ISSN 0973-2063 (online) 0973-8894 (print)

Bioinformation 18(8): 697-702 (2022)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

BIOMEDICAL INFORMATICS

www.bioinformation.net

Volume 18(8)

Research Article

Received July 2, 2022; Revised August 31, 2022; Accepted August 31, 2022, Published August 31, 2022

DOI: 10.6026/97320630018697

Declaration on Publication Ethics:
The author's state that they adhere with COPE guidelines on publishing ethics as described elsewhere at https://publicationethics.org/. The authors also undertake that they are not associated with any other third party (governmental or non-governmental agencies) linking with any form of unethical issues connecting to this publication. The authors also declare that they are not withholding any information that is misleading to the publisher in regard to this article.

Declaration on official E-mail:
The corresponding author declares that lifetime official e-mail from their institution is not available for all authors

Comments from readers:
Articles published in BIOINFORMATION are open for relevant post publication comments and criticisms, which will be published immediately linking to the original article without open access charges. Comments should be concise, coherent and critical in less than 1000 words.

Edited by P Kangueane

Citation: Rafeeq, Bioinformation 18(8): 697-702 (2022)

Molecular docking analysis of phytochemicals with estrogen receptor alpha

Misbahuddin M Rafeeq*

Department of Pharmacology, Faculty of Medicine, Rabigh, King Abdulaziz University, Jeddah - 21589, KSA; *Corresponding author

Institution URL:
https://www.kau.edu.sa/home_english.aspx

Author contacts:
Misbahuddin M Rafeeq - E- mail: marafeeq@kau.edu.sa, misbahuddinrafeeq@yahoo.com

Abstract:
Breast cancer (BC) is linked to estrogen receptor alpha (ER-α) positive. Tamoxifen and other estrogen selective modulators have proven to be beneficial in slowing the progression of ER-α BC. However, tamoxifen resistance emerges as a result of long-term treatment and cancer development. Therefore, it is of interest to document data on the molecular docking analysis of phytochemicals targeting with Estrogen Receptor-alpha. The screening of the phytochemicals from the ZINC database (a total of 87133 compounds) against ER-α protein was completed. We show that ZINC69481841 and ZINC95486083bind strongly to ER- with binding energies of 10.47 and 11.88 Kcal/mol, respectively, which were significantly greater than the control compound (−8.32Kcal/mol).ZINC69481841 and ZINC95486083 were found

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 18(8): 697-702 (2022)

to bind with the key residues (Leu387, Arg394, Glu353, and Thr347) of ER-α protein. Data shows that the lead compounds (ZINC69481841 and ZINC95486083) have an acceptable range of ADMET and drug-likeness properties for further consideration in drug discovery.

Keywords: Breast cancer, estrogen receptor, tamoxifen, phytochemicals

Background:
Cancer is defined as a persistent aberrant cell condition or a fatal disease characterized by immortality and uncontrolled cell proliferation. Cancer cells can be invasive, aggressive, and metastatic, spreading to several organs. Breast cancer (BC) is very heterogeneous in character and disrupts the function of normal mammary epithelial cells. BC is the most prevalent noncutaneous malignancy and the main cause of cancer-related mortality in women globally **[1]**. It affects more than one in every 10 women globally **[2]**. One of the primary causes of BC is excessive estrogen production. The estrogen receptor (ER) is a nuclear receptor that is efficiently activated by binding to 17β-estradiol legend and is also known as estrogen. ER-α and ER-β are naturally present in humans and have a role in the regulation of many physiological processes including cell growth and differentiation; among them, ER-α is mostly expressed in the mammary gland and uterus **[3]**. In women, ER exhibits an important role in BC apoptosis, inflammation, proliferation and differentiation. ER-α is widely known for its role in immune surveillance, apoptosis resistance, metastasis, and cell proliferation **[4,5]**. The overactivity of estrogen hormone may result in the multiplication of ER-α, which may contribute to the maintenance and growth of BC types. Nowadays, phytochemicals are being studied for their potential use in modern medicine and contribute vital role in the synthesis of a wide range of therapeutic agents **[6]**. Phytochemicals have been shown to have a variety of beneficial effects on human cancer models **[7-9]**. Computer-assisted drug design methods have greatly aided in the efficient processing of cheminformatics and bioinformatics information, therefore speeding early drug development efforts through rigorous molecular docking simulations **[10-15]**. Therefore, it is of interest to document data on the molecular docking analysis of phytochemicals targeting with Estrogen Receptor-alpha.

Methodology:
Protein preparation:
The 3D crystal structure of ER-α (PDB ID: 3ERT) was accessed from the protein data bank (https://www.rcsb.org/structure/3ert). As 3ERT is a homo2-mer structure, one chain was removed and a monomer was used for the docking analysis. The protein preparation was done with the help of Discovery Studio's protein preparation tools.

Library preparation and virtual screening:
Phytochemicals from a commercially available ZINC database (natural product + in vitro) (https://zinc.docking.org/substances/subsets/natural-products+in-vitro/) were used (a total of 87133 compounds) for virtual screening in this study using the PyRx 0.8 program. PyRx was employed to prepare the whole ligands before molecular docking to get various binding conformations with the least binding energy (BE).

Molecular docking:
Docking tools like AutoDock and others have made it feasible to quickly screen ligand molecules using posture prediction and ranked list outputs **[16,17]**. Molecular docking of lead compounds were performed using AutoDock 4.2.Grid points were set as 40 × 40 × 40 Å with the spacing of 0.375 Å, and X, Y, and Z values were kept as 27.432, −2.033, and 26.269, respectively. Other parameters in the docking procedure were set as default. For each docking system, 100 independent docking runs were performed. The best postures of each lead compound were chosen based on the lowest BE once the docking calculations were completed.

Pharmacokinetics and toxicity estimation:
Swiss ADME (http://www.swissadme.ch/) **[18]** and pkCSM (http://biosig.unimelb.edu.au/pkcsm/) **[19]** web tools were utilized to predict the physicochemical characteristics, pharmacokinetics, drug-likeness and toxicity properties of the ZINC69481841 and ZINC95486083.

Results and discussion:
BC is one of the most common types of cancer in women. Notably, ER-α positivity accounts for 70% of all BC diagnoses, makes it a key therapeutic target. Prospective therapeutic compounds that modulate ER-α are now being explored for the prevention and treatment of a wide range of pathological disorders including the BC **[3]**. This study screened a library of phytochemicals from the ZINC database against ER-α protein. Among them, lead compounds ZINC69481841 and ZINC95486083 were found to strongly bind with ER-α. **Figure 1** depicts the two-dimensional structures of lead compounds.

ZINC69481841 was observed to interact with Met343, Thr347, Leu349, Ala350, Glu353, Trp383, Leu384, Leu387, Met388, Leu391, Arg394, Phe404, Met421, Ile424, Leu428, and Leu525 residues of ER-α **(Figure 2)**; while Met343, Thr347, Leu346, Leu349, Ala350, Glu353, Trp383, Leu384, Leu387, Met388, Leu391, Arg394, Phe404, Glu419, Met421, Ile424, Leu428, Gly521, and Leu525residues were found to bind with ZINC95486083 **(Figure 3)**. Leu387, Arg394, Glu353 and Thr347 have been determined as active site residues of ER-α protein **[20]**. Interestingly, ZINC69481841 and ZINC95486083 were also found to bind with these ER-α protein residue.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 18(8): 697-702 (2022)

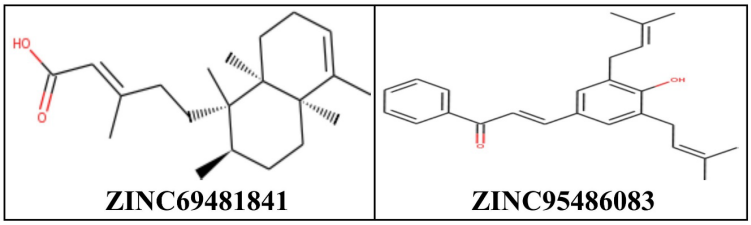

Figure 1: 2D structures of lead compounds.

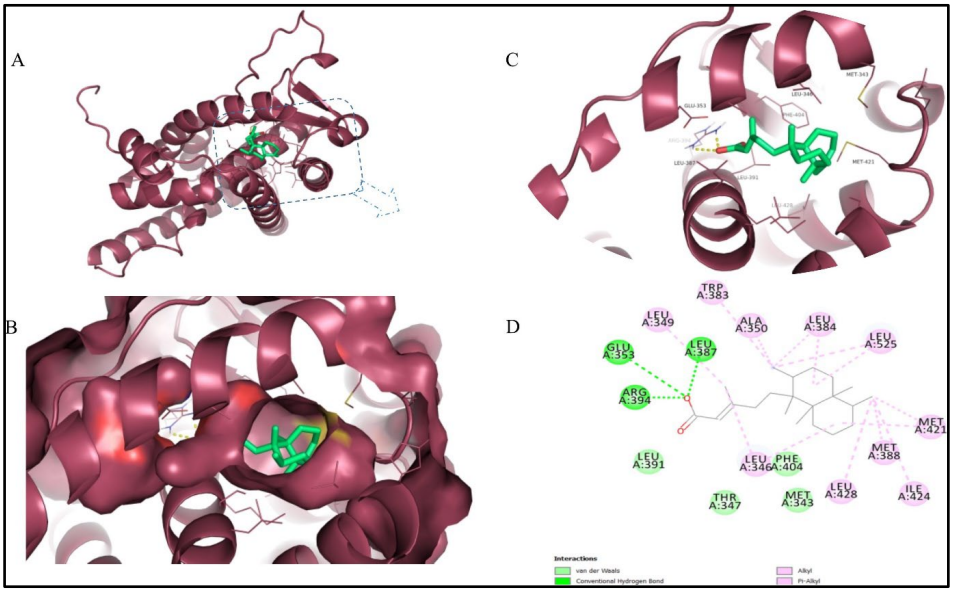

Figure 2: Molecular interaction of ZINC69481841 with at active site residues of ER-α. A) Overall demonstration of interaction of ZINC69481841with the ER-α, B) Visualization of ligand position in the binding pocket of ER-α, C) 3D visualization of interacting residues of ER-α with the ZINC69481841; D)2D visualization of interacting residues of ER-α with the ZINC69481841.

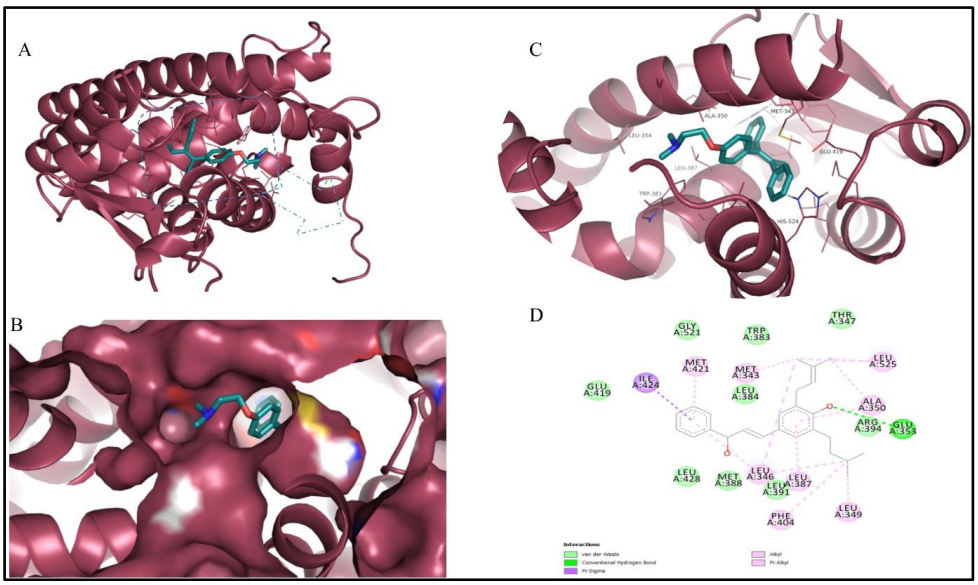

Figure 3: Molecular interaction of ZINC95486083 with at active site residues of ER-α. A) Overall demonstration of interaction of ZINC95486083 with the ER-α, B) Visualization of ligand position in the binding pocket of ER-α, C) 3D visualization of interacting residues of ER-α with the ZINC95486083; D) 2D visualization of interacting residues of ER-α with the ZINC95486083.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 18(8): 697-702 (2022)

Table 1: BE of lead compounds with ER-α protein.

S. No	Target	Compounds	Binding energy (Kcal/mol)	Inhibition constant (μM)
1.		ZINC69481841	−10.47	4.57
2.	ER-α	ZINC95486083	−11.88	3.21
3.		Tamoxifen	−8.32	18.56

The BE values for ZINC69481841 and ZINC95486083 with the ER-α were observed to be −10.47, and −11.88 kcal/mol, respectively, while the inhibition constant were 4.57 and 3.21 μM, respectively **(Table 1)**. Tamoxifen is an antiestrogen **[21]** that was used as a control compound in this study. BE of tamoxifen with ER-α was found to be −8.32 kcal/mol. The H-bond contributes to the stability of the "inhibitor-protein" complex and aid in determining the inhibitor potency to the target protein **[22]**. Glu353was the common H-bond interacting residues of ER-α with ZINC69481841 and ZINC95486083 **(Figure 2 & Figure 3)**. Further, in order to get a better picture of ER-binding residues with the lead compounds, we analyzed ER-binding residues with its co-crystallized ligand (PDB ID: 3ERT) **[23]**, which showed that Met343, Leu346, Thr347, Leu349, Ala350, Asp351, Glu353, Leu354, Trp383, Leu384, Leu387, Met388, Leu391, Arg394, Phe404, Met421, Ile424, Leu428, Gly521, His524, and Leu525 are important in interaction with its co-crystallized ligand **(Figure 4)**. Consistent with this, Met343, Thr347, Leu349, Ala350, Glu353, Trp383, Leu384, Leu387, Met388, Leu391, Arg394, Phe404, Met421, Ile424, Leu428, and Leu525were the common interacting ER-α residues with the ZINC69481841 and ZINC95486083 as well as the co-crystallized ligand **(Figure 2, Figure 3 & Figure 4)**.

Molecular docking has shown to be a useful method and has been utilized in numerous inhibitor discovery investigations to identify potential inhibition mechanisms and to illustrate the nature of molecular interactions between an active molecule and its target **[24-26]**. In docking studies, the strength of interaction between ligand-protein complex is assessed in terms of BE, and the lowest BE (more negative) is the result of the ligands efficient binding to the active site of the target protein **[27]**. Accordingly, lead compounds ZINC69481841 and ZINC95486083 showed strong binding (lower BE) with the ER-α than the reference compound (tamoxifen), suggesting that these compounds could be utilized as an inhibitor of ER-α to fight the BC. In silico pharmacokinetic and toxicity prediction analysis determines that lead compounds (ZINC69481841 and ZINC95486083) have an acceptable range of ADMET and drug-likeness properties **(Table 2 & 3)**.

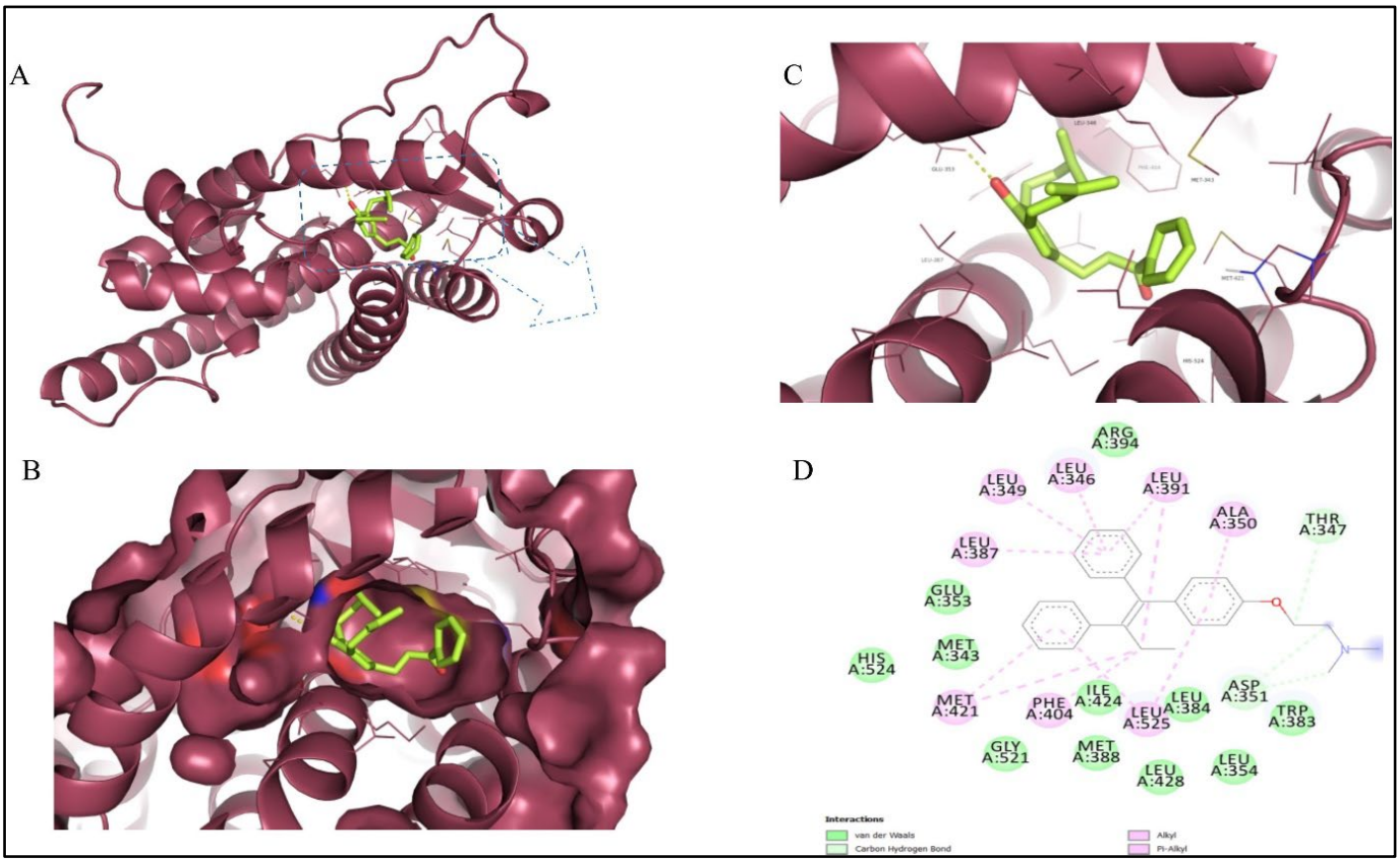

Figure 4: Molecular interaction of co-crystallized ligand with at active site residues of ER-α. A) Overall demonstration of interaction of co-crystallized ligand with the ER-α, B) Visualization of ligand position in the binding pocket of ER-α, C) 3D visualization of interacting residues of ER-α with the co-crystallized ligand, D) 2D visualization of interacting residues of ER-α with the co-crystallized ligand.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 18(8): 697-702 (2022)

Table 2: Drug likeness and physicochemical properties of ZINC69481841 and ZINC95486083

Property	Model Name		Predicted Value	
			ZINC69481841	ZINC95486083
Physicochemical Properties	MW		318.49	360.49
	TPSA		37.3	37.3
Lipophilicity	iLOGP		3.35	4.36
	XLOGP3		6.58	7.19
	WLOGP		5.99	6.2
	MLOGP		4.76	4.9
	Silicos-IT Log P		5.18	7
	Consensus Log P		5.17	5.93
Estimated SOLubility (ESOL)	Log S		-5.7	-6.47
	Solubility (mg/ml)		6.41E-04	1.22E-04
	Solubility (mol/l)		2.01E-06	3.38E-07
	Class		Moderately soluble	Poorly soluble
Pharmacokinetics	GI absorption		High	High
	BBB permeant		No	No
	Pgp substrate		No	Yes
	inhibitor	CYP1A2	No	Yes
		CYP2C19	Yes	Yes
		CYP2C9	Yes	No
		CYP2D6	No	No
		CYP3A4	No	Yes
	log Kp (cm/s)		-3.57	-3.39
Druglikeness	Lipinski	Number of violations	1	1
	Ghose		1	1
	Veber		0	0
	Egan		1	1

Table 3. Excretion and toxicity prediction of ZINC69481841 and ZINC95486083

Property	Model Name	Predicted Value		Unit
		ZINC69481841	ZINC95486083	
Excretion	Total Clearance	0.965	0.288	log ml/min/kg
	Renal OCT2 substrate	No	No	Yes/No
Toxicity	AMES toxicity	No	No	
	Max. tolerated dose (human)	0.411	0.661	log mg/kg/day
	hERG I inhibitor	No	No	Yes/No
	hERG II inhibitor			
	Oral Rat Acute Toxicity (LD50)	2.044	2.146	mol/kg
	Oral Rat Chronic Toxicity (LOAEL)	2.49	2.229	log mg/kg_bw/day
	Hepatotoxicity	Yes	No	Yes/No
	Skin sensitivity	No		
	T.Pyriformis toxicity	0.926	0.722	log ug/L
	Minnow toxicity	-1.14	-1.343	log mM

Conclusion:

We describe the molecular interaction of phytochemicals with the estrogen protein.ZINC69481841 and ZINC95486083 show strong binding with the ER protein as well as satisfied adequate ADME criteria for further consideration in drug discovery.

References:

[1] Yedjou CG *et al. Adv Exp Med Biol* 2019 **1152**:31. [PMID: 31456178]
[2] Torre LA *et al. CA Cancer J Clin* 2015 **65**:87. [PMID: 25651787]
[3] Paterni I *et al. Steroids* 2014 **90:**13. [PMID: 24971815]
[4] Bai Z & Gust R, *Arch Pharm (Weinheim)* 2009 **342**:133. [PMID: 19274700]
[5] Jiang X *et al. Endocrinology* 2006 **147**:1419. [PMID: 16306080]
[6] Hung WL *et al. J Food Drug Anal* 2017 **25**:71. [PMID: 28911545]
[7] De Amicis F *et al. Mol Cancer* 2015 **14**:130. [PMID: 26148846]
[8] Jiang J *et al. Mol Med Rep* 2016 **13**:4745. [PMID: 27082231]
[9] Musa MA *et al. Curr Med Chem* 2008 **15**:2664. [PMID: 18991629]
[10] Laskar YB *et al. J Biomol Struct Dyn* 2021. [PMID: 34854367]
[11] Hossain A, *Curr Comput Aided Drug Des* 2021 **17**:797. [PMID: 32748755]
[12] Spiriti J *et al. PLoS One* 2019 14:e0215694. [PMID: 31013302]
[13] Gonzalez TL *et al. Comput Toxicol* 2019 **10:**1. [PMID: 30740556]
[14] Muchtaridi M *et al. Pharmaceuticals (Basel)* 2017 **10:**81. [PMID: 29035298]
[15] Ahmed MF *et al. Acta Pol Pharm* 2016 **73:**115. [PMID: 27008806]
[16] Ferreira LG *et al. Molecules* 2015 **20**:13384. [PMID: 26205061]
[17] Trott O& Olson AJ. *J Comput Chem* 2010 **31**:455. [PMID: 19499576]
[18] Daina A *et al. Sci Rep* 2017 **7**:42717. [PMID: 28256516]

[19] Pires DE *et al. J Med Chem* 2015 **58**:4066. [PMID: 25860834]
[20] Sahayarayan JJ *et al. Saudi J Biol Sci* 2021 **28**:400. [PMID: 33424323]
[21] Binkhorst L *et al. Clin Pharmacol Ther* 2012 **92:**431. [PMID: 22910442]
[22] Shaikh S *et al.CNS Neurol Disord Drug Targets* 2016 **15**:1216. [PMID: 27697060]
[23] Shiau AK *et al. Cell* 1998 **95**:927. [PMID: 9875847]
[24] Ahirwar R *et al. Sci Rep* 2016 **6:**21285. [PMID: 26899418]
[25] Lu Q *et al. Ecotoxicol Environ Saf* 2014 **101:**83. [PMID:24507131]
[26] Akahori Y *et al. SAR QSAR Environ Res* 2005 **16:**323. [PMID:16234174]
[27] Shaikh S *et al. CNS Neurol Disord Drug Targets* 2014 **13**:1258.[PMID:25230222]