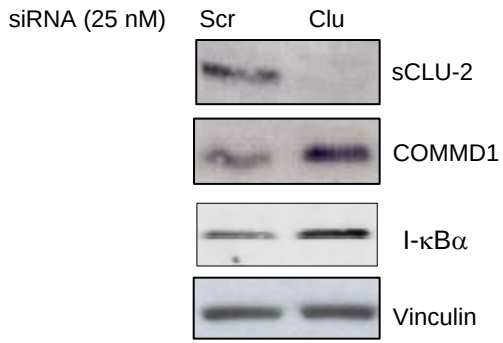


2. sCLU-2 Levels Negatively Correlate with COMMD1 & Ik-B Levels

Clu transient transfection



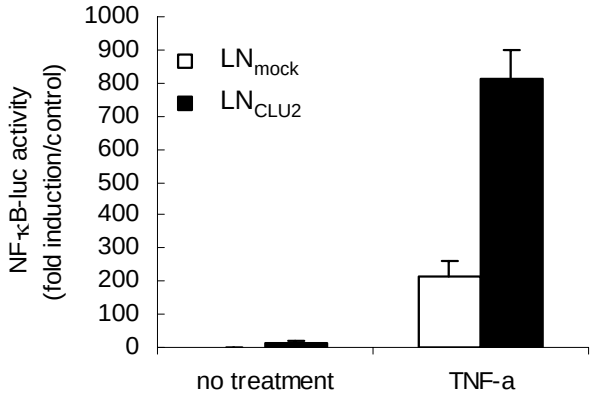
Clu Knockdown increases Levels of COMMD1 & total Iκ-Bα

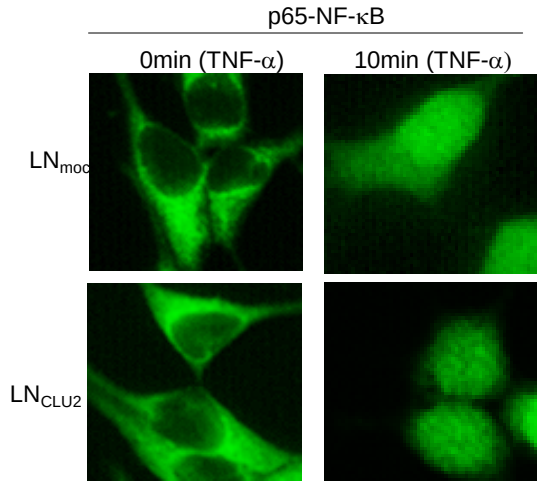


Zoubeidi et al, 2007

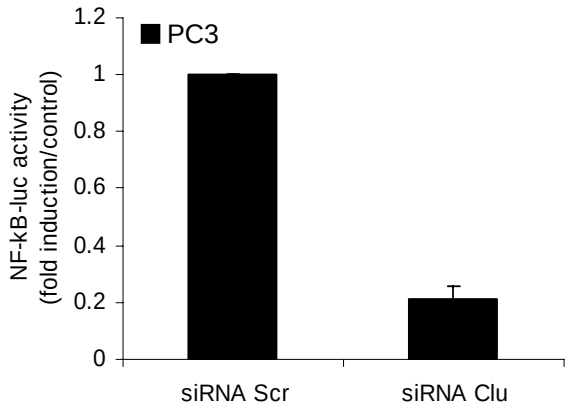
sCLU-2 Enhances TNF-a induced NF-kB Nuclear Translocation and Transcriptional Activity

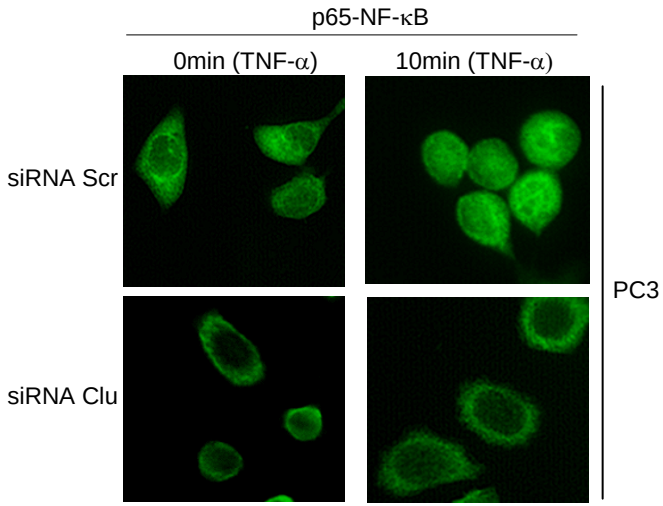
1. sClu-2 Overexpression ↑↑ NF-kB Activity





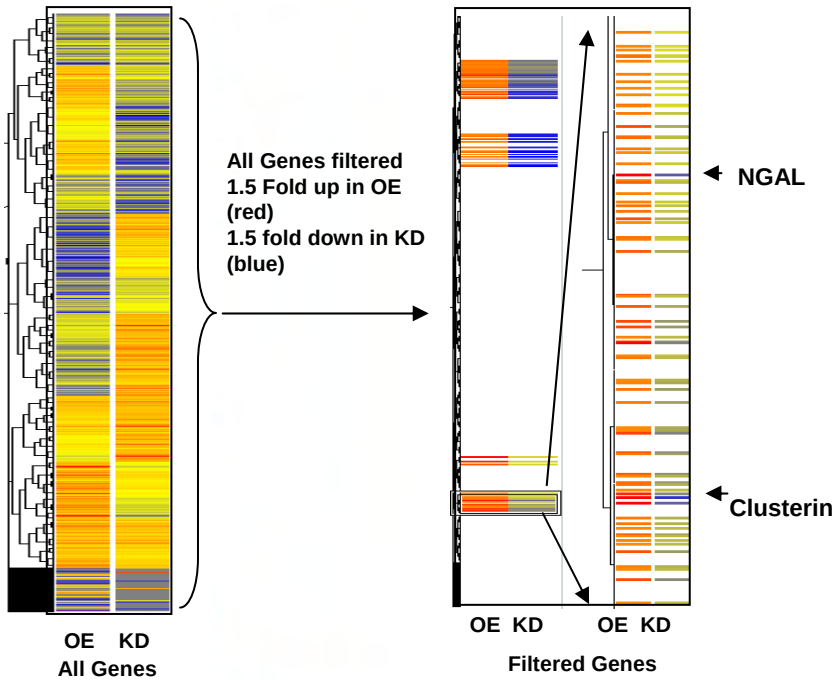
2. sClu-2 Knockdown ↓↓ NF-kB Activity

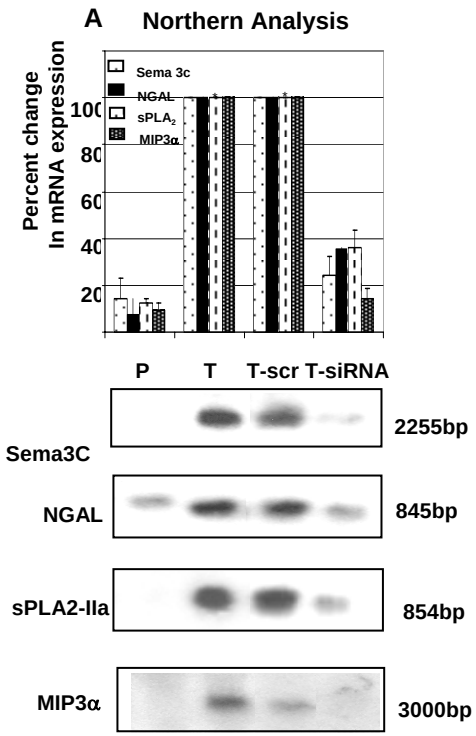


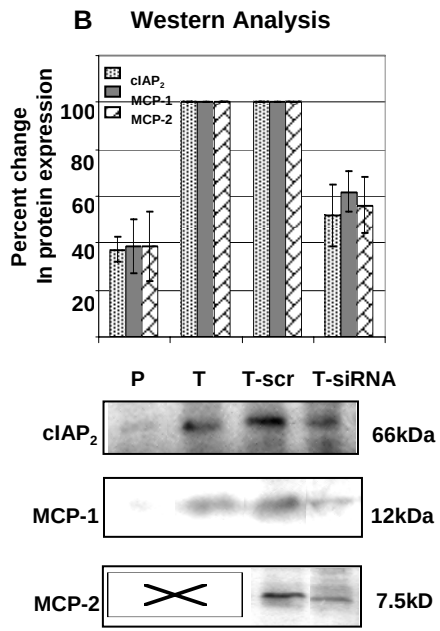


Zoubeidi et al, 2007

Clusterin Expression Levels Positively Correlate with NF-κB - regulated Genes

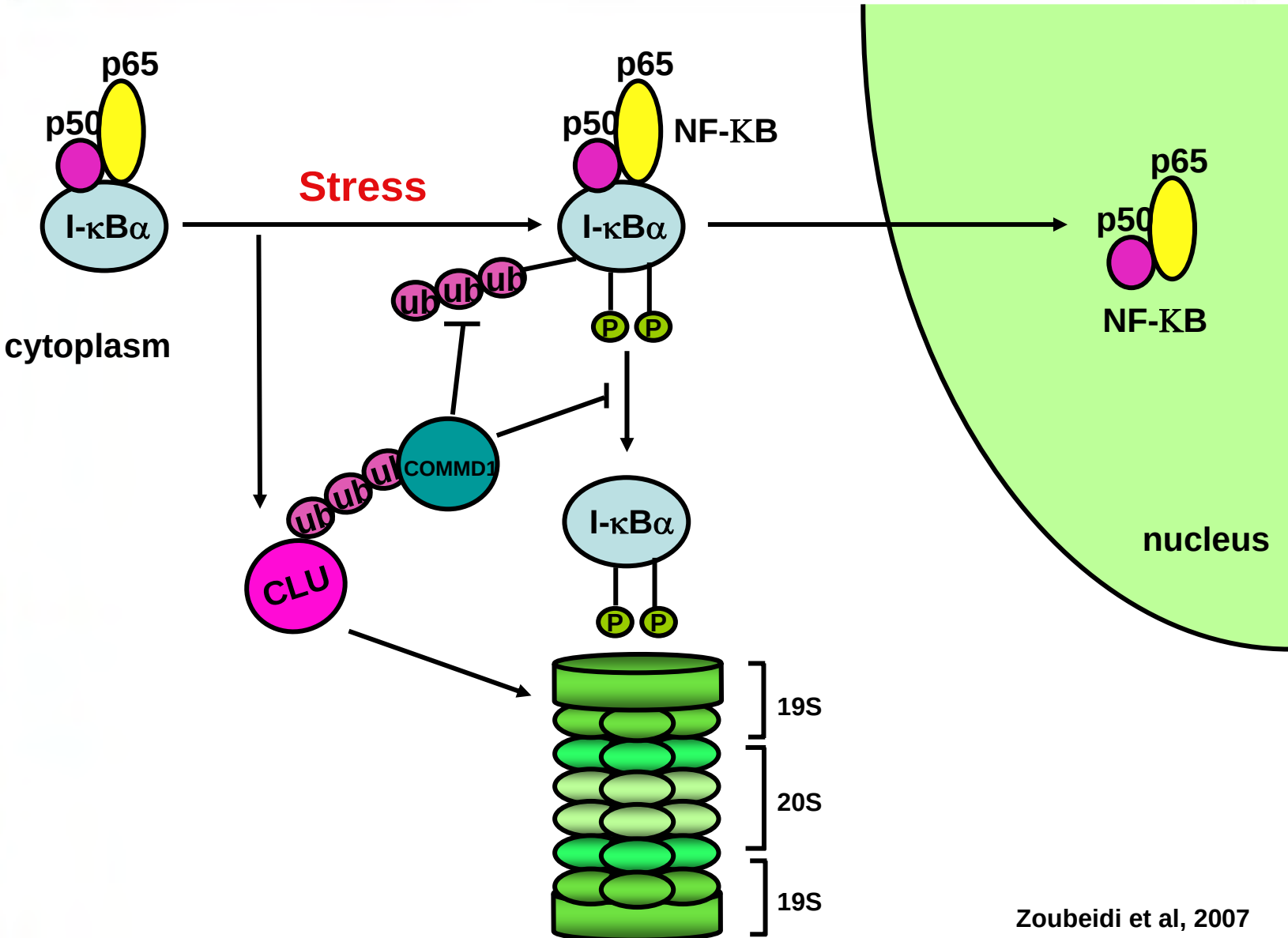






Ettinger et al, 2006

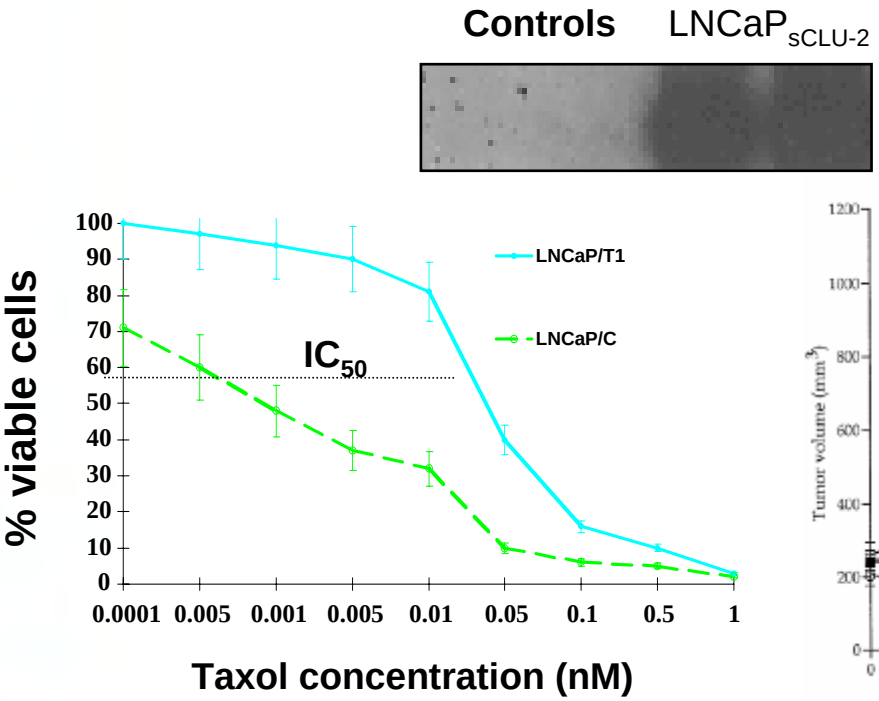
sClu-2 Enhances COMMD1 and I-κBα Degradation by the Proteasome

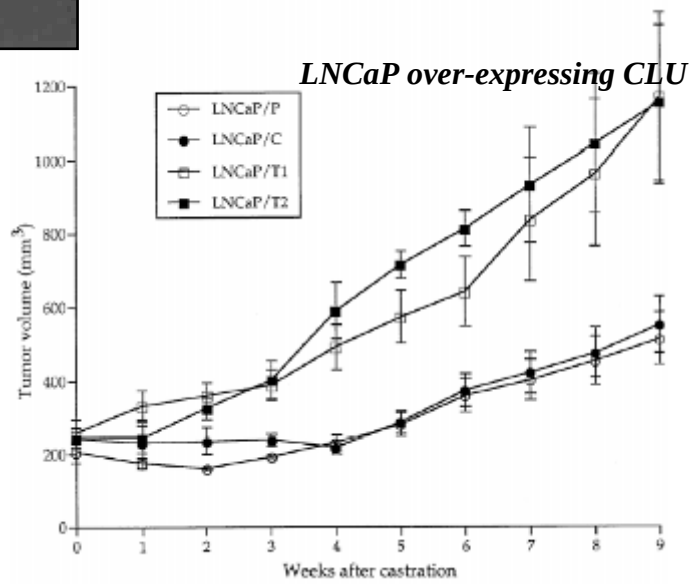


Zoubeidi et al, 2007

Functional Significance of sCLU-2 Over-expression in Prostate Cancer

- **sCLU overexpression is antiapoptotic: confers broad spectrum treatment resistance including hormone, radiation, and chemo-therapy**

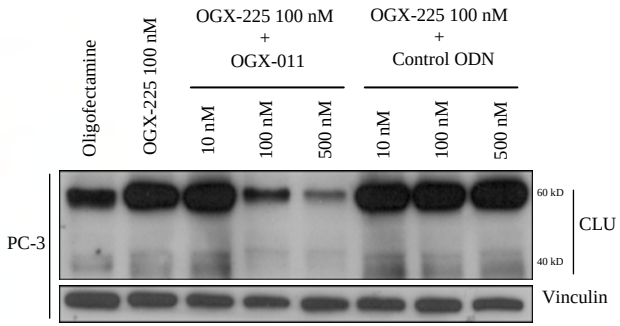


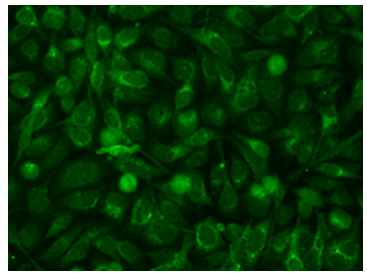


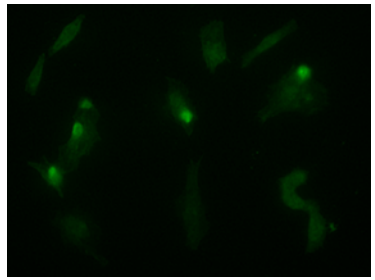
Cancer Research 60;170, 2000; *Cancer Research 60;2547, 2000;* *Clin Can Res 8:3276-84, 2002*

Inhibition of Clusterin Expression Enhances Activity of Chemotherapy in Prostate Cancer Cells

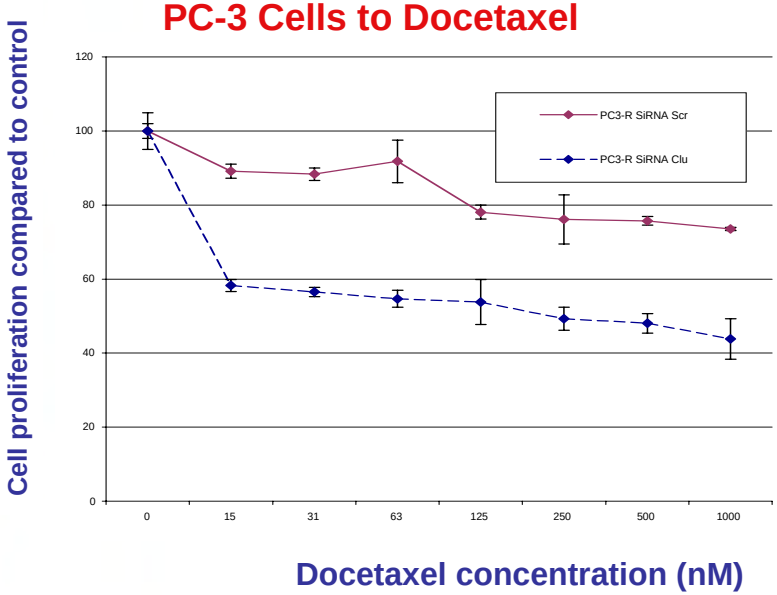
CLU ASO (OGX-011) Suppress Clu Levels in PC-3 Cells



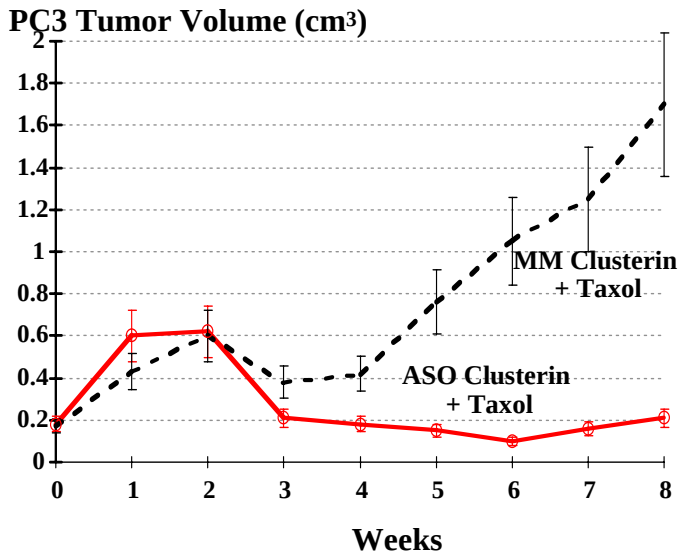




OGX-011 Chemosensitizes PC-3 Cells to Docetaxel



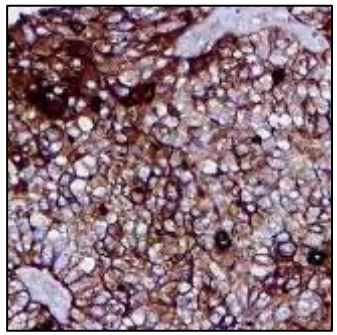
OGX-011 Enhances Taxol Activity in PC3 Tumours in vivo

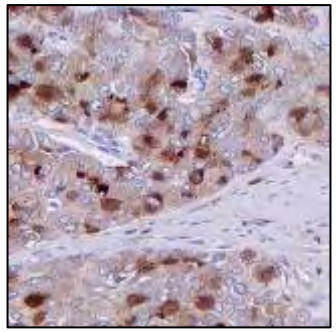


Clin Cancer Res 6:1655, 2000

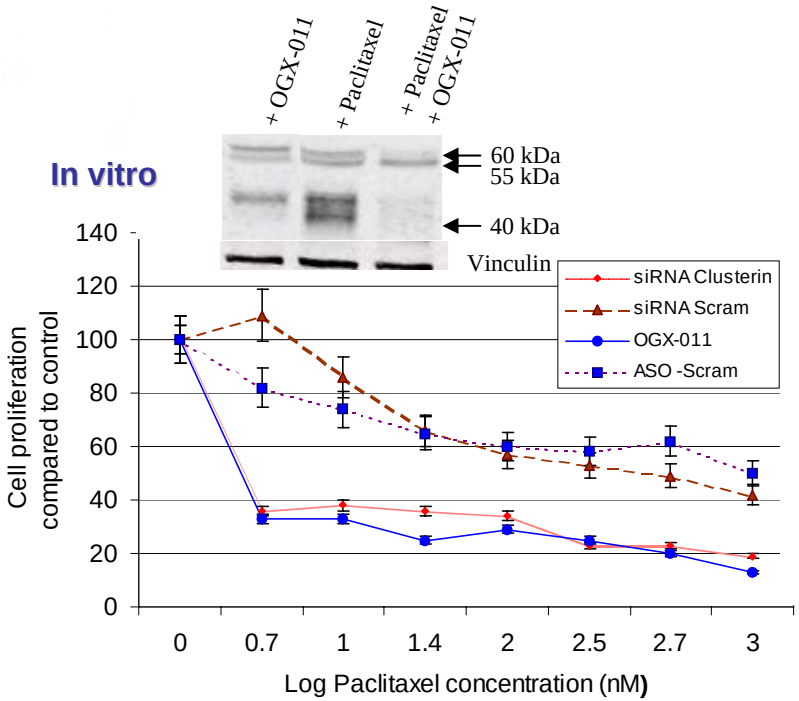
CLU ASO (OGX-011) Suppresses sCLU Levels and Chemosensitizes MCF-7 Xenografts to Paclitaxel in vivo

Clusterin is expressed in 65% of Primary Breast Cancers

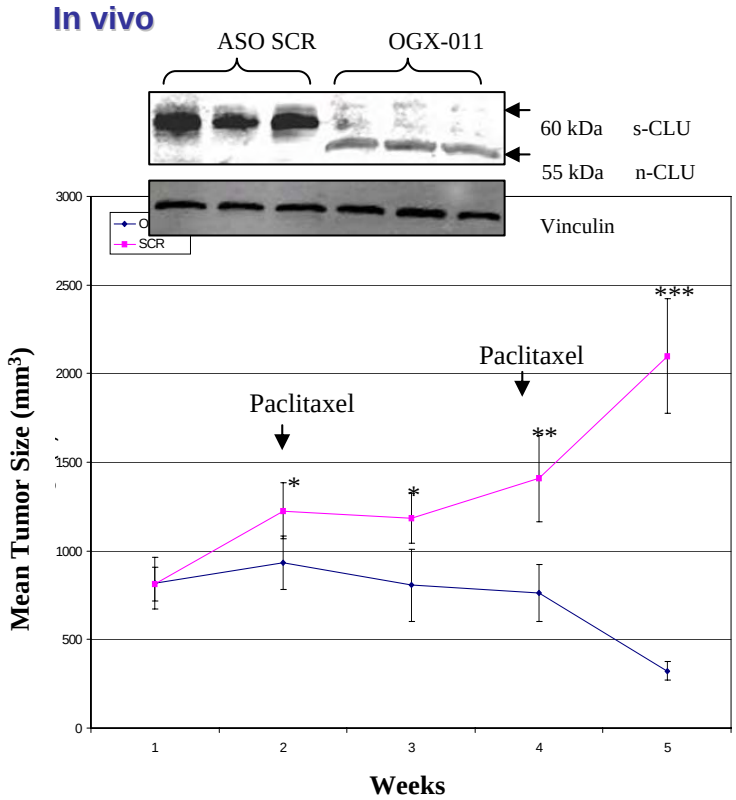




In vitro



In vivo



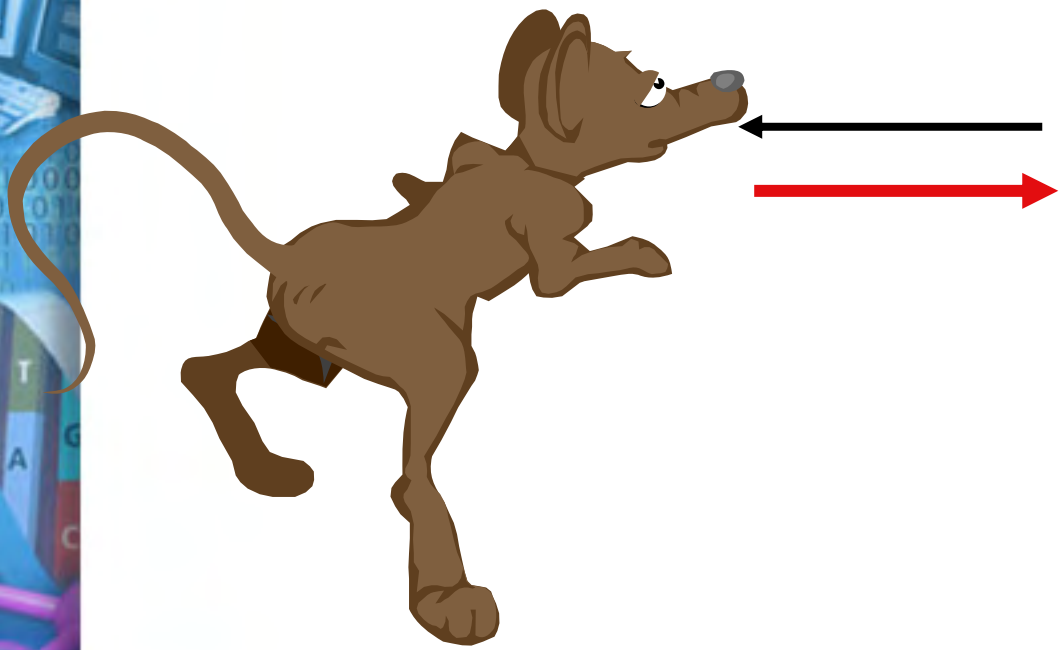
So et al, Mol Cancer Ther, 2005

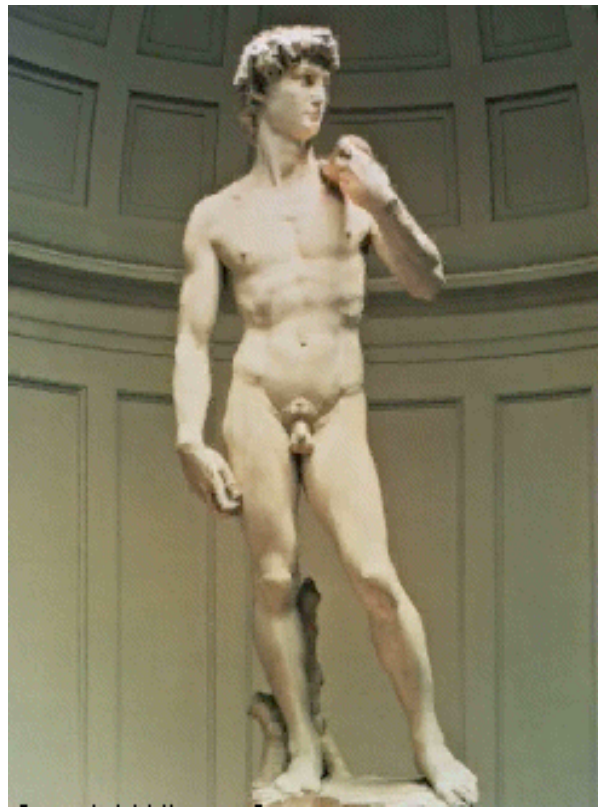
From Bench to Bedside: Translational Research in Action

sCLU as a Therapeutic Target: Preclinical Studies For Proof of Principle

Of Mice and Men

Clusterin:
- **Stress-induced survival response**
- **confers resistance**
- **knockdown enhances chemo & HT in many tumor models**

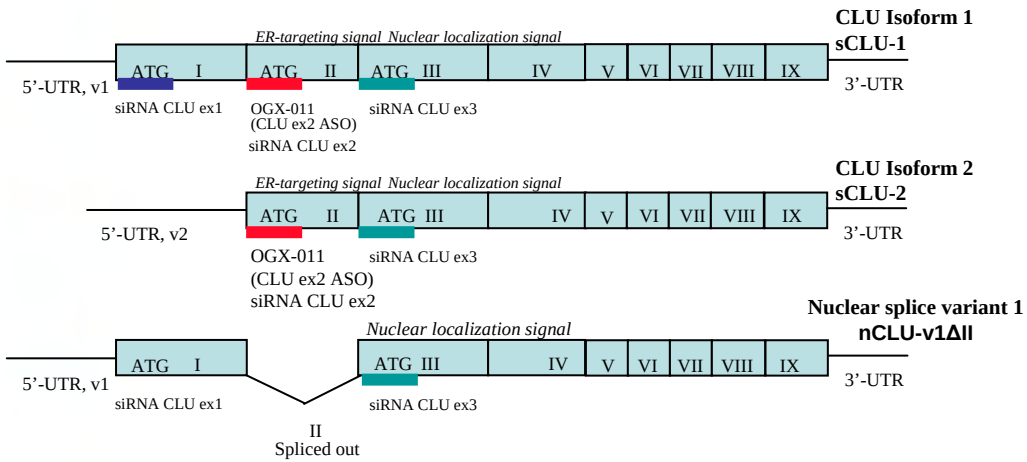


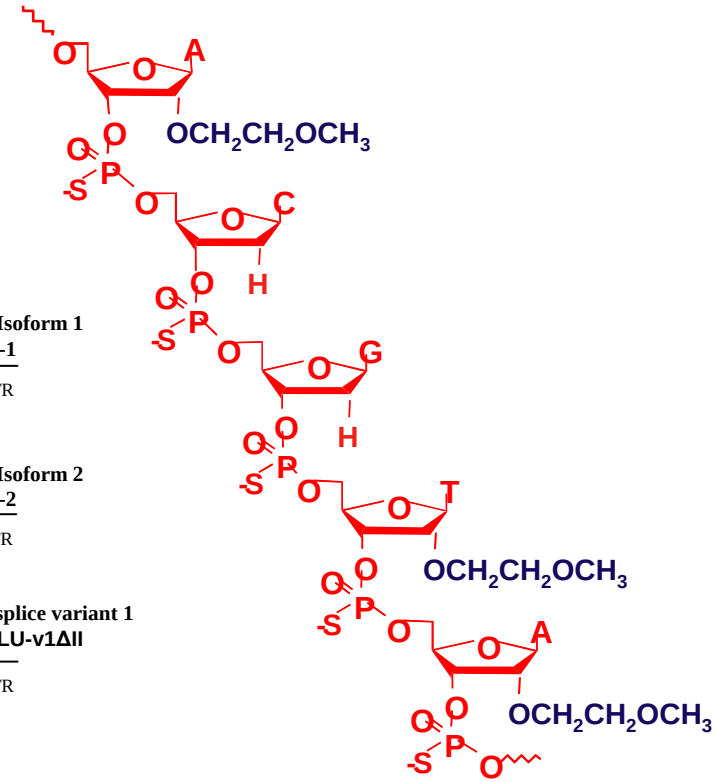


Antisense Clusterin: OGX-011 Product Description

- **Licensed from UBC for development by OncoGenex in collaboration with Isis**
  - **2nd generation antisense molecule**
  - **4-13-4 21-mer MOE gapmer oligonucleotide**

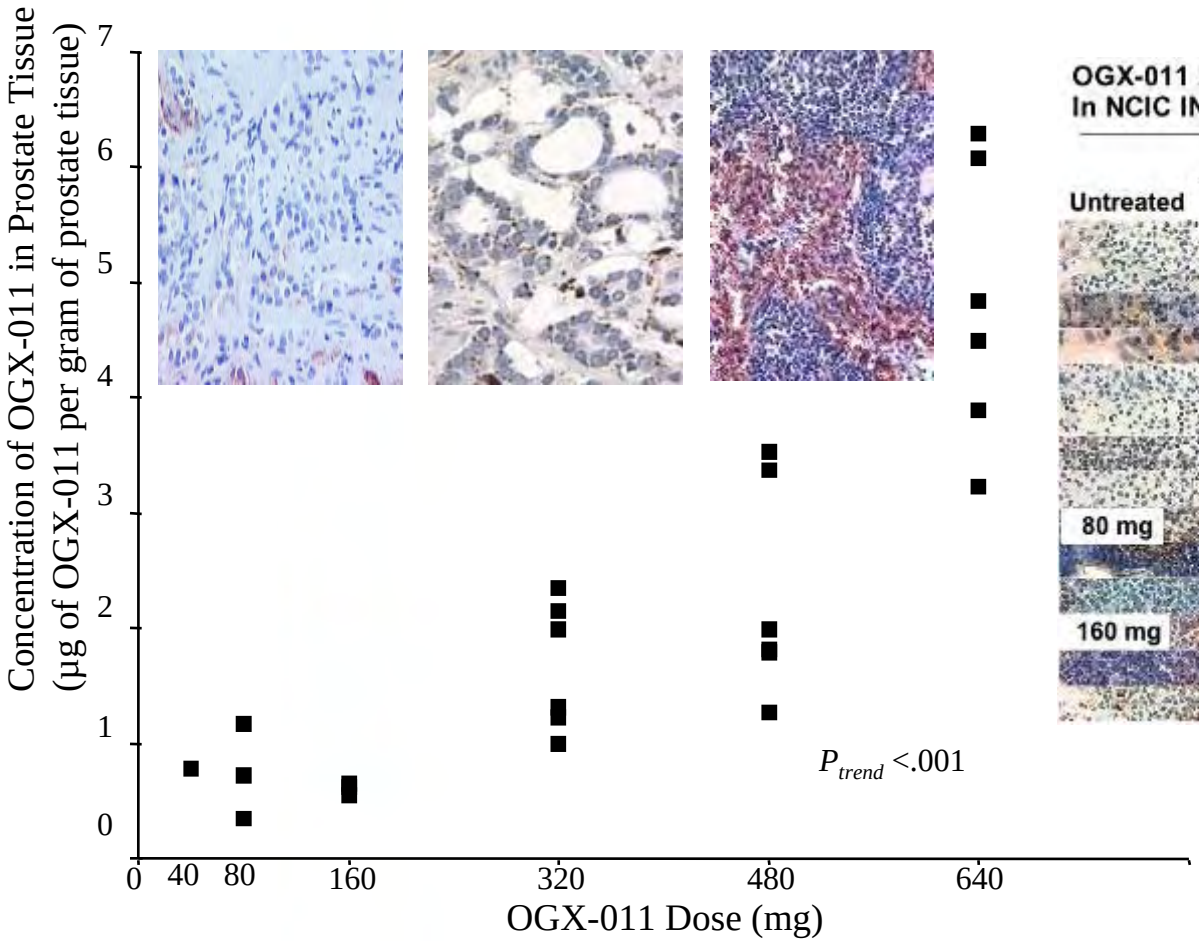
- **Advantages of 2'MOE analogues**
  - **Increased potency and resistance to degradation**
  - **Facilitates more convenient dosing regimen**
    - **once-weekly infusion**
  - J Pharmacol Exp Ther. 298(3):934-40, 2001

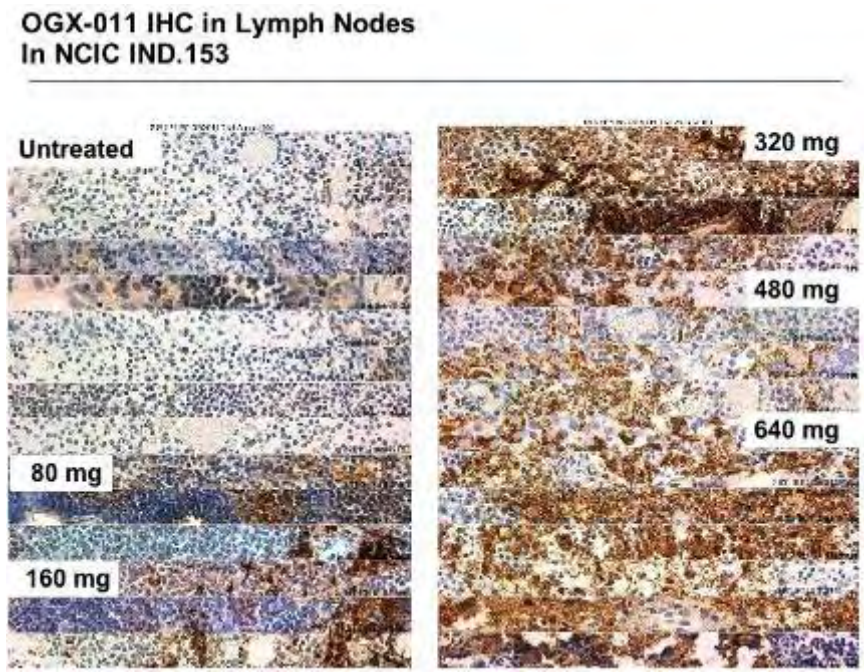




NCIC IND.153: Phase I Pre-Surgery pk/pd Trial of OGX-011 - Tissue Pk data

•25 men with localized CaP treated with 5 weeks of NHT + escalating doses of OGX-011



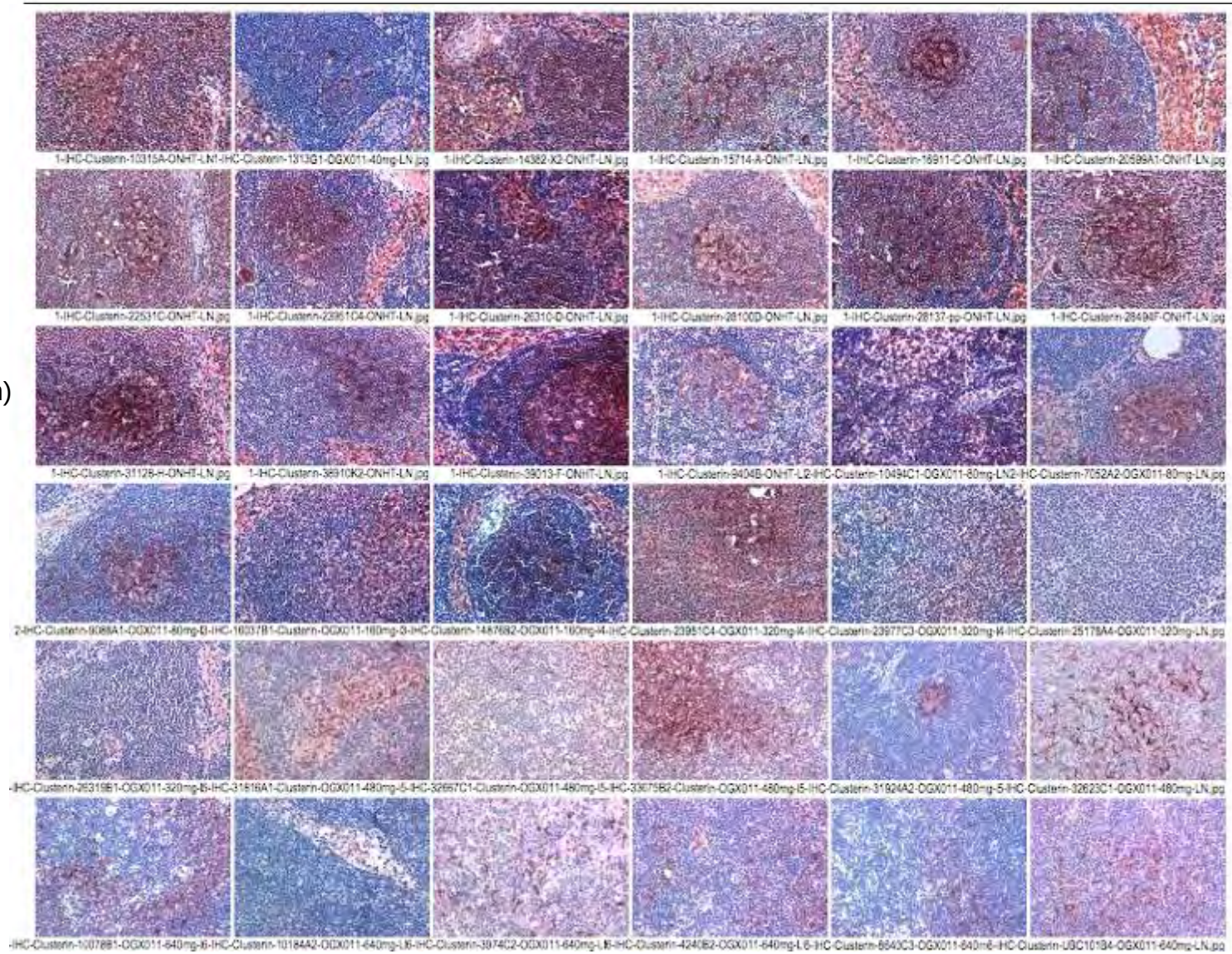


Chi et al, JNCI. 97:1287-96, 2005

IND.153: Target Regulation Data:
Dose-dependent suppression of clusterin in Regional Lymph Nodes

Untreated
Controls

6 weeks NHT
+ OGX-011
(dose escalation)



80 mg

160 mg

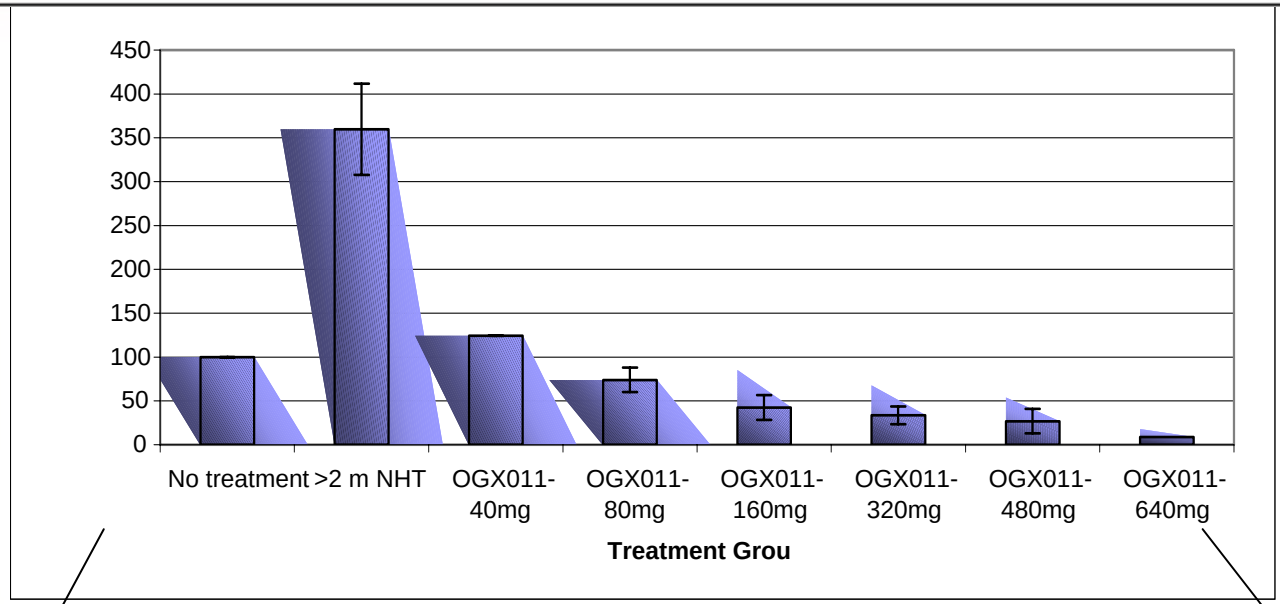
320 mg

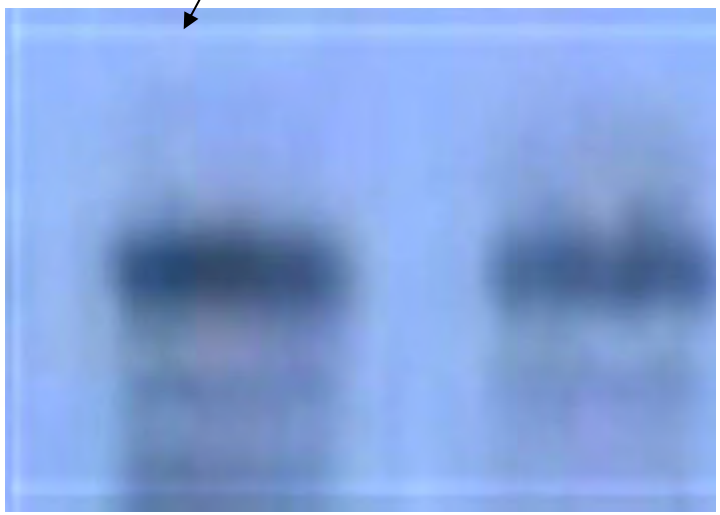
480 mg

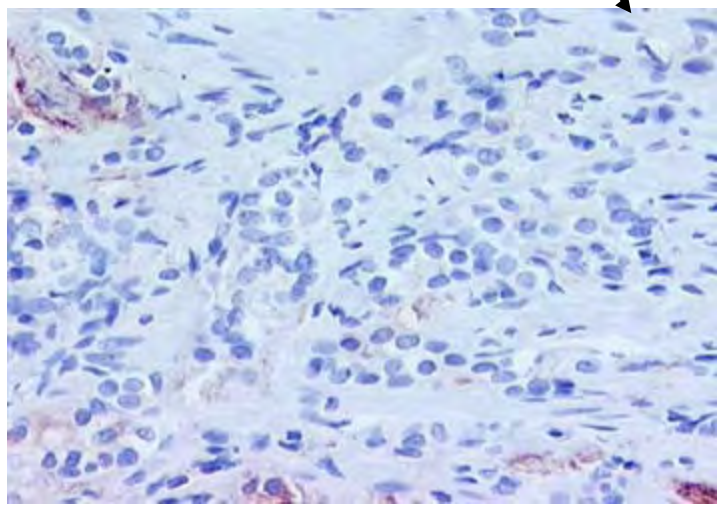
640 mg

Chi et al, JNCI. 97:1287-96, 2005

Clinical Proof-of-Concept: Dose-dependent Decreases in Clusterin Levels in RP Specimens using LCM and Real-Time PCR







Chi et al, J Nat.Canc.Inst. 97:1287-96, 2005

Clinical Trial Development with Clusterin ASO (OGX-011)

Phase I
NHT
Pre - surgery

Established 640 mg once weekly as phase II dose (OBD) based on tissue pk and pd criteria

Phase I
Solid Tumors + docetaxel n = 35

Completed:
2 regimens found well tolerated -
- **OGX-011 + weekly Taxotere**
- **OGX-011 + q 3 weekly Taxotere**

- **30-60% decrease in serum CLU levels**

NCIC IND.165:
First Line mHRPC
Phase II RCT -
Taxotere +/- OGX-011
- **82/80 pts enrolled**
- **ASCO May 2007**

CUOG P-06a:
2nd line mHRPC
Phase RCT Taxotere or mitoxantrone + OGX-011
- **42/40 pts enrolled**

Phase II stage III/IV NSCLC
Gem/cis + OGX-011
- **10 pts Phase I**
- **70 pts Phase II**
- **ASCO May 2007**

NCIC IND.164:
Phase II Metastatic Breast- Taxotere + OGX-011
- **16 pts enrolled**

Phase 2 Study in 1st Line NSCLC: Treatment Schema

- *81 pts with stage IIIB/IV NSCLC treated with gem/cis plus OGX-011*

	Results as of May 24, 2007
Median Follow-up	**12.7 months**
Number of Deaths	**37/81 (46%)**
Median Progression-Free Survival (range)	**4.6 months (0.06-15.6+)**
Estimated Median Survival	**14.1 months**
Number of Patients Surviving ≥ 1 year	**25/46 = 54% ***
Number of Patients Surviving ≥ 18 months	**8/22 = 36%**

	Historical Controls*	Phase 1 and 2 (n=81)
Median Survival	**8.0 – 10.8 months**	**14.1 Months (estimated)**

- *Data from five randomized clinical trials using gemcitabine plus platinum-based chemo in 1st line NSCLC (1260 patients)*

Laskins et al, ASCO, 2007

NCIC IND.165: Taxotere +/- OGX-011 in First-Line mHRPC

- Randomized Open label, multicentre trial comparing docetaxel +/- OGX-011 in men with mHRPC (PI - K. Chi).

PSA Response Rates

BEST RESPONSE CRITERIA	Arm A (OGX-011 + Docetaxel) N=40	Arm B (Docetaxel) N=41	% Change in favor of OGX-011
≥ 50% PSA Decline at 12 weeks	**45%**	**34%**	**32%**
PSA Response (50% decline - confirmed)	**50%**	**51%**	**NA**
≥ 80% PSA Decline	**38%**	**22%**	**73%**
PSA Progression (PSAWG Criteria)	**0%**	**10%**	**100%**
PSA Non-Progression/Non-Response	**45%**	**32%**	**41%**
Inevaluable	**3%**	**2%**	**NA**

Chi et al, ASCO, 2007

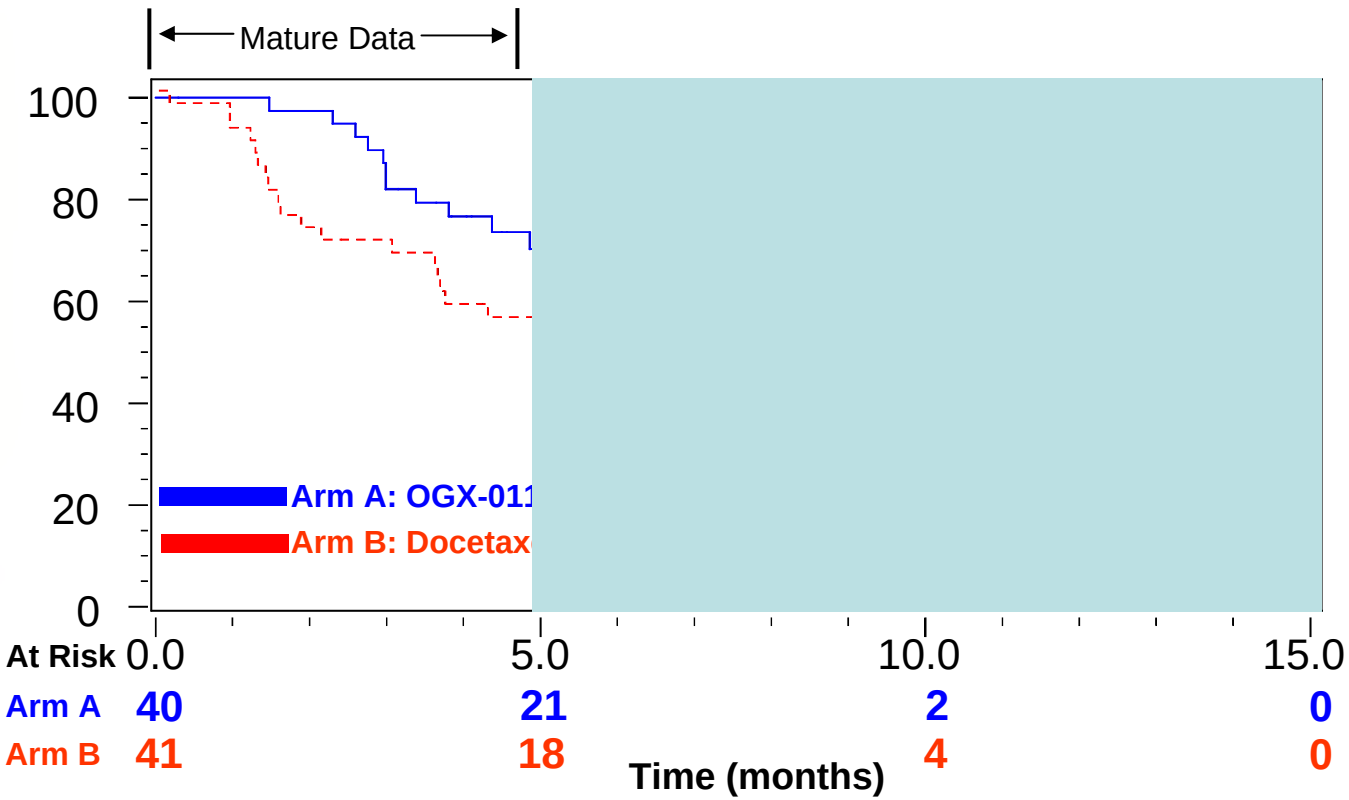
NCIC IND.165: Taxotere +/- OGX-011 in First-Line mHRPC

RECIST CRITERIA	*Arm A (OGX-011 + Docetaxel) n=26*	*Arm B (Docetaxel) n=23*	% Change in favor of OGX-011
Disease Control (CR+PR+SD)	**92%**	**74%**	**24%**
Complete Response	**0%**	**0%**	**N/A**
Partial Response	**19%**	**22%**	**-14%**
Stable Disease	**73%** **9.7 months**	**52%** **7.6 months**	**40%** **28%**
Progressive Disease	**4%**	**22%**	**82%**
Inevaluable	**4%**	**4%**	**N/A**
Median PFS	**7.3 months**	**5.9 months**	**24%**

Chi et al, ASCO, 2007

NCIC IND.165: Taxotere +/- OGX-011 in First-Line mHRPC

Progression Free Survival



Median for Arm A (OGX-011 + Docetaxel): 7.26 months (95%CI 5.22-9.33)

Median for Arm B (Docetaxel): 5.85 months (95% CI 3.61-10.74)

Chi et al, ASCO, 2007

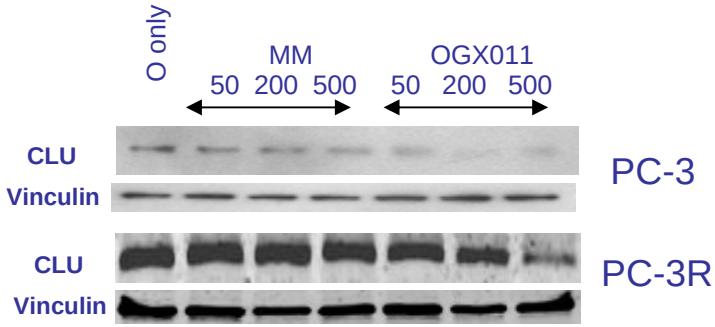
NCIC IND.165: Taxotere +/- OGX-011 in First-Line mHRPC

Indicators of Anti-cancer Activity

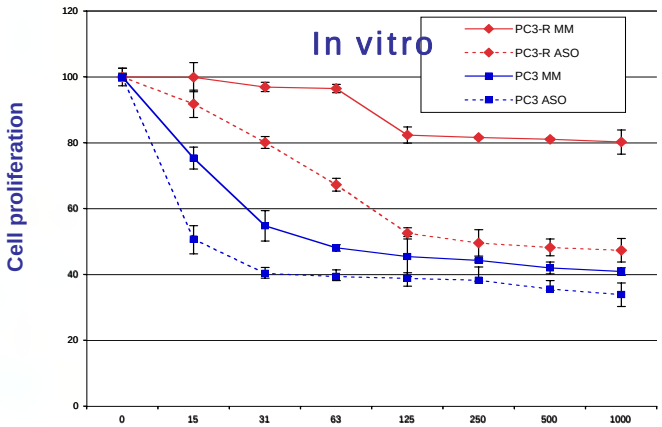
- **Consistent trend in favor of OGX-011/docetaxel arm:**
  - **More patients with a 50% decline in PSA within the first 12 weeks**
  - **More pts (38% vs 22%) with >80% decline in PSA; less pts (0 vs 10%) with primary PSA progression as best response**
  - **Longer time on treatment and a greater median # of treatment cycles.**
  - **Higher frequency and longer duration of stable measurable disease.**
  - **Lower frequency of progressive disease as “best response”.**
  - **Longer time to progression**

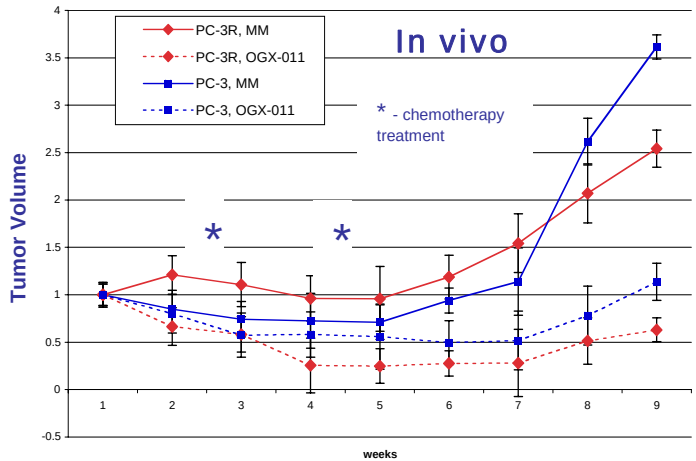
OGX-011 in docetaxel-refractory HRPC:

CLU knockdown chemosensitizes taxane-resistant PC3-dR cells to docetaxel



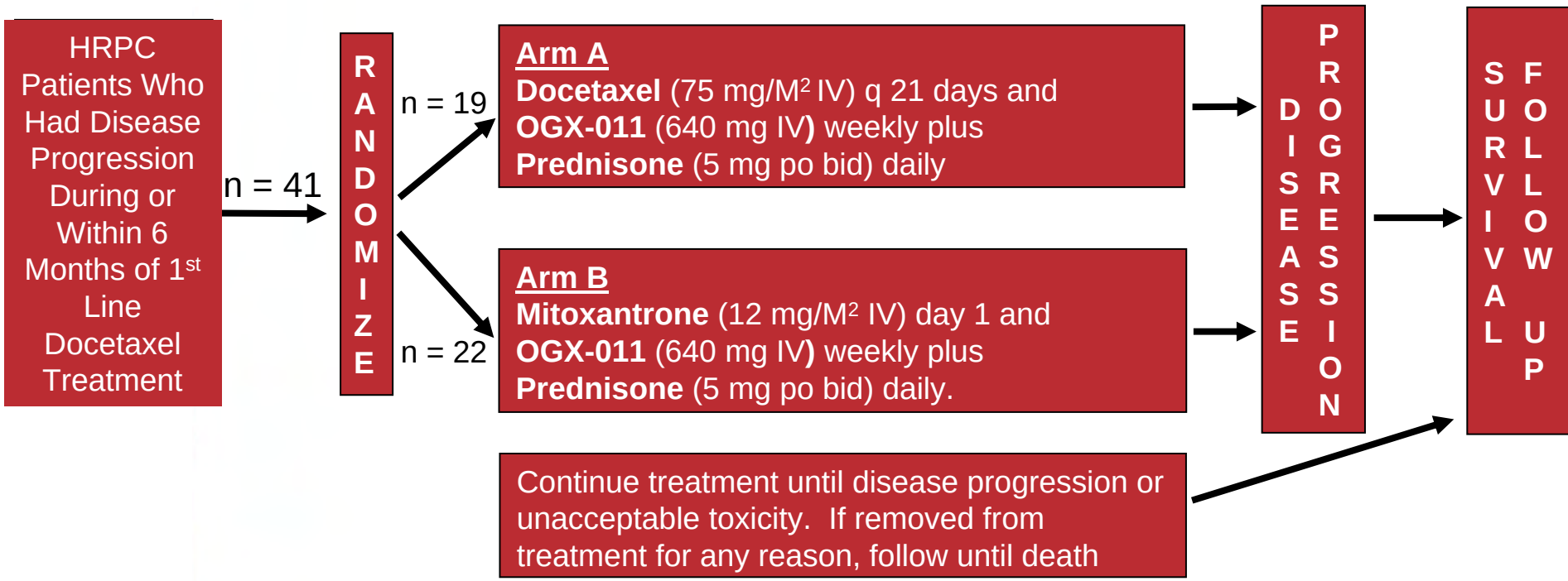
docetaxel +/- OGX-011





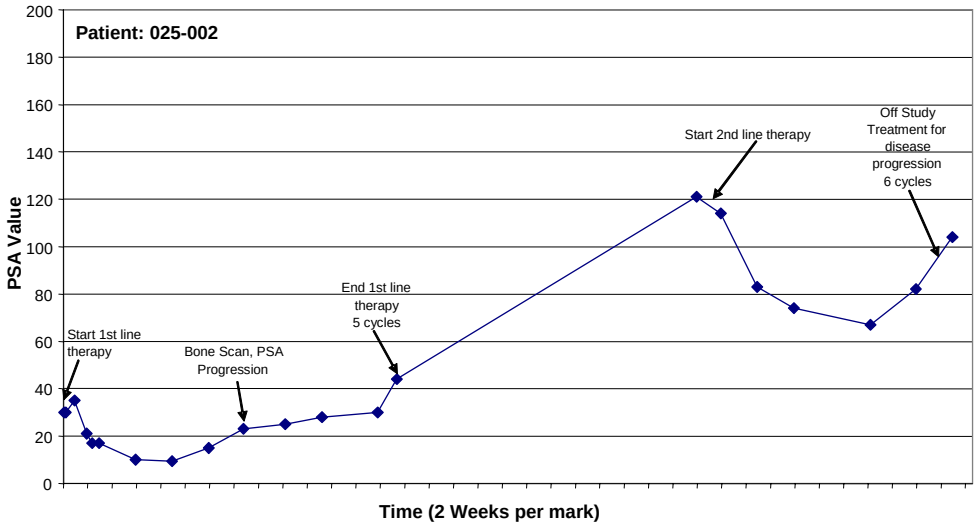
Phase II Feasibility Trial of OGX-011 in 2nd Line Therapy in HRPC:

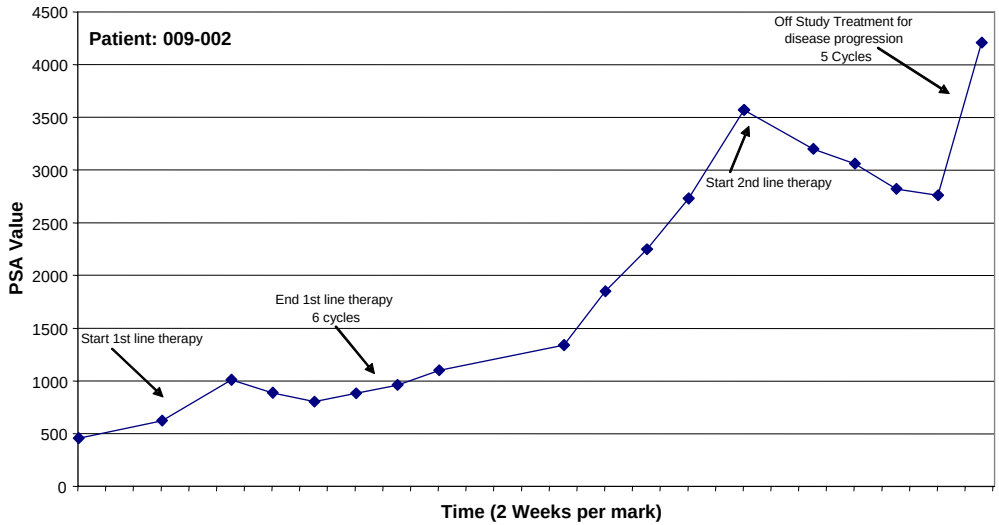
Study treatment ongoing in 11 (26%) of patients



OGX-011 in 2nd Line Therapy in HRPC:

Chemosensitizes taxane-resistant patients to docetaxel

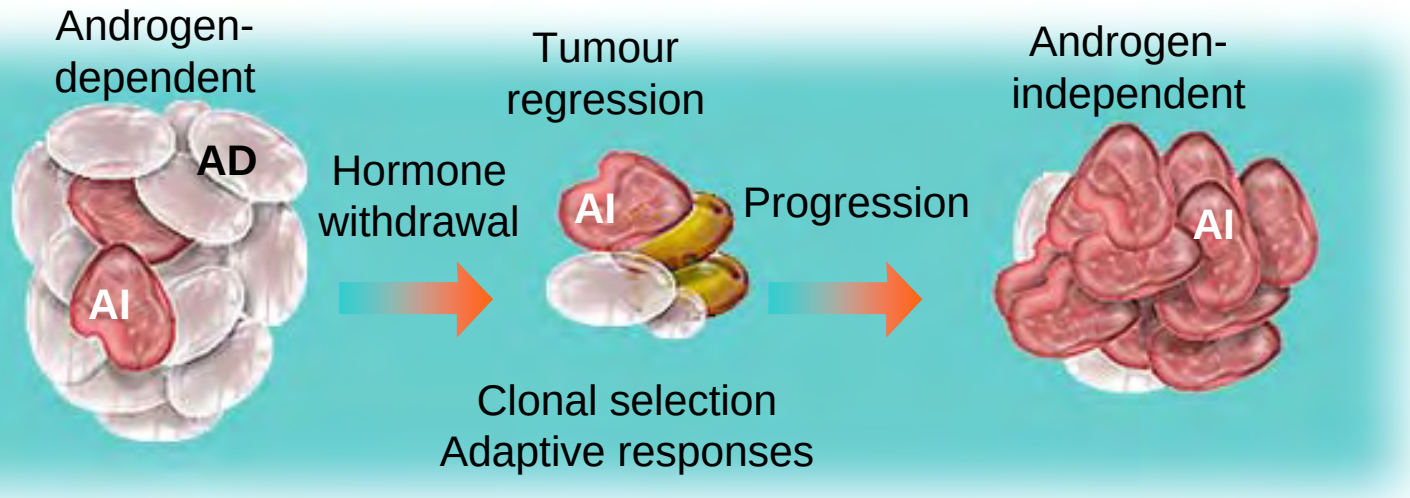




Summary:
Clusterin as a Therapeutic Target in HRPC

- **sCLU is a stress-activated cytoprotective chaperone that is highly expressed in HRPC**
- **Over-expression of sCLU-2 confers broad spectrum treatment resistance**
  - **Inhibits protein aggregation, facilitates proteasome degration of ubiquitinated proteins**
  - **Interacts and and inhibits activated Bax, preventing cytochrome C release**
  - **Increases NF-kB transcriptional activity**
- **CLU knockdown using OGX-011**
  - **Enhances treatment-induced apoptosis in vitro and in vivo**
  - **Pre-clinical proof-of-principle in prostate, breast, lung, urothelial, melanoma, renal cell**
  - **OGX-011, a 2nd generation ASO potently suppresses target CLU levels >90% in human CaP tissues**
    - **Anti-cancer activity observed in multi-centre Phase II trials in breast, HRPC, lung**
    - **Phase III registration trial in second-line HRPC set to begin in 2008**

Changes in Gene Expression After Castration and During AI Progression



++ PSA
- Bcl-2
- EGFR
- clusterin
- IGFBP 2&5
- TGFβ
++IGFBP 3 & 4
-YB-1
++survivin
-Hsp27
+ PKC-α

- PSA
++ Bcl-2
++Bclx-L
- EGFR
+++ clusterin
++++IGFBP 5
IGFBP 3 & 4
+c-*myc*
+YB-1
-survivin
+Hsp27
+ PKC-α

++ PSA
++ Bcl-2
++Bclx-L
+ EGFR
+++ clusterin
++ IGFBP 2
++ IGFBP 5
++YB-1
++ survivin
+++Hsp27

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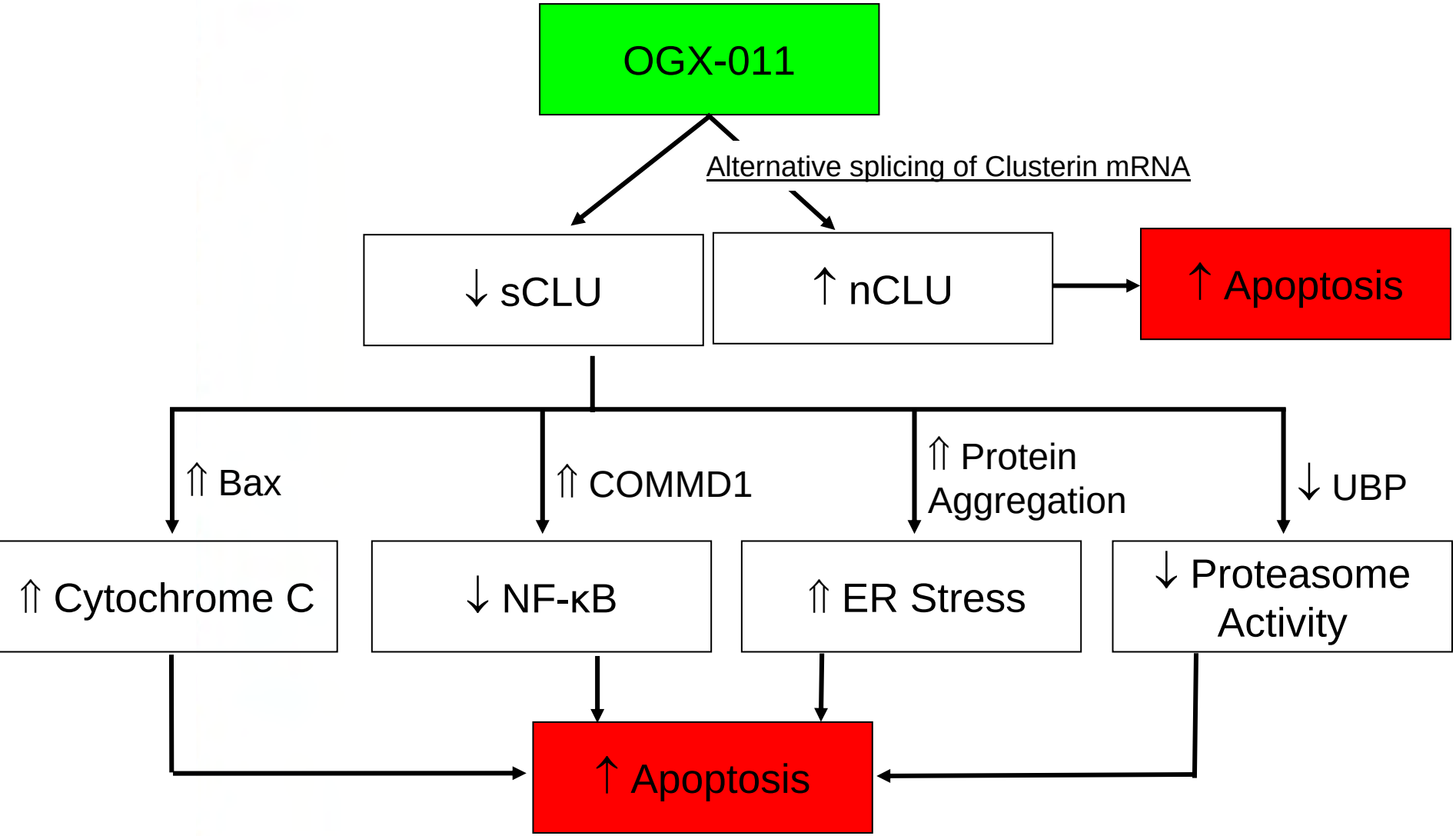
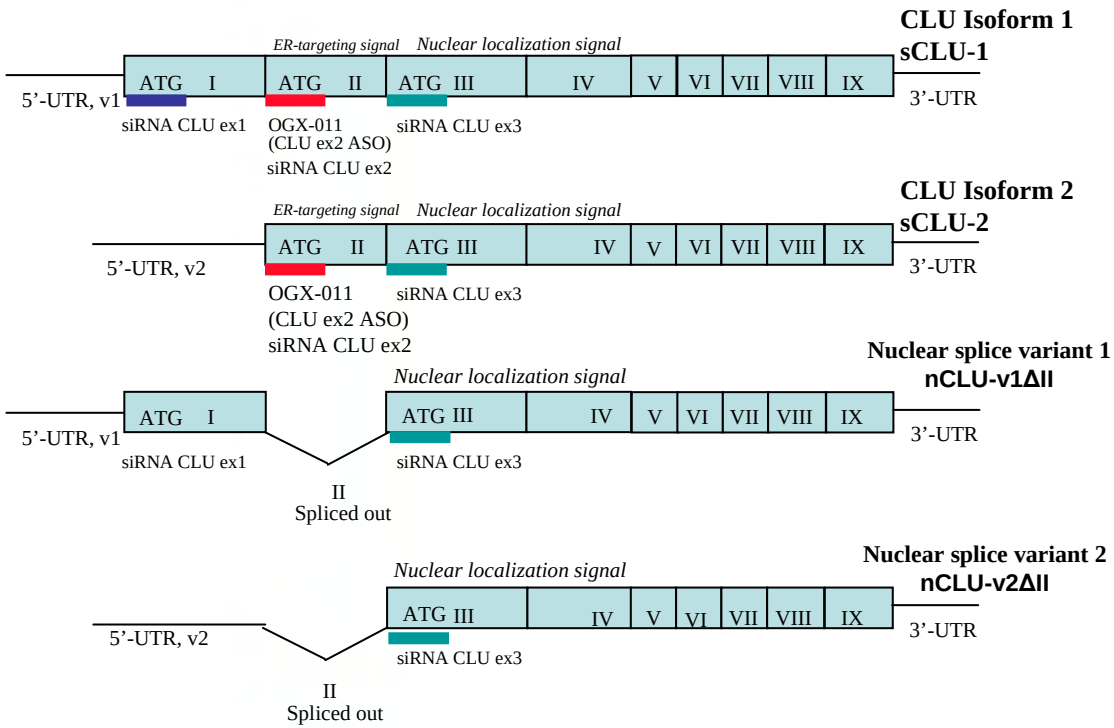
OGX-011: Safety Profile in >270 Patients

- **Well tolerated in all Phase 1 and Phase 2 studies to date**
- **Safety profile of OGX-011 in combination with docetaxel vs docetaxel alone**
  - **Increase in Grade 1 or 2 AE's events (fever, rigors/chills and sweating during the loading-dose week and sensory neuropathy during therapy)**
  - **lymphopenia was more prevalent in the OGX-011 + docetaxel arm (no clinical sequelae)**
  - **No increase in SAEs in the OGX-011 + docetaxel arm**
- **OGX-011 in combination with gemcitabine/platinum-based or mitoxantrone regimens**
  - **Safety profile similar to that expected for regimen (no increase in expected rate of Grade 3 or higher AEs)**

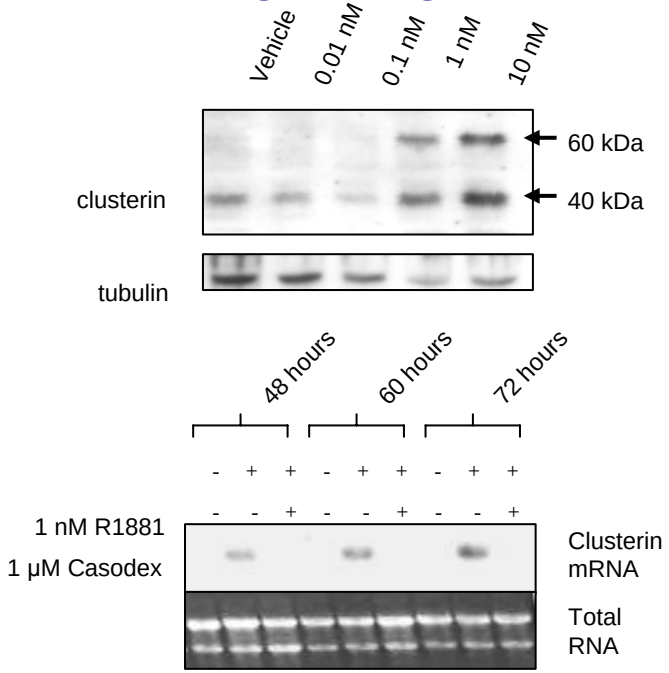
OGX-011 Mechanism of Action

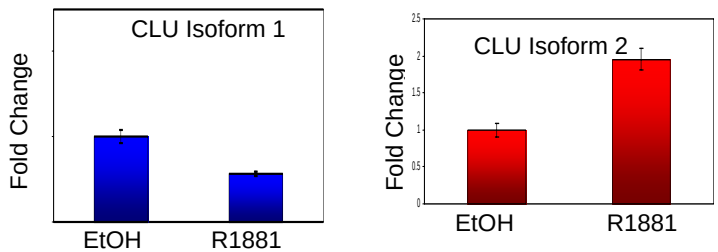


Clusterin: Isoforms and Splice Variants



CLU is an androgen-regulated gene





Cochrane et al, JBC, 2006