



Receptores de Andrógenos

Podem influenciar na escolha do tratamento do câncer de mama?

Charles Huggins

Nobel Prize for Physiology and Medicine (1966)

Elwood Jensen

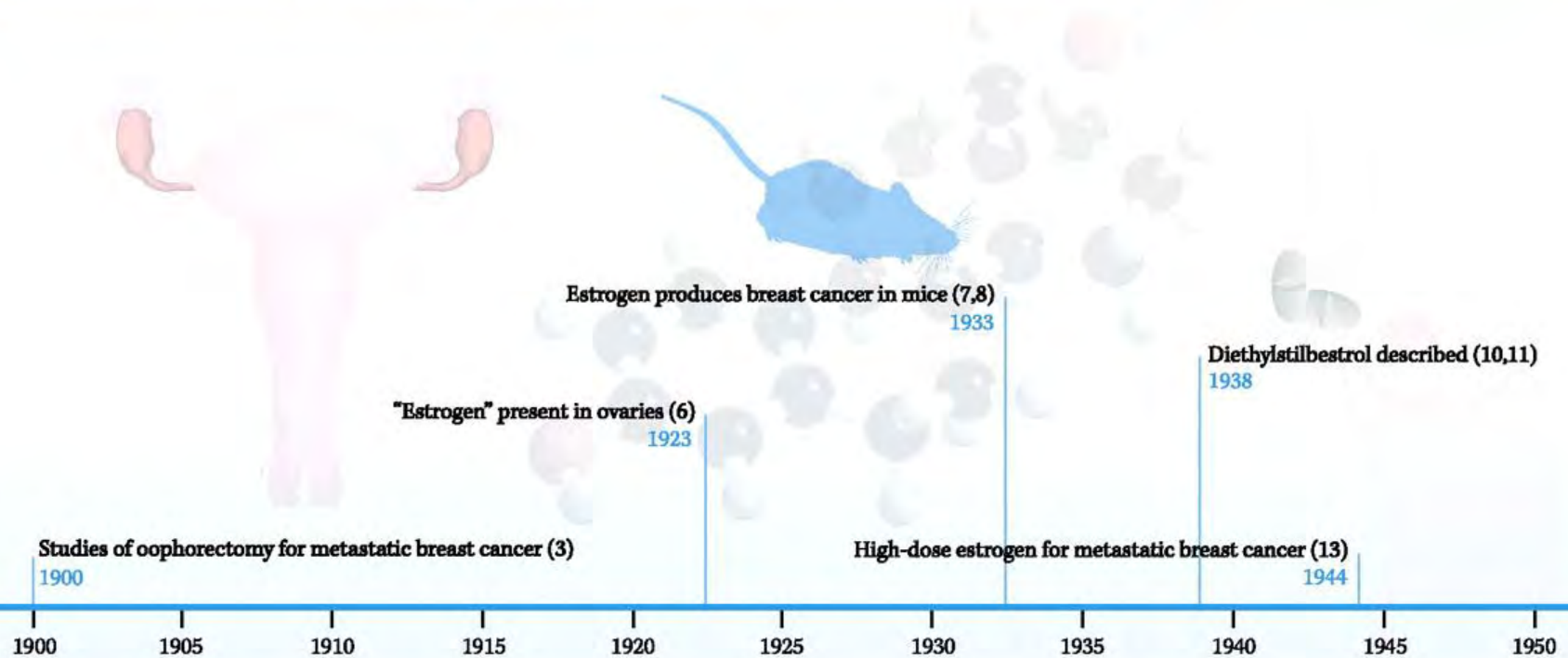
Lasker Award (2004)



V. Craig Jordan, *Cancer Res*, Feb 15th 2009; 69: 1243-54

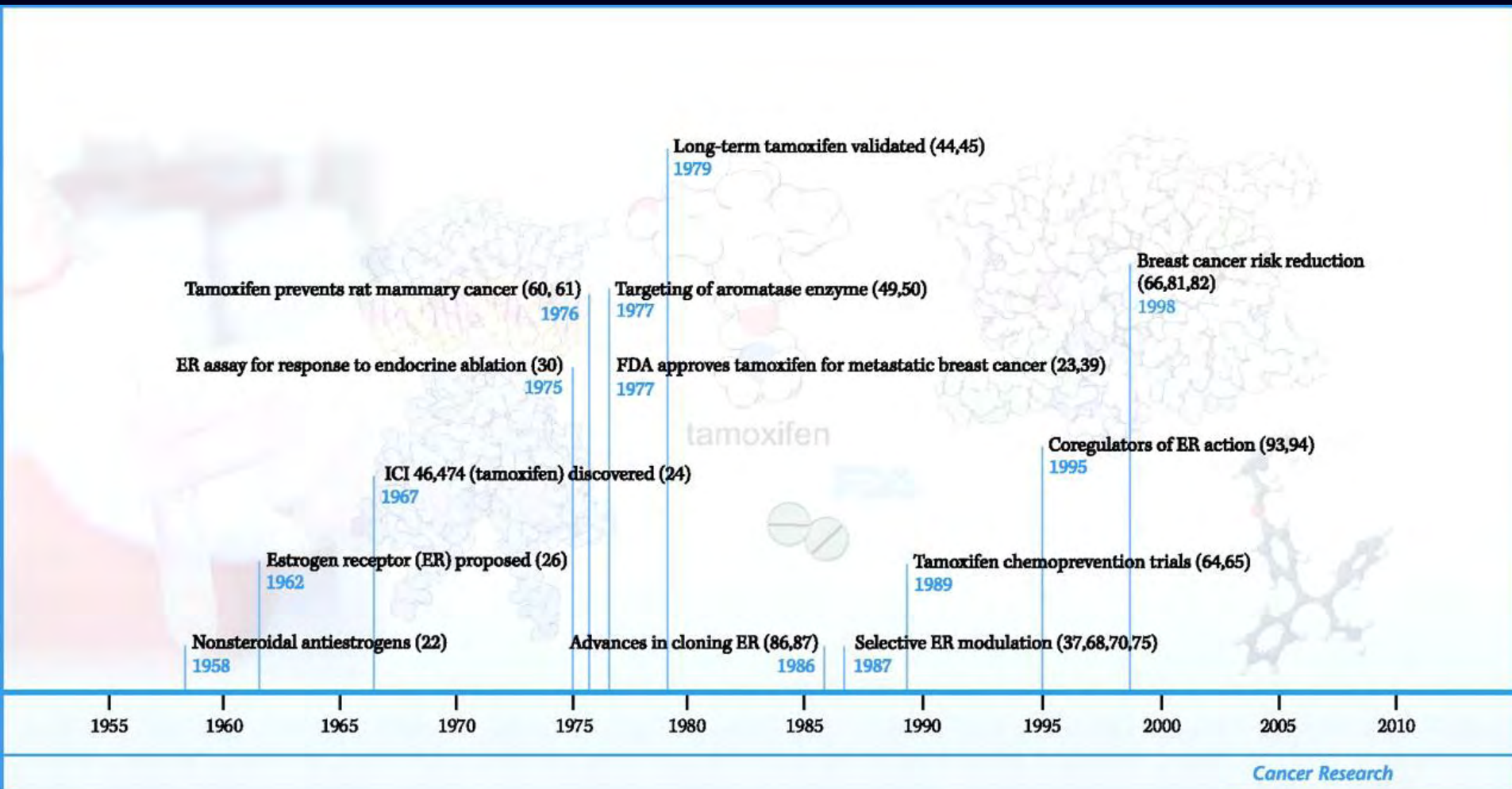
Um século na terapia endócrina !

Hormones: Key Dates in Deciphering Estrogen Action in Breast Cancer 1900–Present



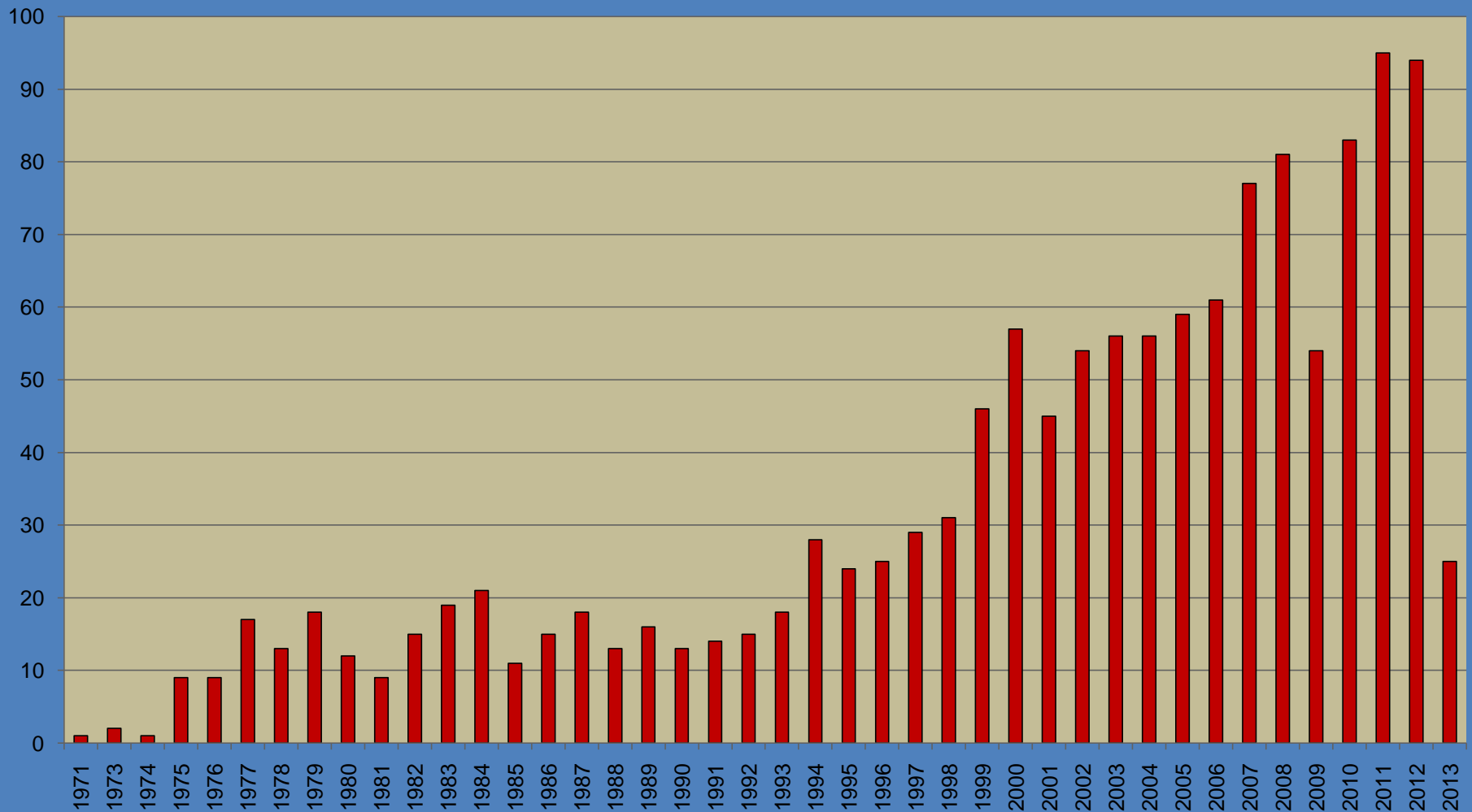
AACR Centennial Series

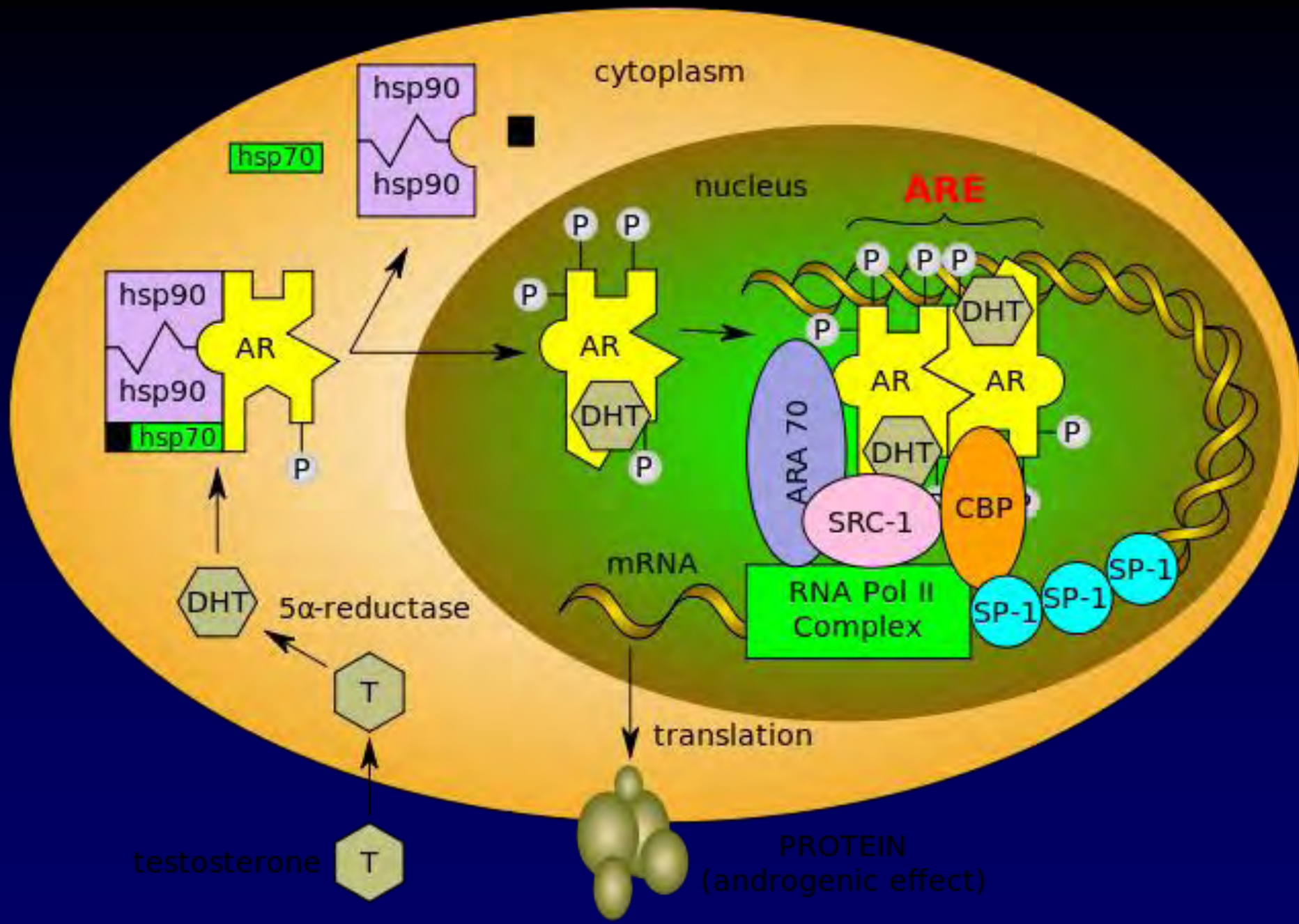
Um século na terapia endócrina !



“Androgen Receptor” AND “Breast Cancer”

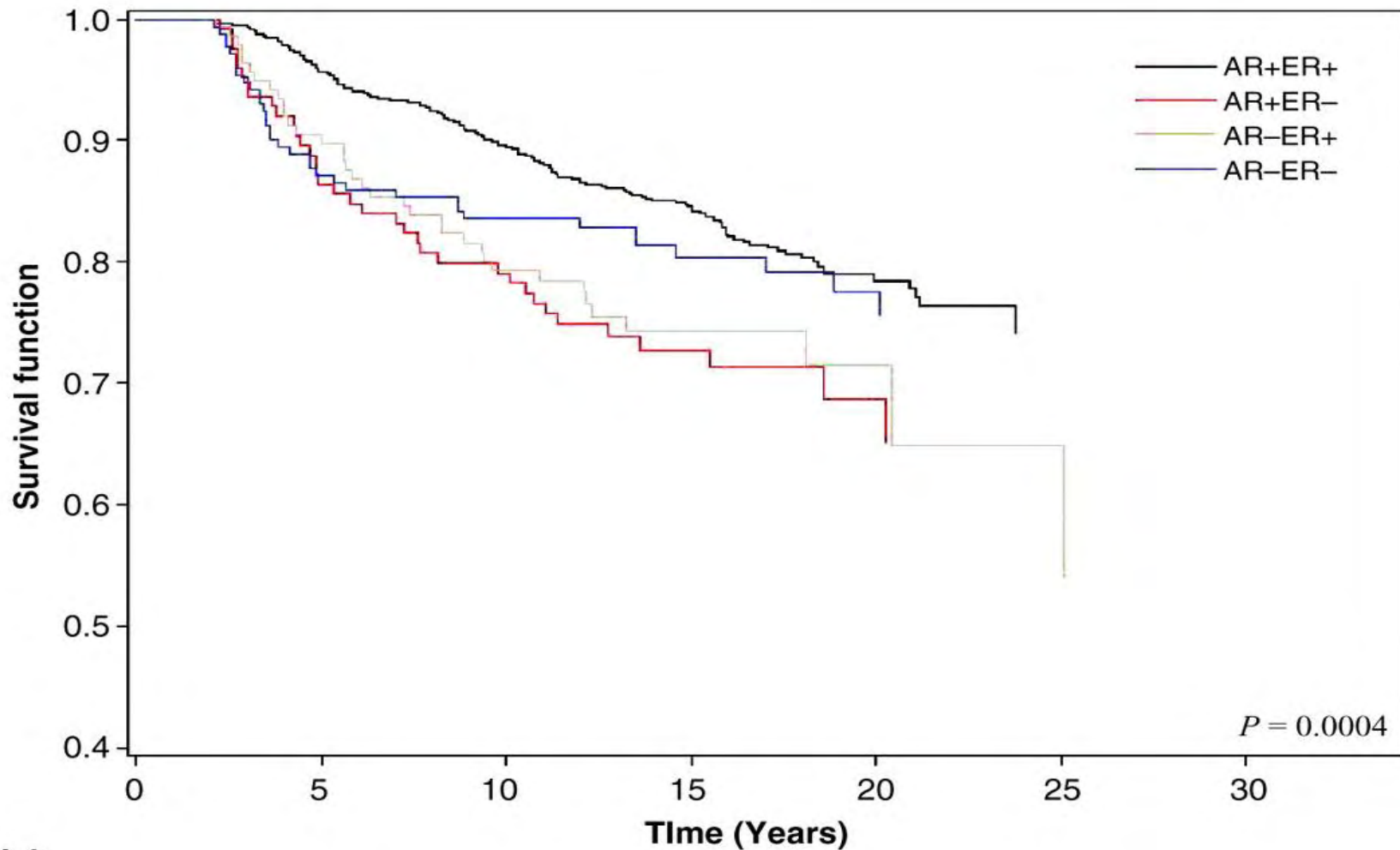
Citações no PubMed





Nurses' Health Study

- Estudo prospectivo em mulheres na pós menopausa
- Neoplasia de mama estágio I a III
- Diagnosticadas entre 1976 e 1997
- E seguidas até 1º de janeiro de 2008 ou óbito
- Análises pelo método de Kaplan–Meier e modelo de riscos proporcionais de Cox
- Objetivo: Determinar a associação do RA com a sobrevida



Number at risk

AR+ER+	1024	946	828	485	150	4	4
AR+ER-	130	107	95	52	20	0	0
AR-ER+	140	122	101	44	11	6	3
AR-ER-	173	148	137	78	40	2	2

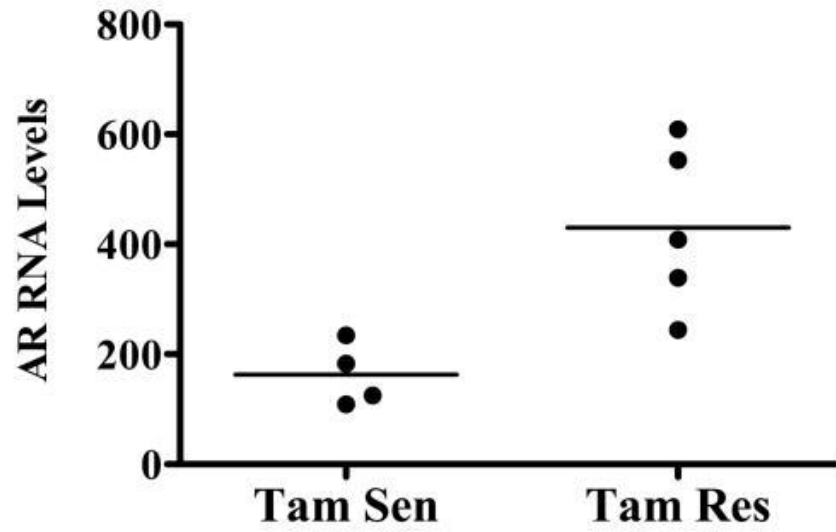
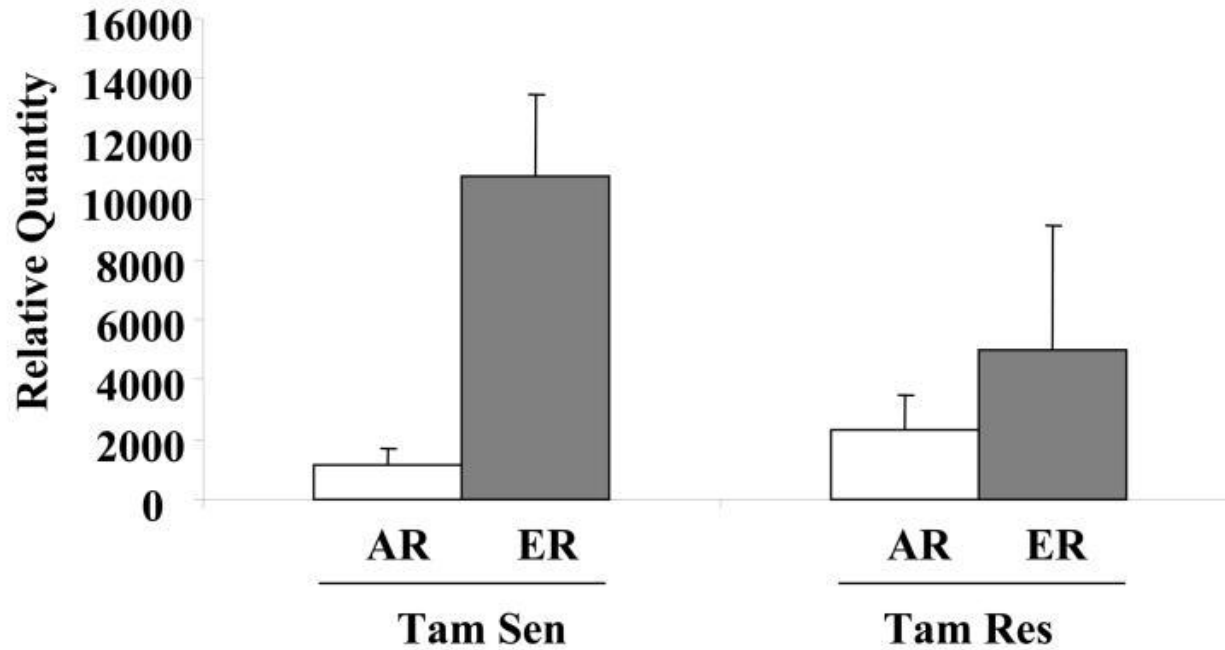
* $P = 0.003$ for AR+ER+ versus AR-ER+ and $P = 0.14$ for AR+ER- versus AR-ER-.

Androgen Receptors in Breast Cancer

ROBERT M. BRYAN, FRCS,*† RONALD J. MERCER, FRACS,*‡ RICHARD C. BENNETT, MS,*§
GEORGE C. RENNIE, MA,*|| TAT H. LIE, BAppSc,*¶ FRANCIS J. MORGAN, MD#**

Androgen receptor assays have been performed on 1371 specimens of histologically confirmed primary and recurrent breast cancer. Forty-two patients who had received tamoxifen as treatment for advanced disease were assessed for objective response. Another 42 patients who had received chemotherapy were similarly studied. Patients with androgen receptor-negative tumors had a significantly poorer response rate to hormone therapy than those with receptor-positive tumors ($P < 0.05$). This clinical correlation is supported by survival data of 1181 patients with primary breast cancer which showed that patients with androgen receptor-negative tumors had a highly significant trend toward shorter overall survival than those with receptor-positive tumors ($P < 0.001$). Androgen receptor data added significantly to the information provided by estrogen receptor data both in terms of response to hormone treatment and survival.

Cancer 54:2436-2440, 1984.

A**B**

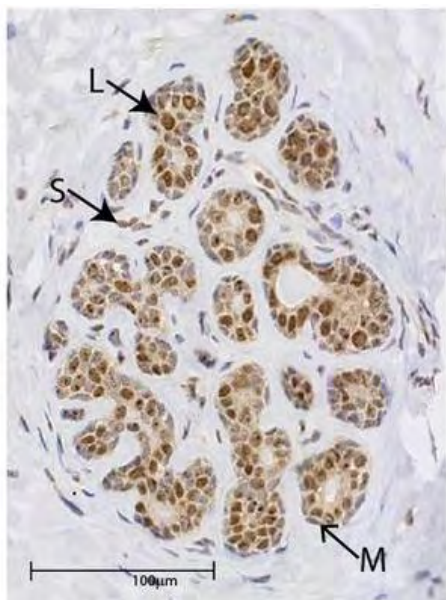
Fator preditivo de resposta

Em células com sobre-expressão do RA

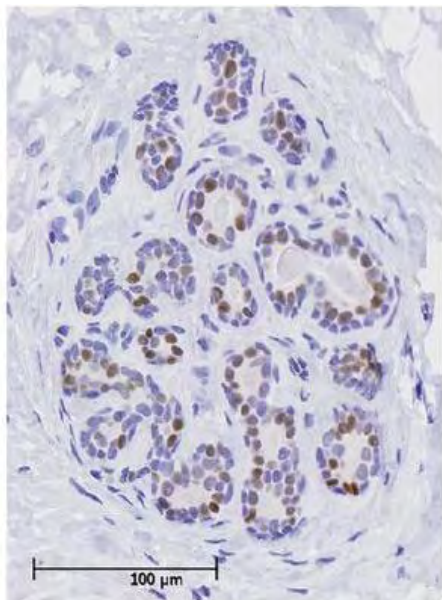
- Tamoxifeno induz atividade transcricional via RE α
- Essa atividade pode ser bloqueada pela bicalutamida
- Aumento da atividade agonista do tamoxifeno
- Mecanismo de resistência endócrina

Mammary acini

RA

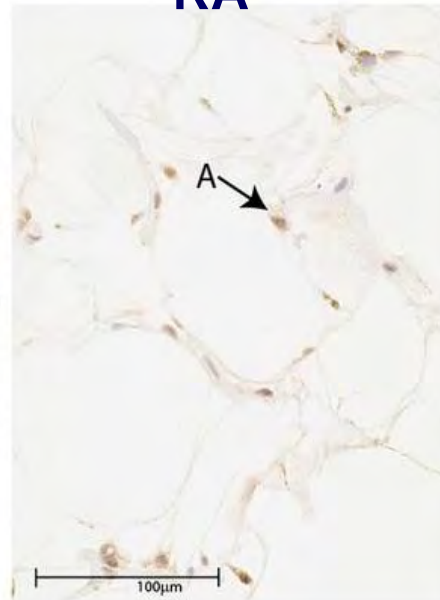


RE α

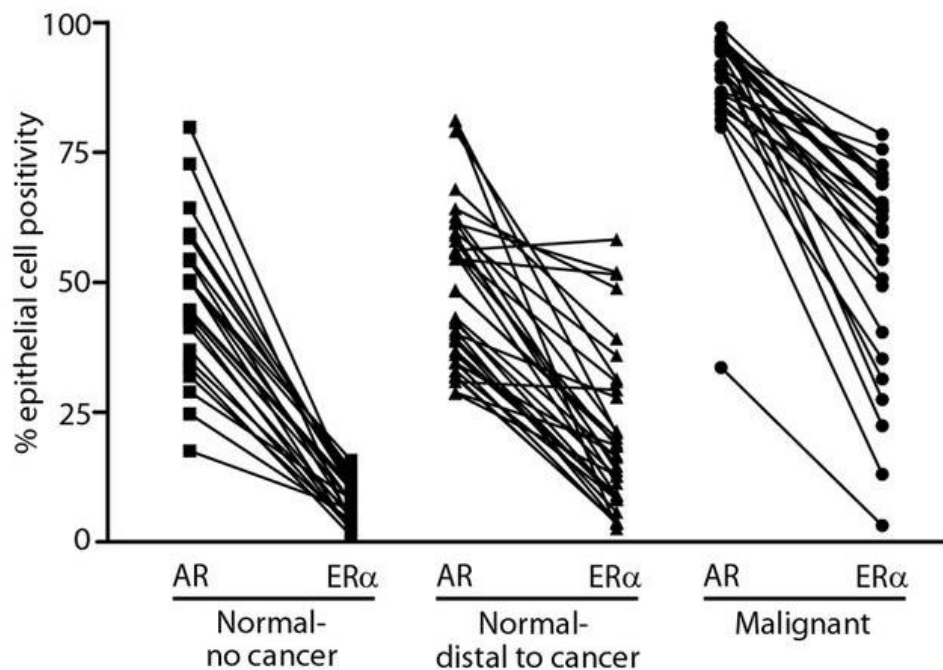
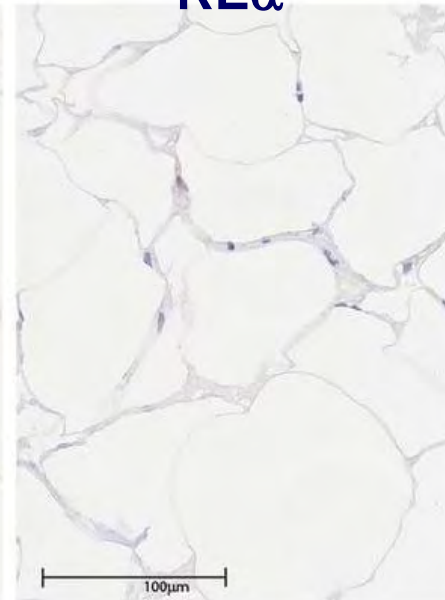


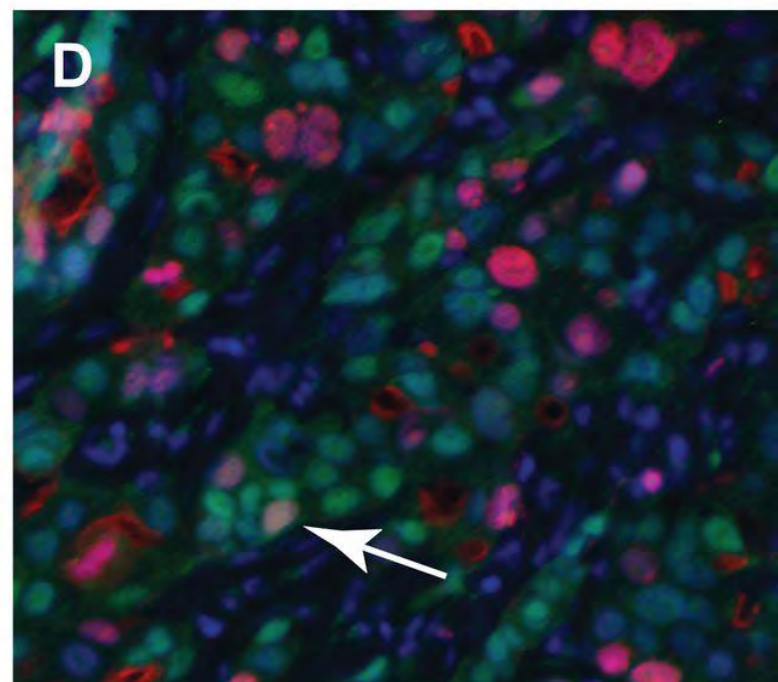
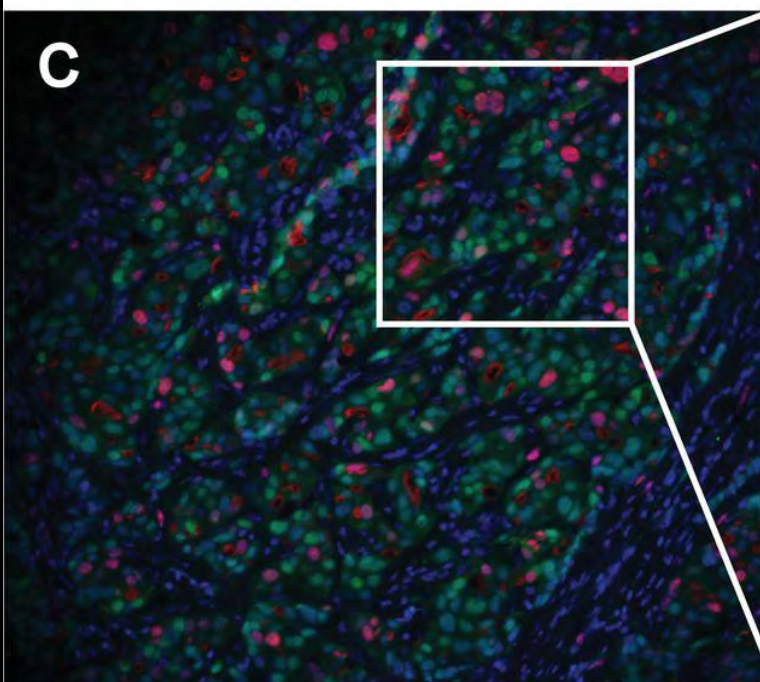
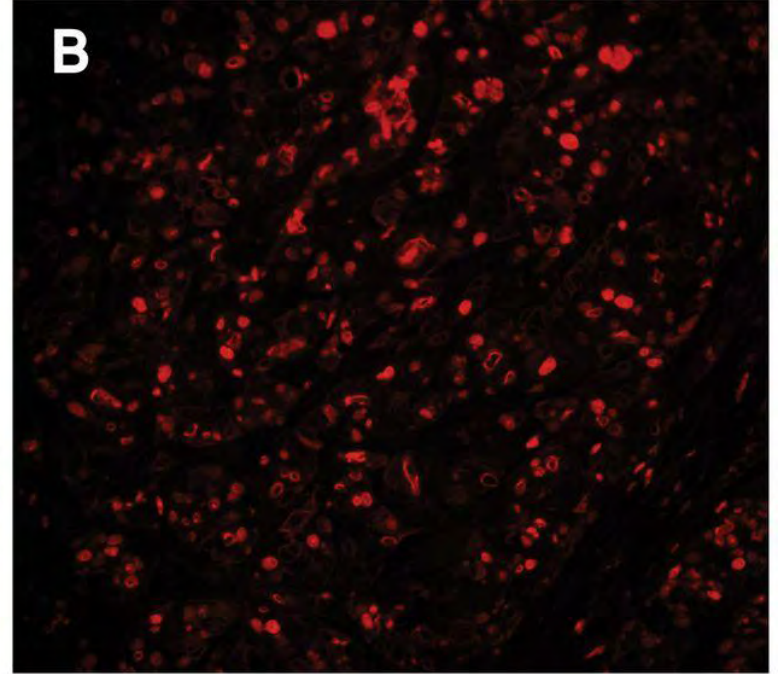
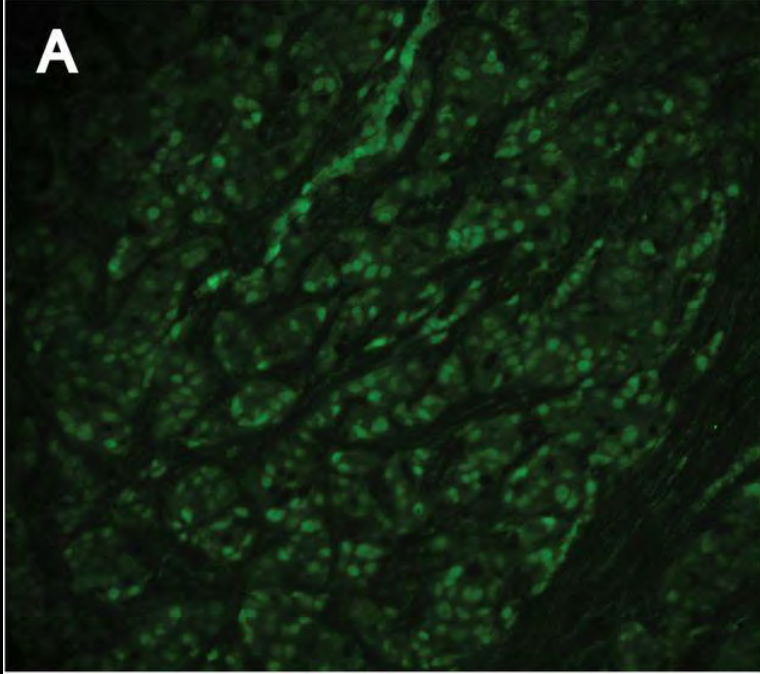
Mammary adipose

RA

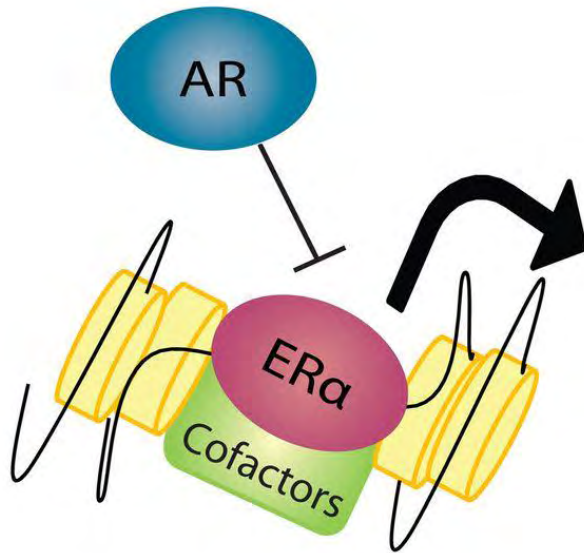


RE α





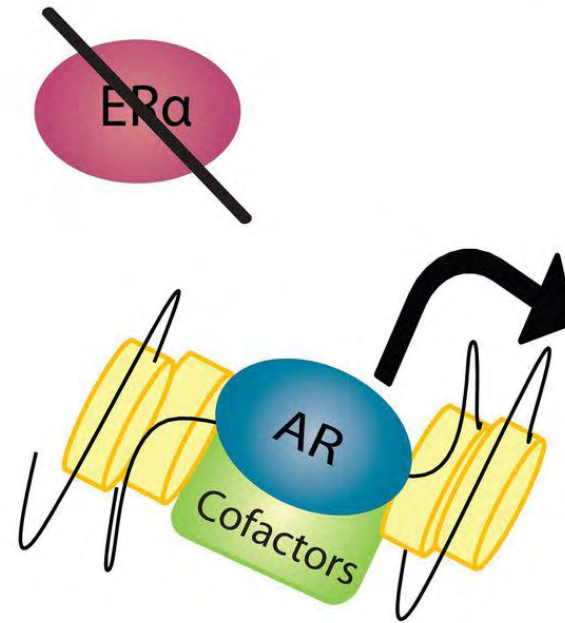
ER α + Breast Cancer



In the presence of comparable levels of AR and ER α , AR is an ER α competitor and can suppress ER α -mediated growth

TUMOR SUPPRESSOR

ER α - Breast Cancer and ER α + Drug Resistant Breast Cancer



In absence of ER α , AR levels increase, cofactor interactions change and AR becomes an ER α mimic

ONCOGENE

Androgen receptor expression is a predictive marker in chemotherapy-treated patients with endocrine receptor-positive primary breast cancers

Isabell Witzel · Monika Graeser · Thomas Karn · Markus Schmidt · Ralph Wirtz · Dina Schütze · Alma Rausch · Fritz Jänicke · Karin Milde-Langosch · Volkmar Müller

Received: 31 December 2012 / Accepted: 21 January 2013
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Abstract

Purpose The androgen receptor (AR) is intensively discussed as a prognostic and/or predictive marker in breast cancer patients.

Methods We evaluated the value of AR mRNA expression with the Affymetrix HG-U 133A array in 3 different cohorts: a cohort of breast cancer patients who received adjuvant treatment (cohort A; $n = 165$), a cohort of untreated breast cancer patients (cohort B; $n = 200$) and a cohort of chemotherapy-treated breast cancer patients with estrogen receptor (ER)-positive tumors (cohort C; $n = 223$).

Results AR mRNA expression was associated with lower grading (Grades 1 and 2) as well as ER and progesterone receptor (PgR) positivity in all cohorts. In the treated cohort (cohort A), low androgen receptor expression was associated with shorter event-free survival (OR 2.34,

95 % CI 1.01–5.43, $p = 0.047$) which was not seen in the untreated cohort B. Subgroup analysis revealed that shorter survival of patients with low AR mRNA expression was observed mainly in the ER-positive subgroup of patients treated with adjuvant chemotherapy. In the validation cohort C we could confirm a benefit of chemotherapy for the group of tumors with high AR mRNA expression (5-year event-free survival (EFS) 74 % versus 57 %, $p = 0.013$). In this cohort, low AR mRNA expression was associated with shorter event-free survival also in multivariate analysis (OR 2.86, 95 % CI 1.29–6.35, $p = 0.010$) adjusted for HER2, ki-67, tumor size, age and tumor grade. **Conclusions** We provide evidence that AR expression is associated with chemotherapy responsiveness in ER-positive patients.

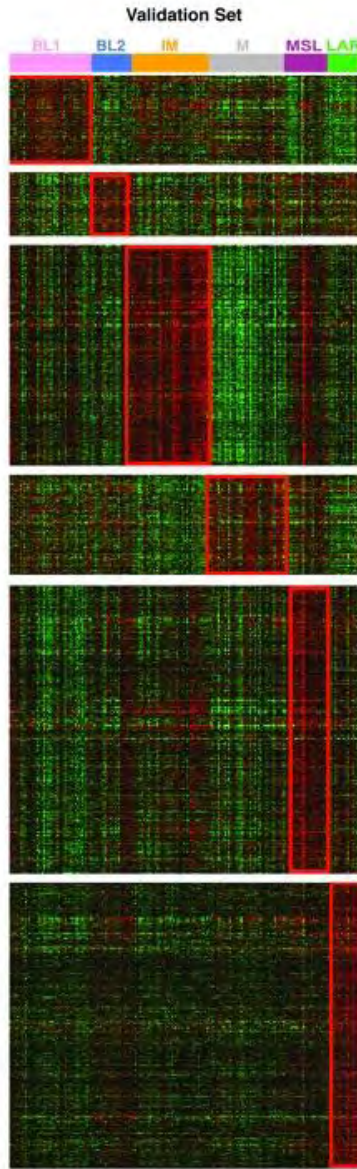
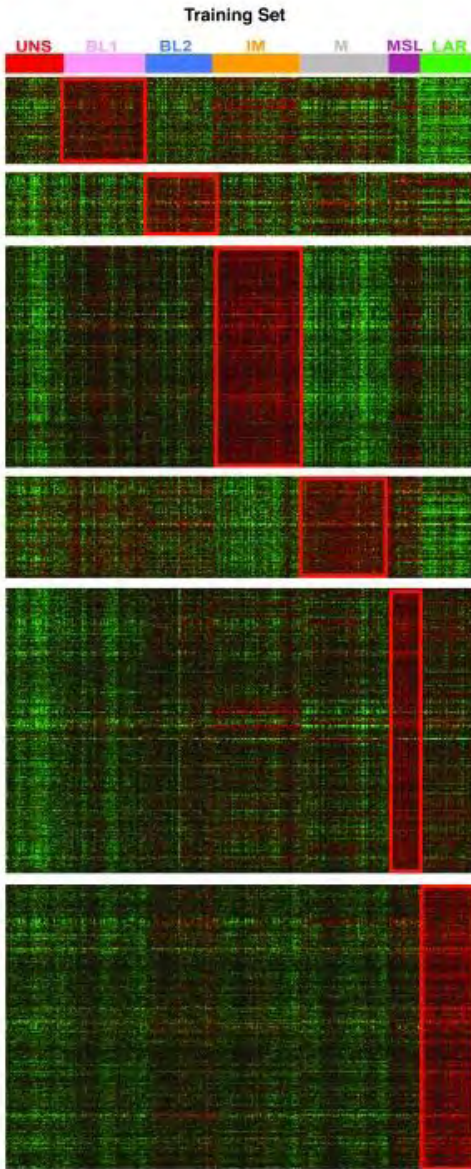
Keywords Androgen receptor · Breast cancer · Prognosis · Prediction



Subclassificação dos TN

Com base na expressão gênica

- Basal simile 1 (BL1) / Basal simile 2 (BL2)
 - Alta expressão de genes de proliferação e resposta ao dano do DNA
 - Respondem a Cisplatina
- Imunomodulatório (IM)
- Mesenquimal (M) / Célula tronco mesenquimal simile (MSL)
 - Alta expressão de genes de transição epitelial-mesenquimal e fatores de crescimento
 - Respondem a NVP-BEZ235 (um inibidor de PI3K/mTOR) e Dasatinibe (inibidor abl/src)
- Luminal com receptor de andrógeno (LAR)
 - Menor sobrevida livre de recidiva
 - Sensíveis a Bicalutamida



**GO Terms/
Canonical Pathways**

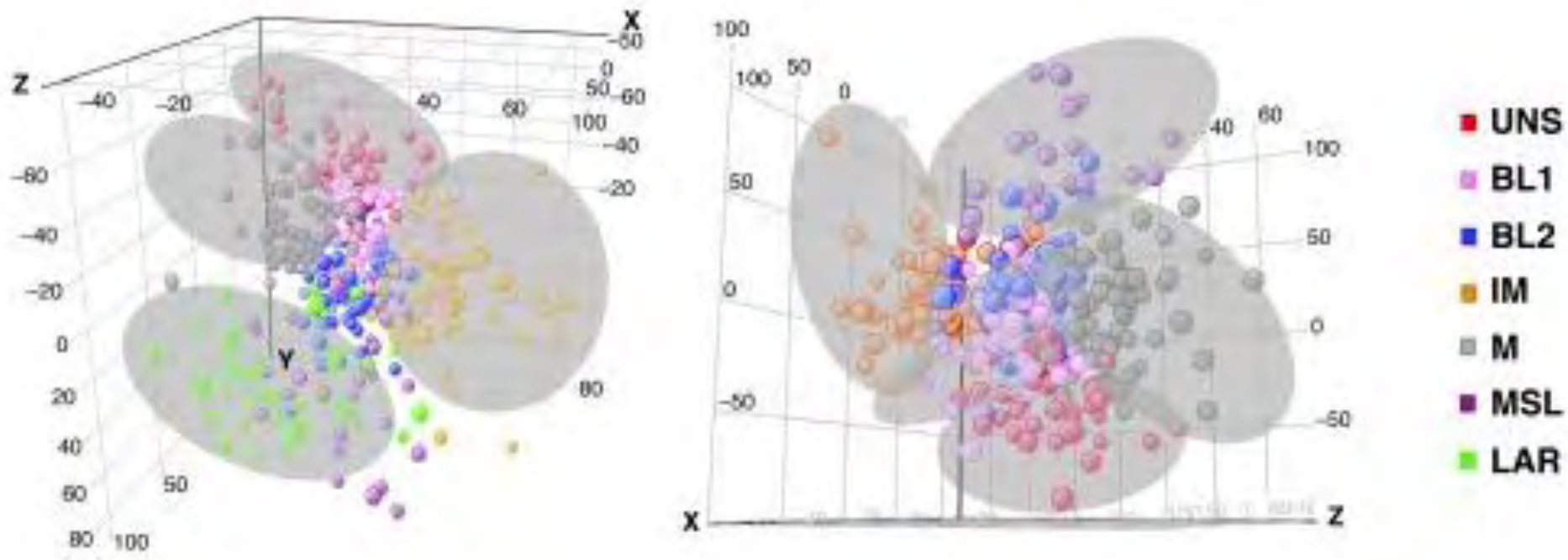
- Basal-like 1**
 Cell Cycle
 DNA Replication Reactome
 G₂ Pathway
 RNA Polymerase
 ATR/ BRCA Pathway
 G₂ to S Cell Cycle
- Basal-like 2**
 EGF Pathway
 NFκB Pathway
 MET Pathway
 WNT β-catenin Pathway
 IGF1R Pathway
 Glycolysis/ Gluconeogenesis
- Immunomodulatory**
 CTLA4 Pathway
 IL12 Pathway
 NK Cell Pathway
 Th1/Th2 Pathway
 IL7 Pathway
 Antigen Processing/ Presentation
 NFκB Pathway
 TNF Pathway
 T Cell Signal Transduction
 DC Pathway
 BCR Signaling Pathway
 NK Cell Mediated Cytotoxicity
 JAK/ STAT Signaling Pathway
 ATR/ BRCA Pathway
- Mesenchymal-like**
 IGF/ mTOR Pathway
 ECM Pathway
 Regulation of Actin by RHO
 WNT Pathway
 ALK Pathway
 TGFβ Pathway
- Mesenchymal Stem-like**
 ECM Receptor Interaction
 TCR Pathway
 WNT β-catenin
 Focal Adhesion
 Inositol Phosphate Metabolism
 NFκB Pathway
 EGF Pathway
 ALK Pathway
 GR Pathway
 NK Cell Mediated Toxicity
 RAC1 Pathway
 GPCR Pathway
 ERK1/2 Pathway
 Integrin Mediated Adhesion
 ABC Transporters General
 RHO Pathway
 Smooth Muscle Contraction
 Calcium Signaling Pathway
 Adipocytokine Signaling Pathway
 PDGF Pathway
 TGFβ Pathway
- Luminal AR**
 Pentose/Gluconate Interconversion
 Glutathione Metabolism
 Tyrosine Metabolism
 Steroid Biosynthesis
 Porphyrin Metabolism
 Androgen and Estrogen Metabolism
 Glycosphingolipid Metabolism
 Flagellar Assembly
 Citrate Cycle TCA
 Phenylalanine Metabolism
 ATP Synthesis
 Starch and Sucrose Metabolism
 Arginine and Proline Metabolism
 Metabolism by Cytochrome P450
 Fructose and Mannose Metabolism
 Fatty Acid Metabolism
 Alanine and Aspartate Metabolism
 Eicosanoid Synthesis
 CHREB Pathway
 Tryptophan Metabolism

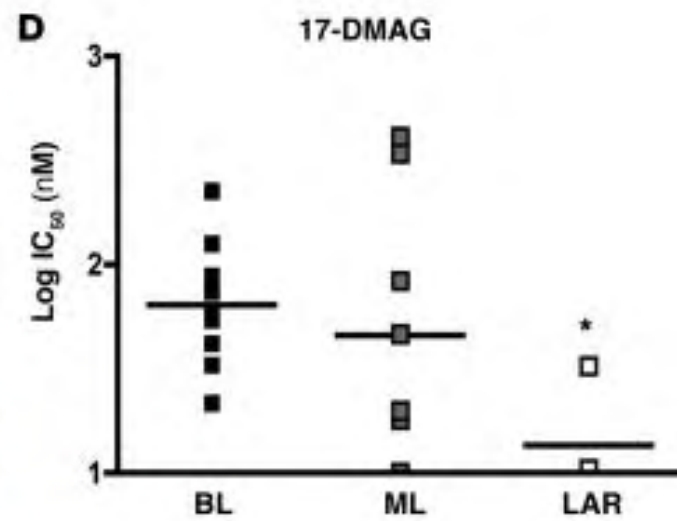
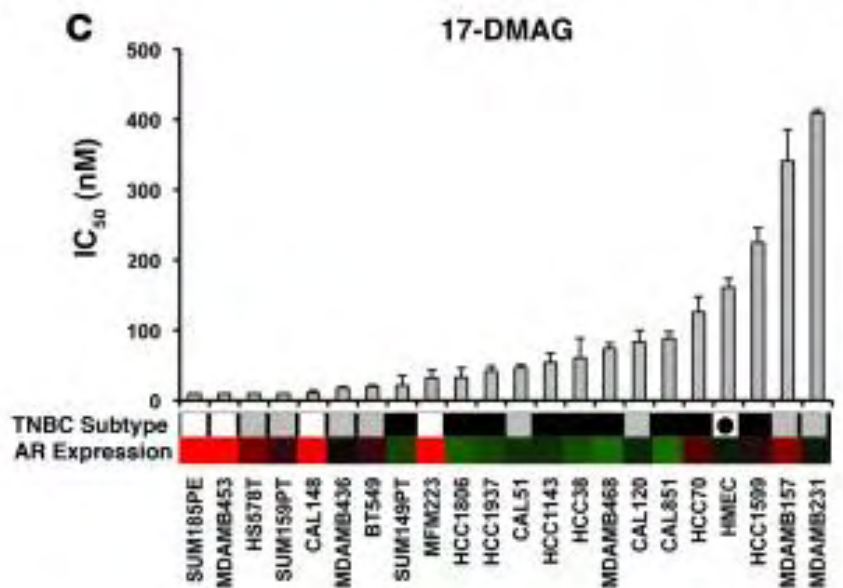
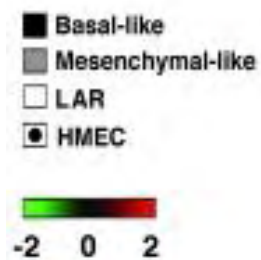
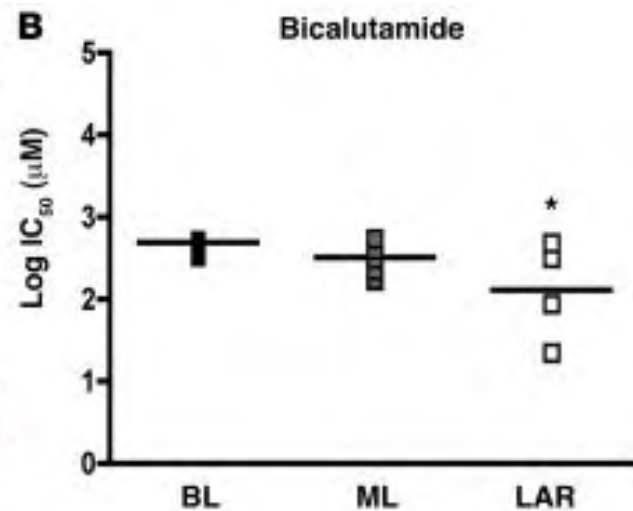
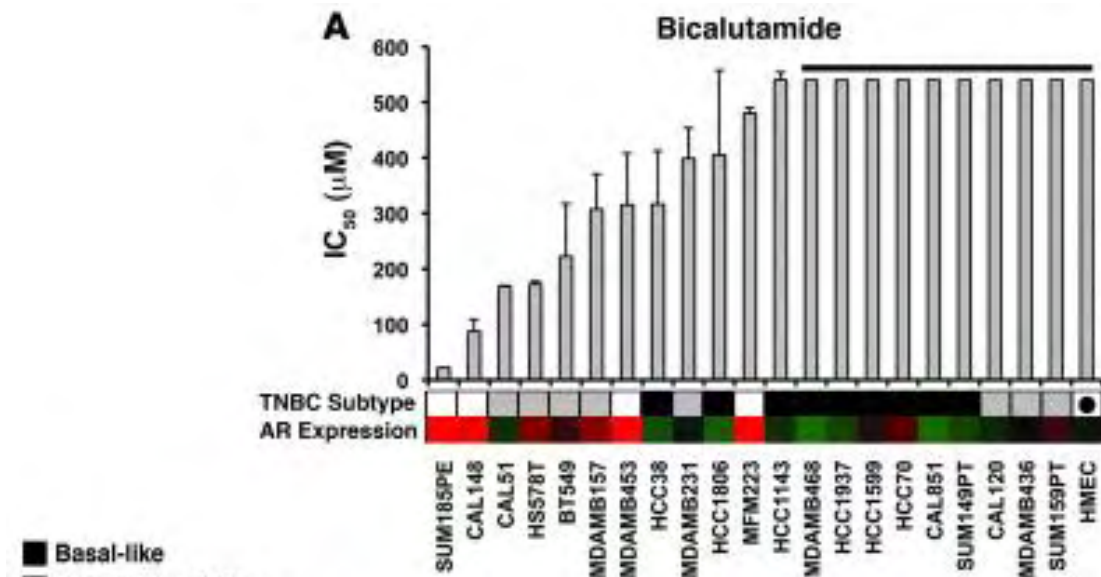


SUBGRUPOS

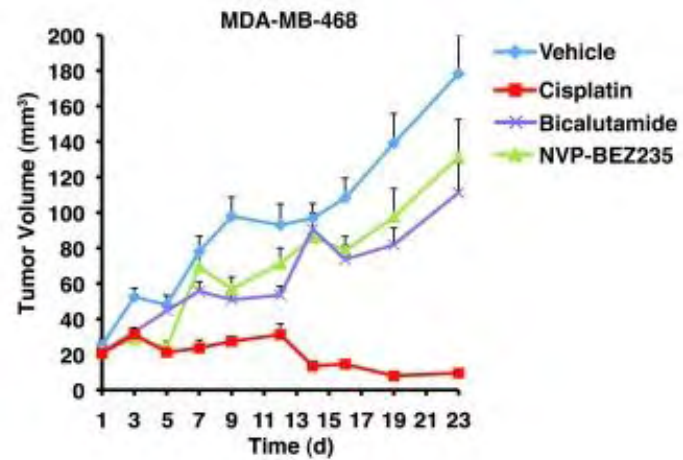
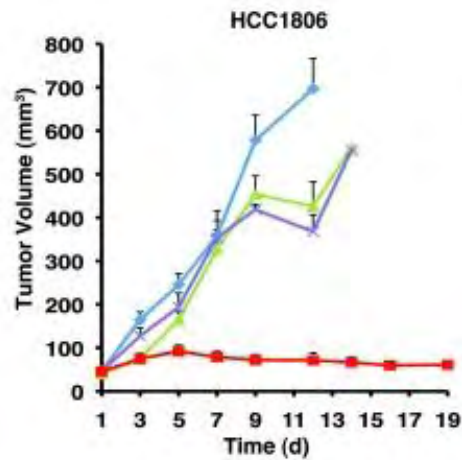
- Basal-símile 1
- Basal-símile 2
- Imunomodulatório
- Mesenquimal-símile
- Mesenquimal tronco-símile
- Luminal Rec. de Andrógeno

Identificação de subtipos na neoplasia triplo-negativa

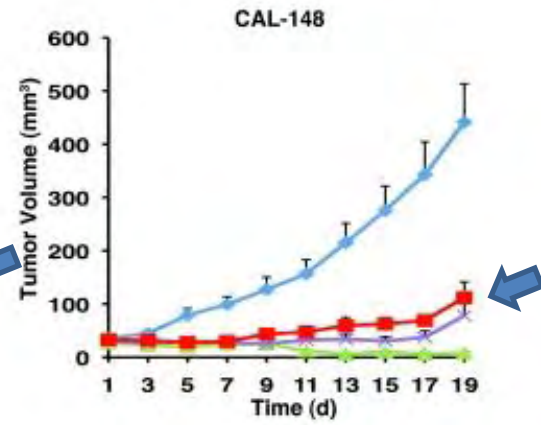
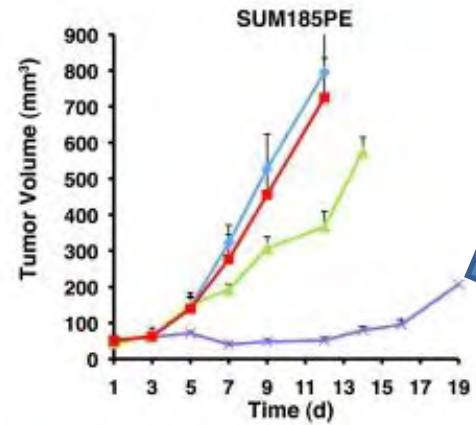




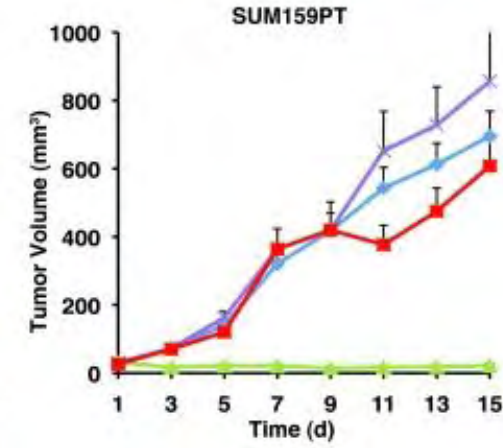
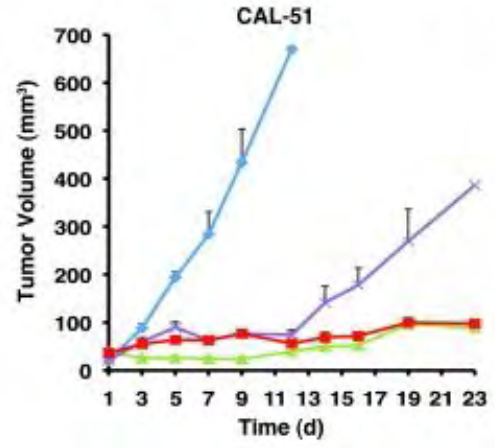
Basal-like

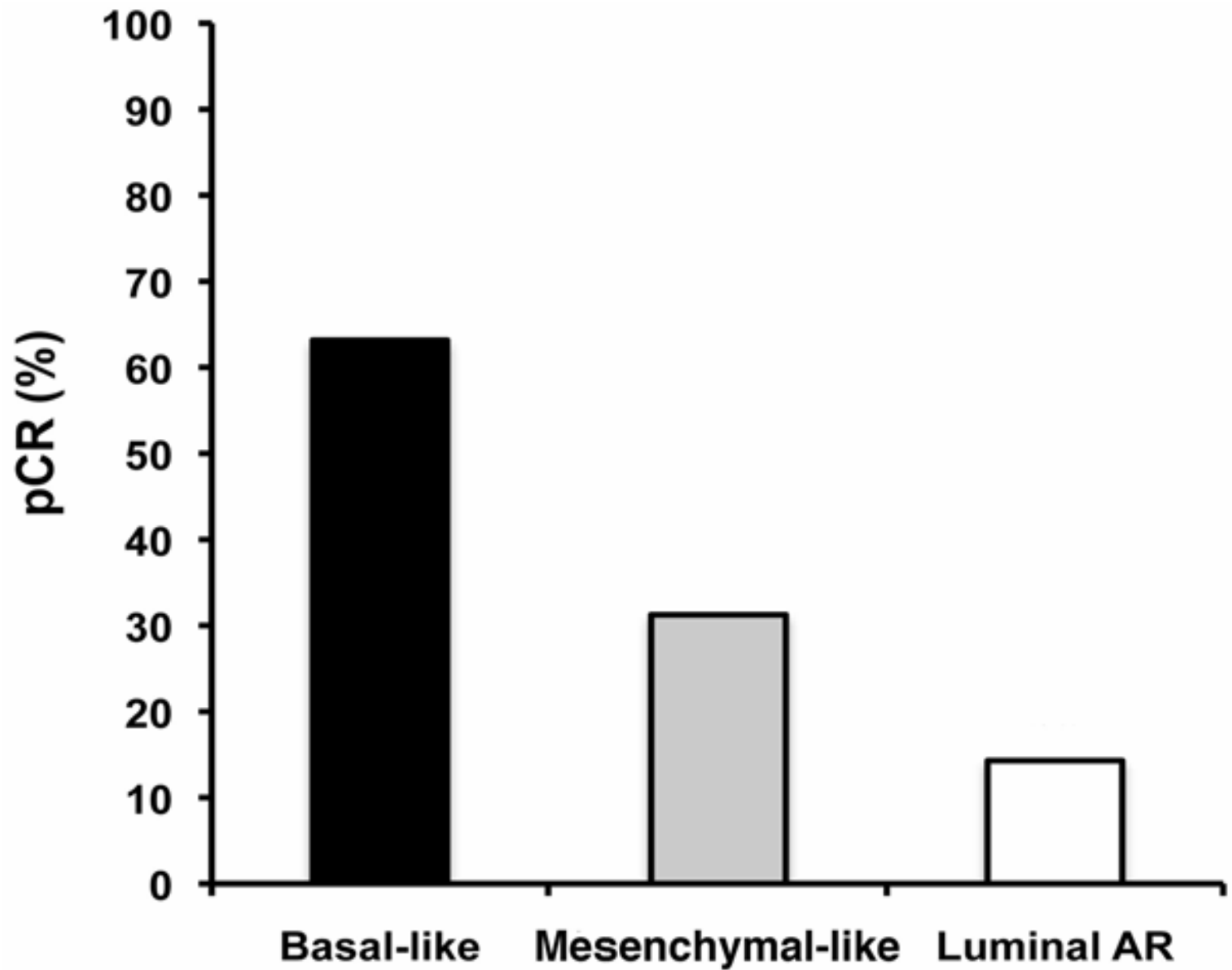


LAR



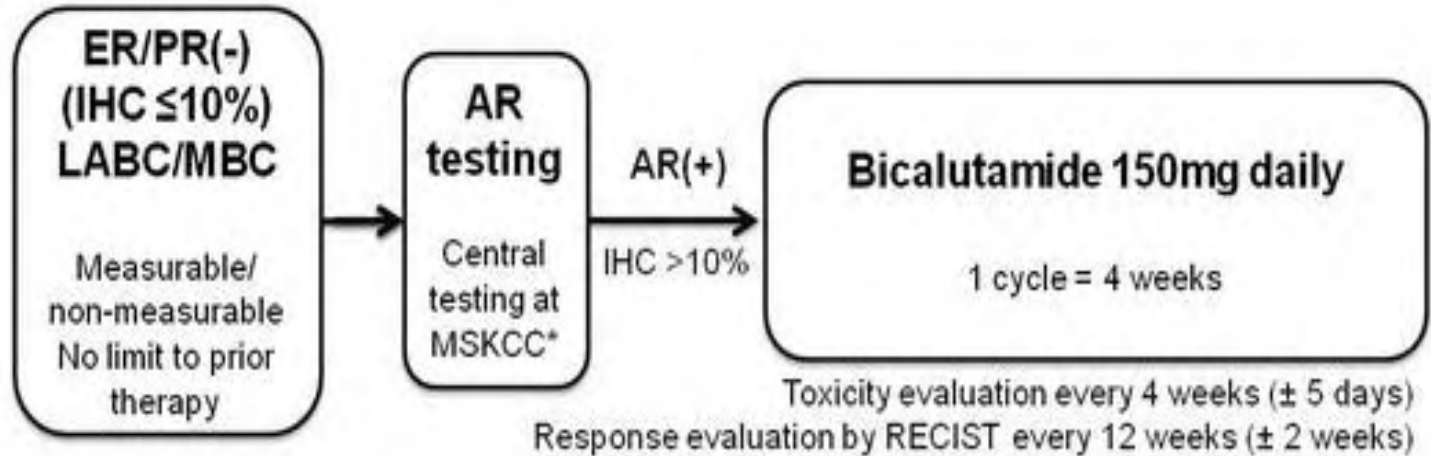
Mesenchymal-like



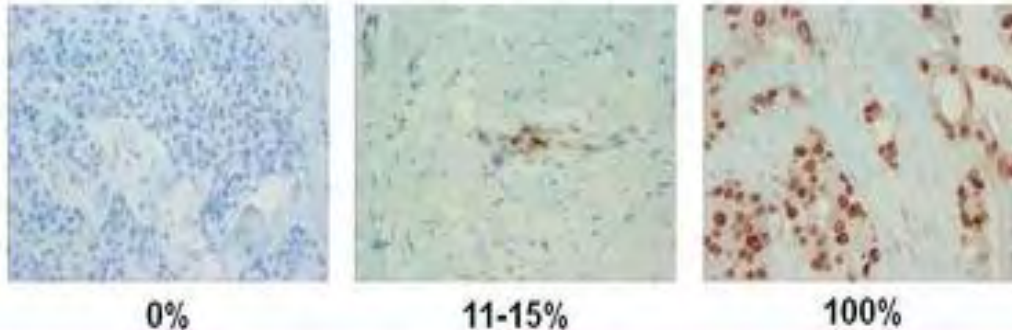


Bicalutamida - Fase II (NCT00468715)

Study Design



*AR tested using primary antibody AR 441 (Dako; dilution: 1:300)



Bicalutamida - Fase II (NCT00468715)

M1 RE-/RPg- RA+ (IHQ < 10%)

- Até 21/12/2011, 436 elegíveis para o teste do RA
- 47/400 testados (12%): RA+
- Receberam bicalutamida 150mg/dia: 26 pacientes
- Taxa de benefício clínico: (21 avaliáveis): 19%
(IC95%: 5 - 42%)
 - DE>6m: 4, CR/PR: 0, SD<6m: 3, PD: 14.

92 anos, lúcida, frágil. Dor intensa na mama, uso de opioide
AP-IMH carcinoma invasor, grau III, triplo negativo, Ki 67: 60%



Cortesia do **Dr. Carlos Sampaio**. *Clínica AMO - Salvador - BA*

Resposta após 100mg de bicalutamida (DE por 6 meses)



Cortesia do **Dr. Carlos Sampaio**. *Clínica AMO - Salvador - BA*

Imunohistoquímica - 15/03/2012

MACROSCOPIA:

Recebido(s) para estudo imuno-histoquímico um bloco(s) de parafina, rotulado(s) como 12/239 (Procedentes da CAM). Acompanha, ainda, laudo correspondente, emitido na CAM constando das descrições macroscópica, microscópica e conclusão. NS 29/02/12

MATERIAL: bloco de parafina: Pele de mama direita.

FIXAÇÃO: formol 10%

RELATÓRIO DE EXAME IMUNO-HISTOQUÍMICO:

Sistema de amplificação e leitura: estreptoavidina-biotina-peroxidase (LSAB+) DAB

Recuperação antigênica: calor úmido.

Controles positivos e negativos atestam a fidelidade das reações.

MICROSCOPIA:

ANTICORPOS	REAÇÃO	PADRÃO	SCORE
RE (1D5)	Negativa	_____	
RP (1 A 7)	Negativa	_____	
c-erbB-2 (CB11 e Herceptest)	Negativa	_____	
Ki67 (MIB-1)	Positiva	Núcleo	10-15%
Mamaglobina	Positiva		
Breast	Positiva		

CONCLUSÃO:

CARCINOMA MAMÁRIO INFILTRATIVO EM DERME (PELE DE MAMA DIREITA), NEGATIVO PARA RECEPTORES HORMONAIS E NEGATIVO PARA A PROTEÍNA c-erbB-2.

Exame Anatomopatológico

MACROSCOPIA

Recebido em formalina, fragmento alongado de pele que mede 3,5 x 0,7 x 0,7 cm. Exibe superfície epidérmica irregular. Todo o material foi submetido: 2F/1B.

MICROSCOPIA

Pele com epiderme mantida, nesta amostra, sem crescimento neoplásico intraepitelial (não há Paget), nem ulceração. Na derme e parte da tela subcutânea há maciça infiltração neoplásica por blocos e trabéculas de células epiteliais atípicas, com núcleos grau III e mitoses frequentes. Existem focos (escassos) de invasão angiolinfática e venular. O processo não atinge a epiderme e não há tecido mamário na amostra, para avaliar sua relação com a neoplasia.

DIAGNÓSTICO

Biópsia de lesão de pele (região mamária):

CARCINOMA SÓLIDO, POUCO DIFERENCIADO, DE ALTO GRAU, COM EXTENSA INVASÃO DERMO-HIPODÉRMICA. C44.5 M8230/3

PRESENÇA DE FOCOS RESTRITOS DE INVASÃO ANGIOLINFÁTICA E DE VÊNULAS.

AUSÊNCIA, NESTA AMOSTRA DE RELAÇÃO COM A EPIDERME E COM TECIDO MAMÁRIO (NÃO REPRESENTADO).

Cortesia do Dr. Carlos Sampaio. *Clínica AMO - Salvador - BA*

Revisão imunohistoquímica

MÉTODO

As ampliações foram obtidas pelo sistema de Streptavina-biotina-peroxidase, com recuperação antigênica através do método de digestão enzimática, calor úmido e utilização de controles para a reação. Tempo de fixação em formalina tamponada 24h.

PAINEL DE ANTICORPOS

Reatividade nas células neoplásicas:

Receptor de estrógeno (clone 1D5): Negativo

Receptor de progesterona (clone PgR 636): Negativo.

C-erb-B2 (HERCEPTEST): Negativo.

Receptor de andrógeno (clone AR441) **Positivo** forte em 100% das células.

Ki-67 (Clone MIB-1): **Positivo** em cerca de 60% das células.

CK-7 (clone OVTL12/30): **positivo**.

CK-20 (clone KS20.8): negativo.

Mamaglobina (clone 304 1 A5): negativa

BRST-2 (clone 23A3): **positivo**

CONCLUSÃO

Neoplasia em pele da região mamária:

CARCINOMA POUCO DIFERENCIADO DE ALTO GRAU, COM RECEPTORES DE ESTRÓGENO, PROGESTERONA E C-ERB-B2, NEGATIVOS [TRIPLO NEGATIVO].

RECEPTOR DE ANDRÓGENO POSITIVO FORTE EM 100% DAS CÉLULAS NEOPLÁSICAS

MAMAGLOBINA NEGATIVA, BRST-2 POSITIVO.

ALTA ATIVIDADE PROLIFERATIVA [KI-67 = 60%].

Nota: pela imuno-histoquímica a neoplasia poderia ser tanto de anexos sudoríparos da pele, como da mama. A integração com os dados da clínica poderá elucidar.

MDV 3100 (Enzalutamida)

- Inibe o crescimento estimulado por E2 de xenoenxertos de MCF7 RE+/RA+, tão efetivamente como o tamoxifeno.

Conclusões

Receptores de andrógeno no câncer de mama

- Talvez possa ser uma alvo em determinado subtipo de tumores triplo-negativo (Luminal com RA).
- O arrazoado teórico ainda não se traduziu em efeitos clínicos significativos.
- Ainda uma perspectiva a ser explorada.



Obrigado

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May 23-25, 2013

local/venue: Castro's Park Hotel

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