Errenina-angiotentsina sistema eta minbizia: hipertentsioaren aurkako farmakoak minbiziaren tratamendurako?

[1,2]Maider Beitia San Vicente, [2]Peio Errarte Yarza, [1,2]Itxaro Perez Urzelai, [2]Lorena Blanco Criado, [2]Usue Ariz López de Castro, [2]Ainhoa Fernández Atutxa, [3]Jose Ignacio López Fernández de Villaverde, [2]Begoña Sanz Echevarria, [1,2]Gorka Larrinaga Enbeita.

[1]Erizaintza I Saila, Erizaintza Unibertsitate Eskola (UPV/EHU).
[2]Fisiologia Saila, Medikuntza eta Odontologia Fakultatea (UPV/EHU).
[3]Anatomia Patologia Zerbitzua, Gurutzetako Unibertsitate Ospitalea.

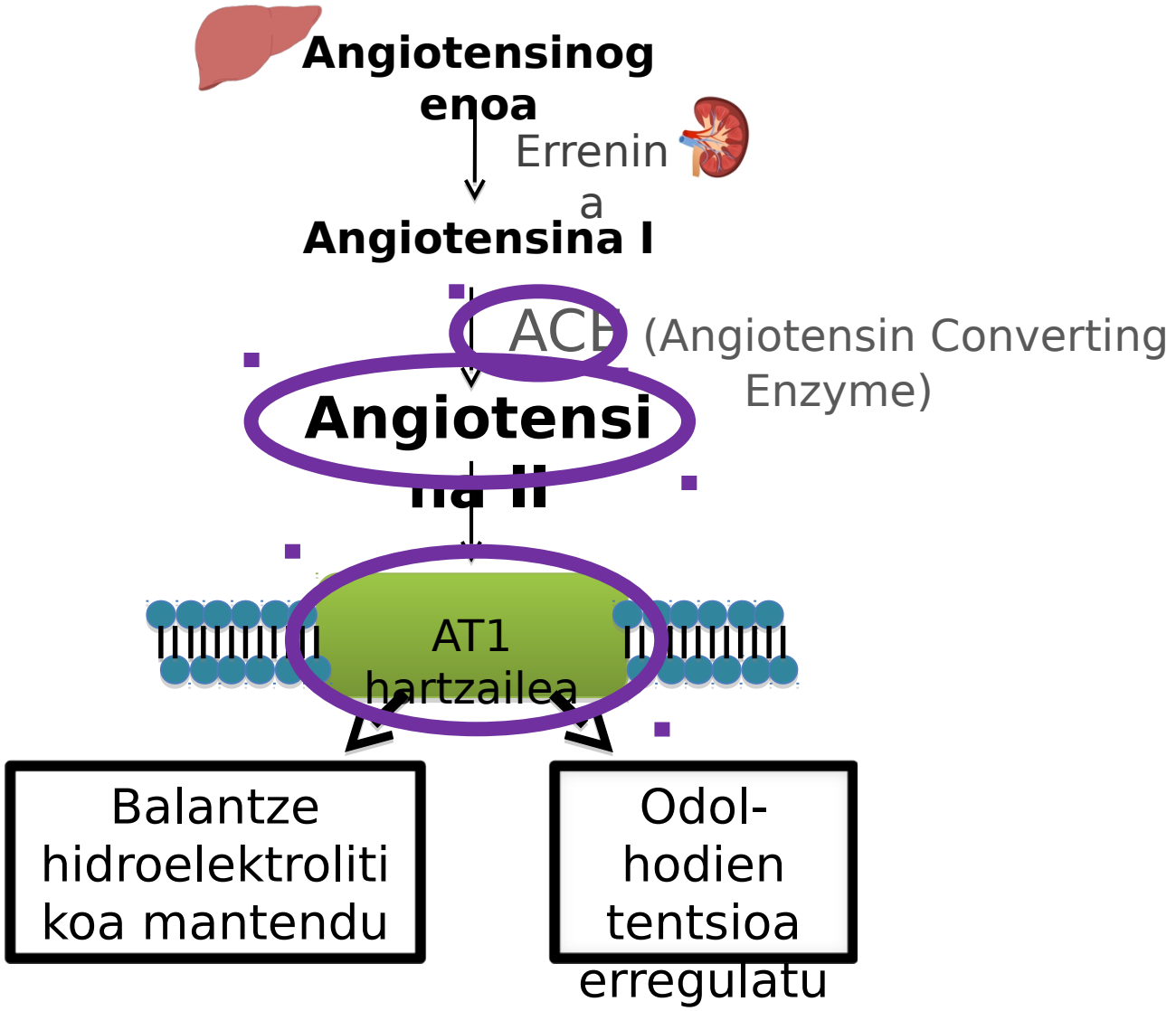
1- Errenina Angiotentsina Sistema (RAS)

1.-RAS-ren ikuspuntu klasikoa

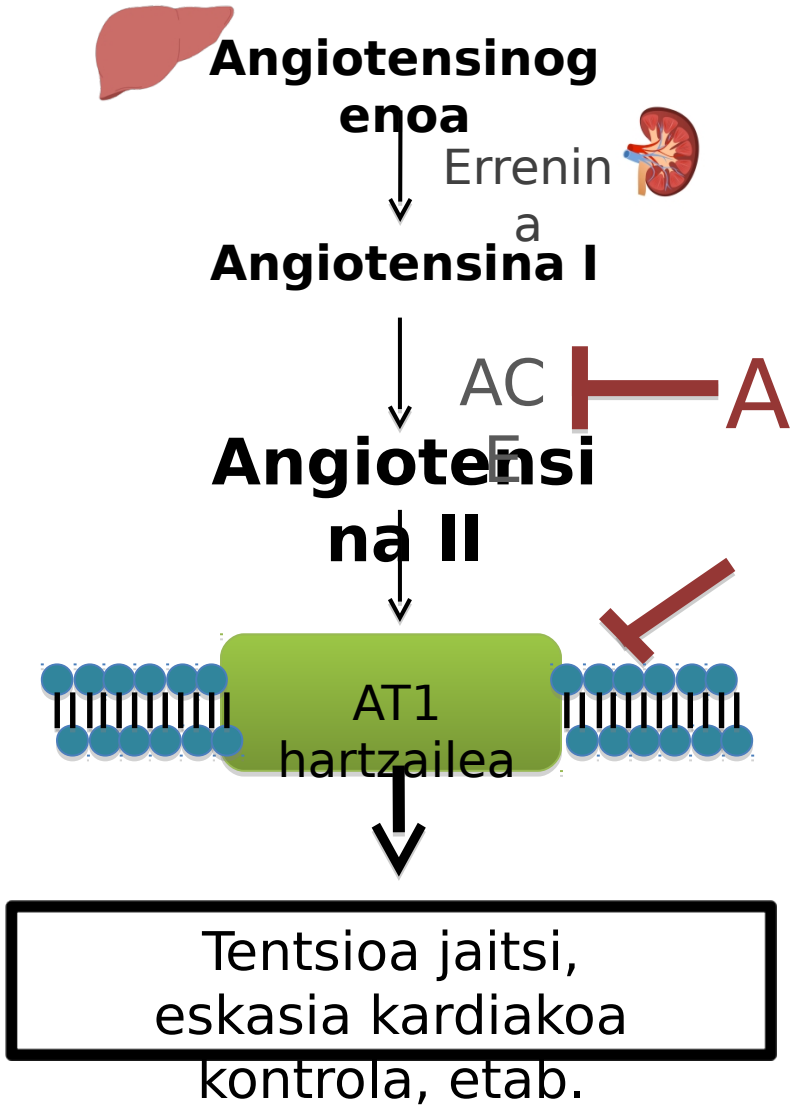
2.-Osagai berrien aurkikuntza

3.-RAS lokalak

1.-RAS-ren ikuspuntu klasikoa:
Sistema endokrino zirkulatzailea



1.-RAS-ren ikuspuntu klasikoa:
Sistema endokrino zirkulatzailea

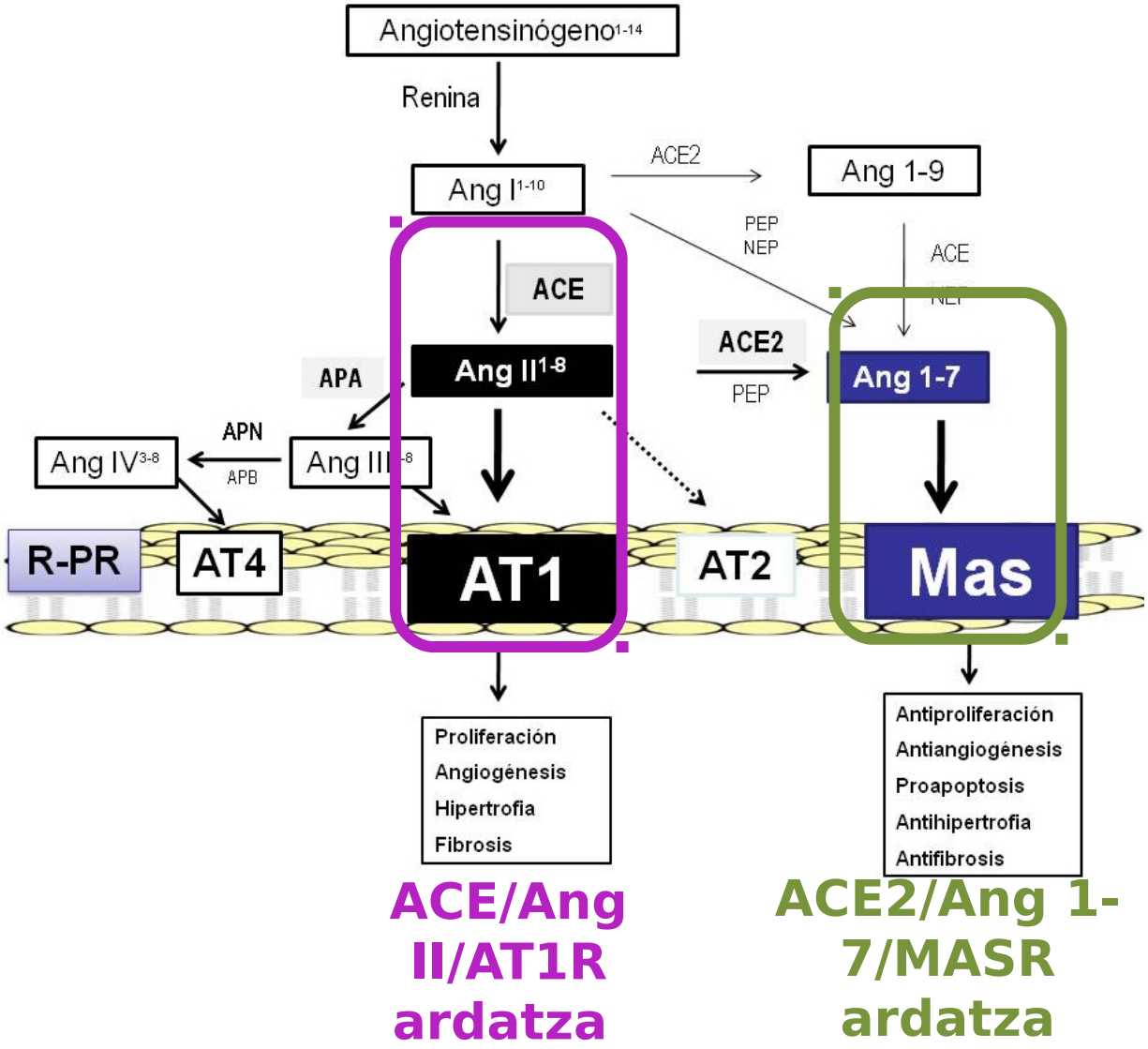


Bihotzeko gaixotasunen tratamendurako farmakoak

ACEI (- pril)

ARB (- sartan)

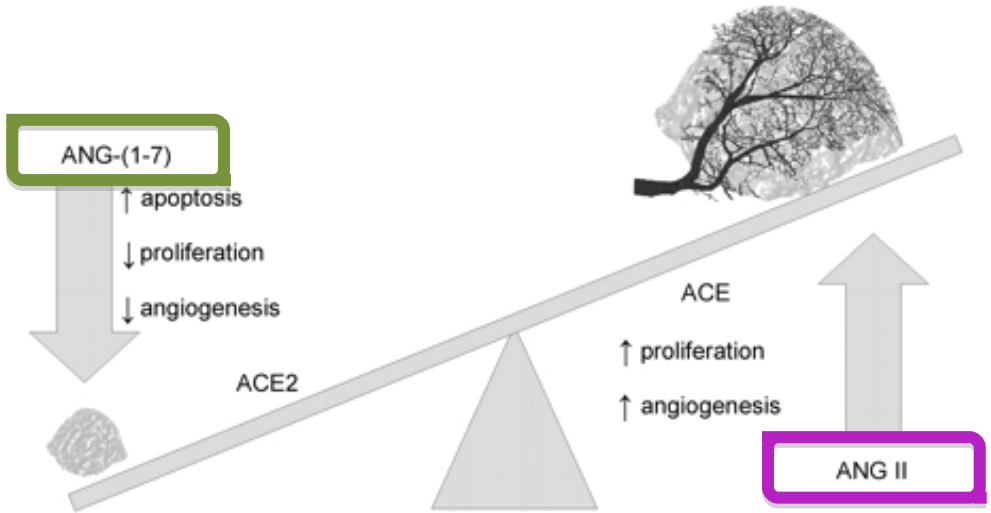
2.-RAS-ren ikuspuntu berria: Osagai berrien aurkikuntza



2.-RAS-ren ikuspuntu berria:

RAS lokalak

- ✓ **Organo bakar batean** osagai guztiak daude.
- ✓ **Funtzio berriak**: hazkuntza zelularra, diferentziazioa, inflamazioa etab.
- ✓ Sistema zirkulatzailearekiko **modu independientean erregulatzen** dira.



2- RAS-ren eragina prozesu tumoraletan

-Oinarrizko ikerketak

-Ikerketa kliniko eta epidemiologikoak

OINARRIZKO IKERKETAK

1. RAS-ren osagaien adierazpena tumore ezberdinetan asaldatuta dago.

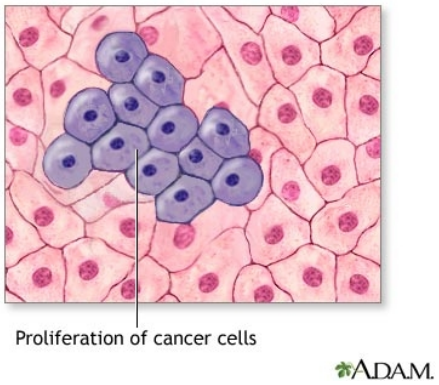
Table 1. Expression of RAS components in cancer tissues or cell lines[a]

Tissue	Cell line	ACE	AngII	AT1R	AT2R	Refs
Glioblastoma		+		+	+	[2][b,c]
	Astrocytoma			+	+	[3][b]
	Rat Glioma (C6)			+	+	[3,37][b]
Breast hyperplasia				↑	↑	[4,5][c]
Ductal *in situ* carcinoma				↑	↑	[4,5][c]
Invasive carcinoma				↓	↑	[4,5][c]
	Breast primary culture			↑		[51][b]
	Breast cells MCF-7			+	±	[50][b]
Ovarian carcinoma				↑		[8][c]
	Ovarian cells SKOV-3			+		[8][c]
Skin carcinoma				↑	−	[6][c]
Keratoacanthoma				+	−	[6][c]
Cervix carcinoma				↑		[7][c]
Prostate (BPH)		↑	↑	↓	−	[10–12][b,c]
Prostate carcinoma				↑		[9][b]
Pancreatic cells	Pacan-2, PANC-1, Mia-Paca			↑		[49][b,c]
Gastric cancer		+				[27][c]

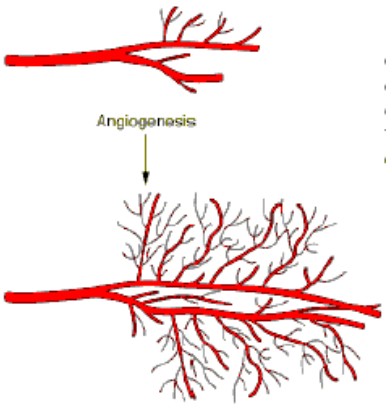
Deshayes et al, Trends in Endocrinology and Metabolism, 2010.

OINARRIZKO IKERKETAK

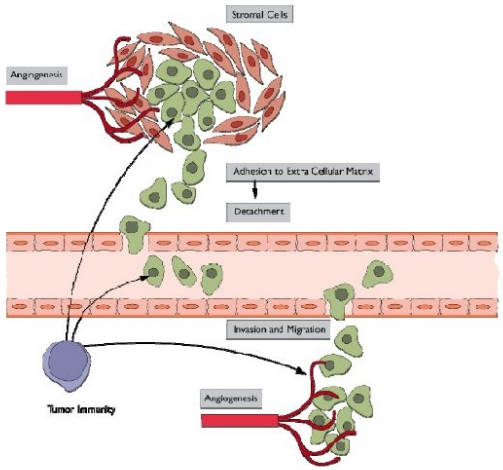
2. RAS-k hazkuntza, angiogenesia eta inbasioan parte hartzen du.



Hazkuntza



Angiogenesia

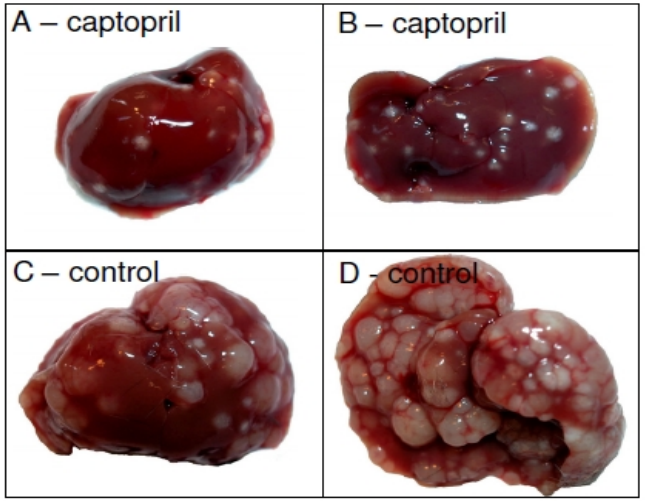


Inbasioa

OINARRIZKO IKERKETAK

3. –pril eta -sartan-ek animali eta kultibo zelularretan prozesu hauek inhibitzen dituzte.

Cell line/model	Agent	Tumour volume	Metastases
Lewis lung carcinoma 3LL	Captopril	Decreased	Decreased
Rat fibrosarcoma	Captropril	Decreased	N/A
Renal carcinoma SN12K-1	Captopril	Decreased	N/A
Lewis lung carcinoma 3LL	Captoril (alone and combined with batimastat)	Decreased	Decreased
Murine hepatocellular carcinoma	Captopril, perindopril and temocapril	Decreased	N/A
Lung metastases of renal carcinoma	Candesartan	Decreased	Decreased
Ovarian carcinoma SKOV-3	Candesartan	Decreased	N/A
Bladder cancer KU-19-19	Candesartan	Decreased	N/A
Mouse colorectal cancer liver metastases	Captopril	Decreased	Decreased
MKN-28 human gastric cancer mouse xenograft	Candesartan	Decreased	N/A



Anger et al, 2009.

Neo et al, BMC Cancer,2010.

IKERKETA KLINIKO ETA EPIDEMIOLOGIKOAK

1. Antihipertentsiboekin tratatutako pazienteek minbiziaren inzidentzia baxuagoa eta pronostiko hobea aurkezten dute.

Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer?

THE LANCET • Vol 352 • July 18, 1998

Anthony F Lever, David J Hole, Charles R Gillis, Iain R McCallum, Gordon T McInnes, Pauline L MacKinnon, Peter A Meredith, Lilian S Murray, John L Reid, James W K Robertson

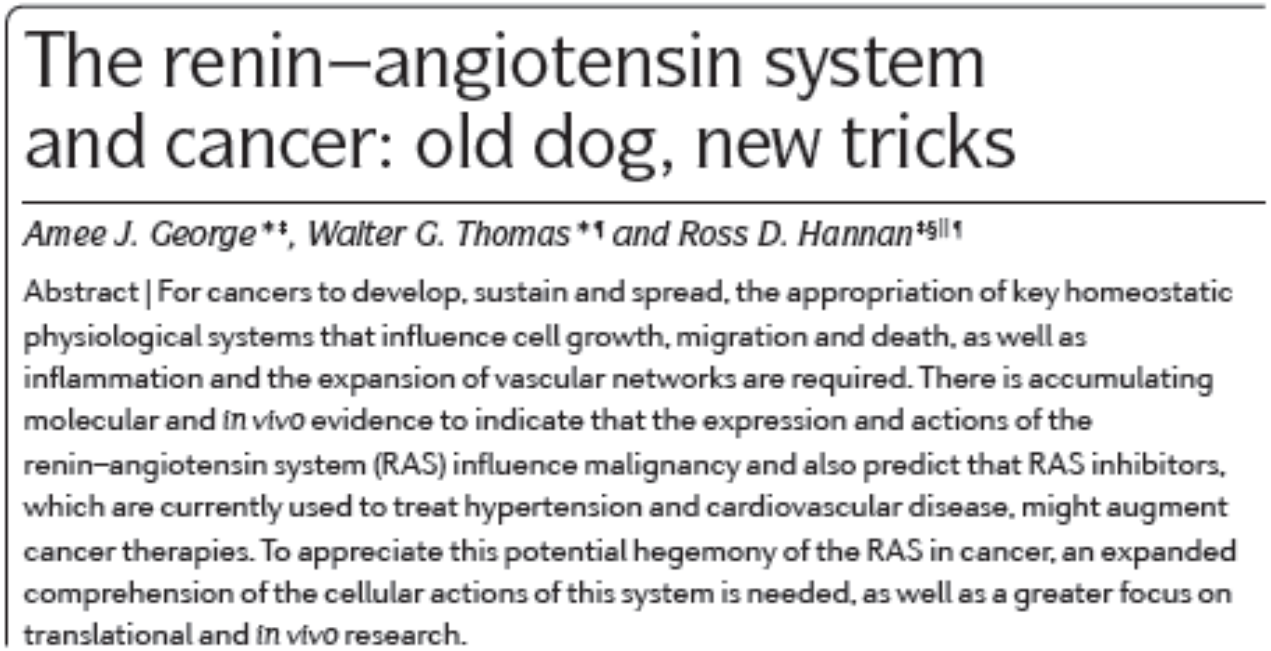
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in cancer progression and survival: a systematic review

Úna C. Mc Menamin · Liam J. Murray · Marie M. Cantwell · Carmel M. Hughes

Cancer Causes Control (2012) 23:221–230

IKERKETA KLINIKO ETA EPIDEMIOLOGIKOAK

2. Entsegu klinikoek –pril, -sartan eta ang 1-7 proposatzen dituzte minbiziaren tratamendu lagungarri moduan.



The renin–angiotensin system and cancer: old dog, new tricks

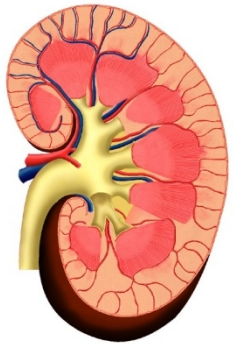
Amee J. George[*‡], *Walter G. Thomas*[*¶] *and Ross D. Hannan*[‡§‖¶]

Abstract | For cancers to develop, sustain and spread, the appropriation of key homeostatic physiological systems that influence cell growth, migration and death, as well as inflammation and the expansion of vascular networks are required. There is accumulating molecular and *in vivo* evidence to indicate that the expression and actions of the renin–angiotensin system (RAS) influence malignancy and also predict that RAS inhibitors, which are currently used to treat hypertension and cardiovascular disease, might augment cancer therapies. To appreciate this potential hegemony of the RAS in cancer, an expanded comprehension of the cellular actions of this system is needed, as well as a greater focus on translational and *in vivo* research.

Amee et al, Nature Reviews Cancer, 2010.

HELBURUA

RAS-aren eragina aztertu giltzurruneko eta heste lodiko minbizietan sistemaren osagaien analisi sakonaren bitartez.



MATERIALAK ETA METODOAK

DESKRIPTIBOA (ehuna)

1. OSAGAIEN ESPRESIOA

- ✓ WB eta IHQ (adierazpen proteikoa)
- ✓ qRT-PCR (adierazpen genikoa)

2. ENTZIMEN AKTIBITATEA

- ✓ Entsegu fluorimetrikoak

FUNTZIONALA (kultiboak)

1. PROLIFERAZIOA

- ✓ MTT entsegua

2. ANGIOGENESIA

3. MIGRAZIOA

4. INBASIOA

EMAITZAK:

I. Ikerketa deskriptiboak

- RAS-an parte hartzen duten **entzima** ezberdinen **aktibitateak eta adierazpenak**, minbizi mota ugarietan **desorekak** azaltzen ditu.
  - ✓ **Tumorea ≠ Inguruko ehun normala**
  - ✓ **Tumore azpimoten** arteko ezberdintasunak
  - ✓ Tumorearen **agresibitatearen** araberako ezberdintasunak

Diagnostiko eta pronostikorako MARKATZAILE BERRIAK?

EMAITZAK:

I. Ikerketa deskriptiboak

Regulatory Peptides 165 (2010) 218–223

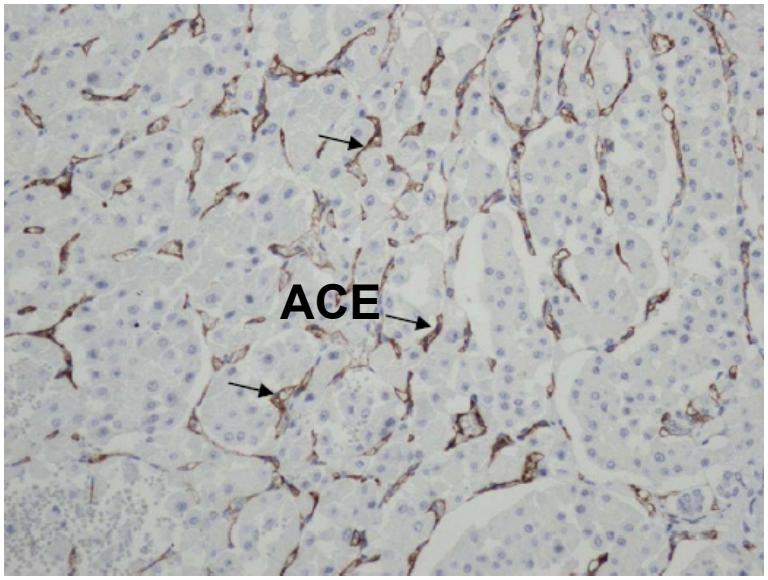
Contents lists available at ScienceDirect

Regulatory Peptides

journal homepage: www.elsevier.com/locate/regpep

Angiotensin-converting enzymes (ACE and ACE2) are downregulated in renal tumors

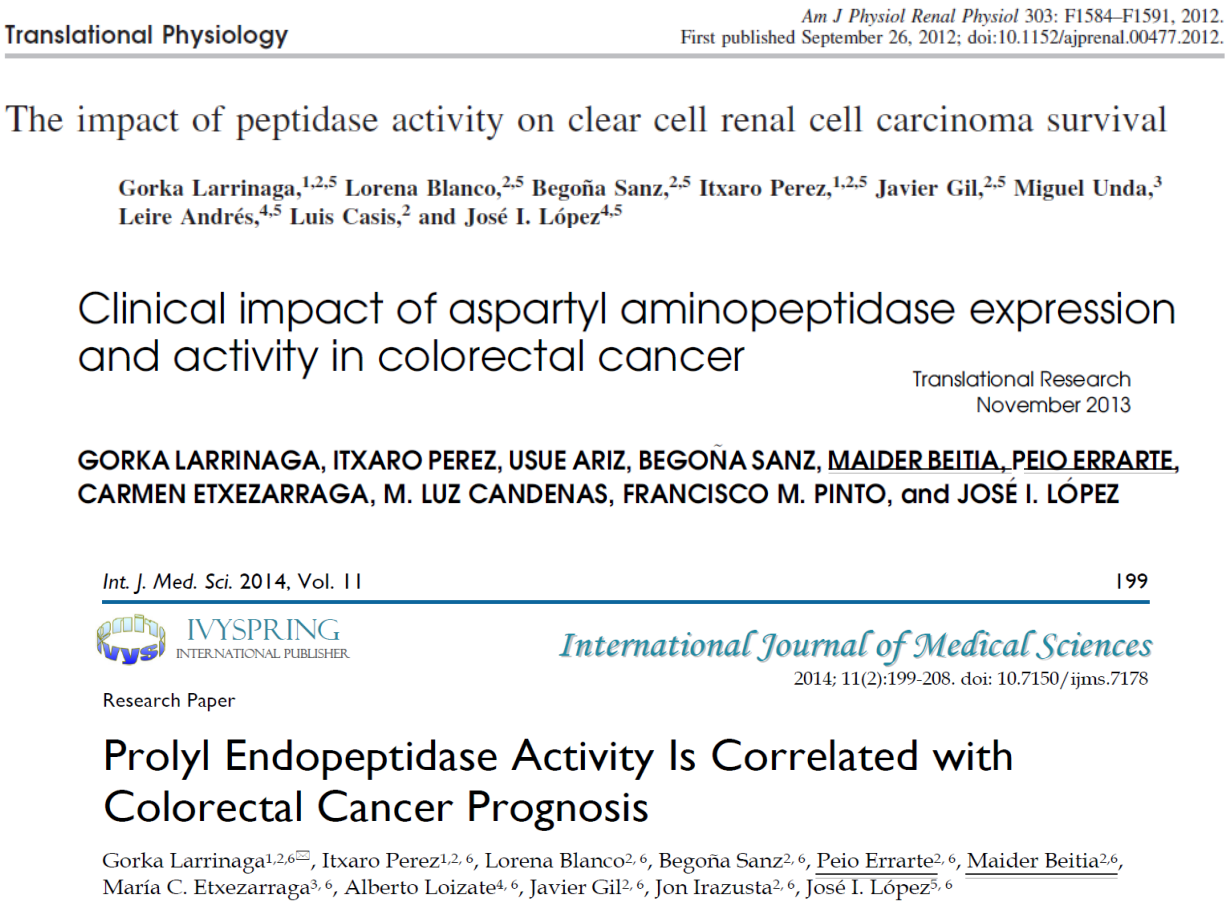
Gorka Larrinaga [a,*], Itxaro Pérez [a], Begoña Sanz [a], Lorena Blanco [a], Jose I. López [b], M. Luz Cándenas [c], Francisco M. Pinto [c], Javier Gil [a,d], Jon Irazusta [a,d], Adolfo Varona [a,1]



Zelula argien giltzurruneko kartzinoma (ugariena)

EMAITZAK:

I. Ikerketa deskriptiboak



Translational Physiology

Am J Physiol Renal Physiol 303: F1584–F1591, 2012.
First published September 26, 2012; doi:10.1152/ajprenal.00477.2012.

The impact of peptidase activity on clear cell renal cell carcinoma survival

Gorka Larrinaga,[1,2,5] Lorena Blanco,[2,5] Begoña Sanz,[2,5] Itxaro Perez,[1,2,5] Javier Gil,[2,5] Miguel Unda,[3] Leire Andrés,[4,5] Luis Casis,[2] and José I. López[4,5]

Clinical impact of aspartyl aminopeptidase expression and activity in colorectal cancer

Translational Research
November 2013

GORKA LARRINAGA, ITXARO PEREZ, USUE ARIZ, BEGOÑA SANZ, MAIDER BEITIA, PEIO ERRARTE, CARMEN ETXEZARRAGA, M. LUZ CANDENAS, FRANCISCO M. PINTO, and JOSÉ I. LÓPEZ

Int. J. Med. Sci. 2014, Vol. 11 199

IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2014; 11(2):199-208. doi: 10.7150/ijms.7178

Research Paper

Prolyl Endopeptidase Activity Is Correlated with Colorectal Cancer Prognosis

Gorka Larrinaga[1,2,6], Itxaro Perez[1,2,6], Lorena Blanco[2,6], Begoña Sanz[2,6], Peio Errarte[2,6], Maider Beitia[2,6], María C. Etxezarraga[3,6], Alberto Loizate[4,6], Javier Gil[2,6], Jon Irazusta[2,6], José I. López[5,6]

EMAITZAK:

I. Ikerketa deskriptiboak

Research Article

Altered Peptidase Activities in Thyroid Neoplasia and Hyperplasia

Hindawi Publishing Corporation
Disease Markers
Volume 35 (2013), Issue 6, Pages 825–832
http://dx.doi.org/10.1155/2013/970736

Gorka Larrinaga,[1,2,3] Lorena Blanco,[2,3] Peio Errarte,[2,3] Maider Beitia,[2,3] Begoña Sanz,[2,3] Itxaro Perez,[1,2,3] Amaia Irazusta,[1,3] Clara E. Sánchez,[1] Francisco Santaolalla,[4] Leire Andrés,[3,5] and José I. López[3,5]

INCREASED APN/CD13 AND ACID AMINOPEPTIDASE ACTIVITIES IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

HEAD & NECK—DOI 10.1002/hed October 2009

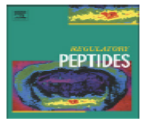
Itxaro Pérez, BSc,[1] Adolfo Varona, PhD,[1] Lorena Blanco, BSc,[1] Javier Gil, PhD,[1] Francisco Santaolalla, MD, PhD,[2,3] Aitor Zabala, MD, PhD,[2] Agustin Martínez Ibarguen, MD, PhD,[2,3] Jon Irazusta, PhD,[1] Gorka Larrinaga, MD, PhD[4]

Regulatory Peptides 163 (2010) 102–106

Contents lists available at ScienceDirect

Regulatory Peptides

journal homepage: www.elsevier.com/locate/regpep



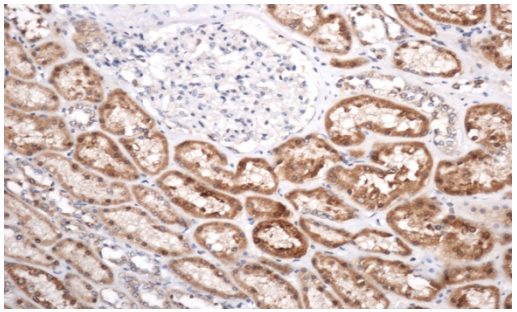
Increased prolyl endopeptidase activity in human neoplasia

Gorka Larrinaga [a,*], Itxaro Perez [a], Lorena Blanco [a], José I. López [b], Leire Andrés [b], Carmen Etxezarraga [c], Francisco Santaolalla [d,e], Aitor Zabala [e], Adolfo Varona [a,1], Jon Irazusta [a,f]

EMAITZAK:

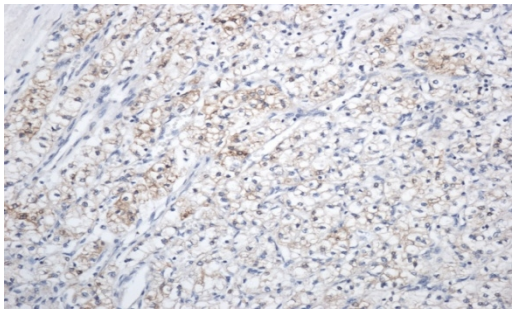
I. Ikerketa deskriptiboak

Ang 1-7-ren **MAS hartzailea**



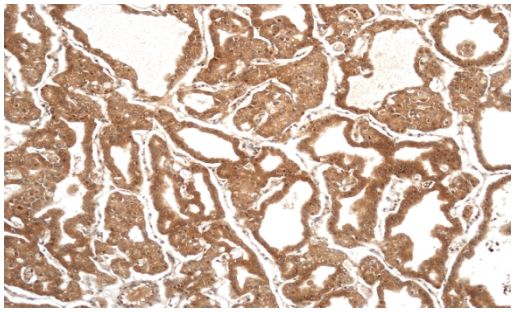
Giltzurrun normala

(+++)



Zelula argien giltzurruneko kartzinoma

(+)



Zelula kromofoboen giltzurruneko kartzinoma

(+++)

LXXIX Congreso Nacional de Urología. Tenerife 2 014

Ang II-ren **AT1 hartzailea**

Angiotensin-2 receptors (AT1-R and AT2-R), new prognostic factors for renal clear-cell carcinoma?

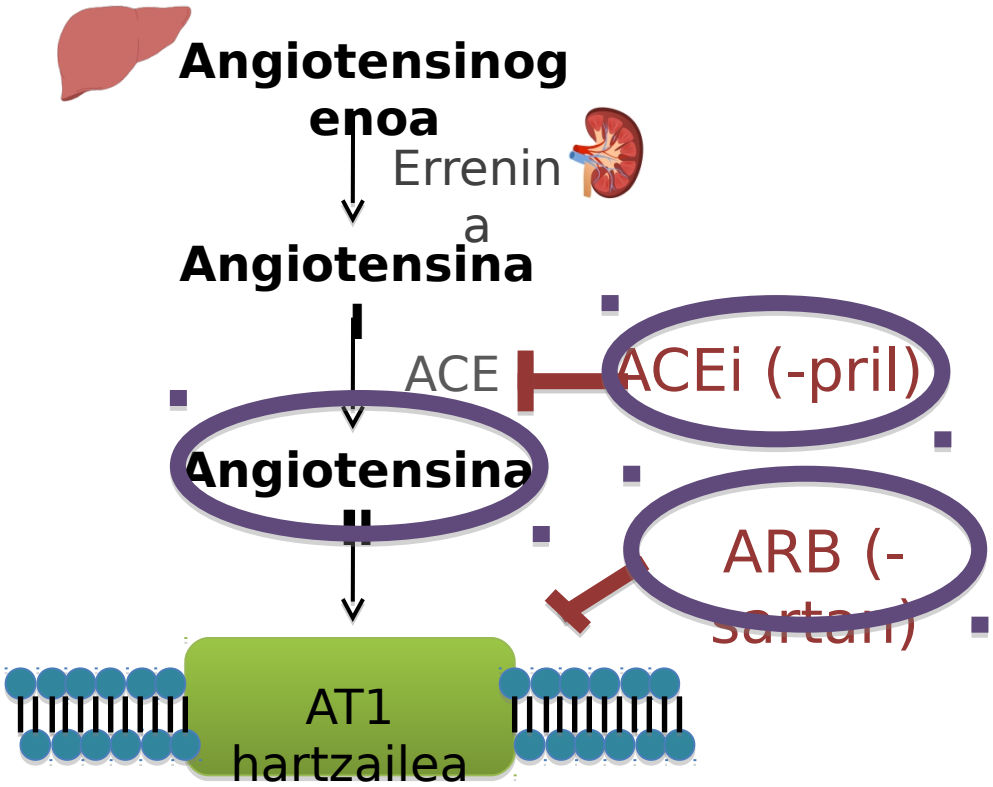
British Journal of Cancer (2010) 103, 1698–1705

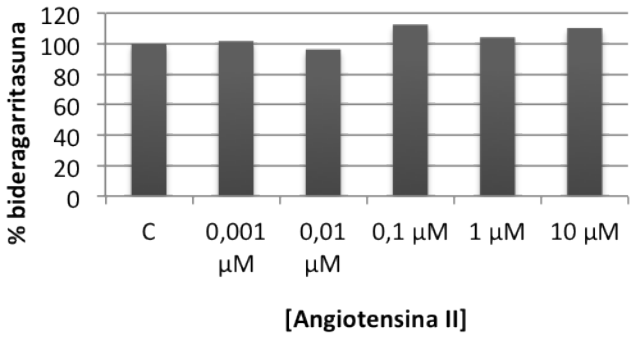
www.bjcancer.com

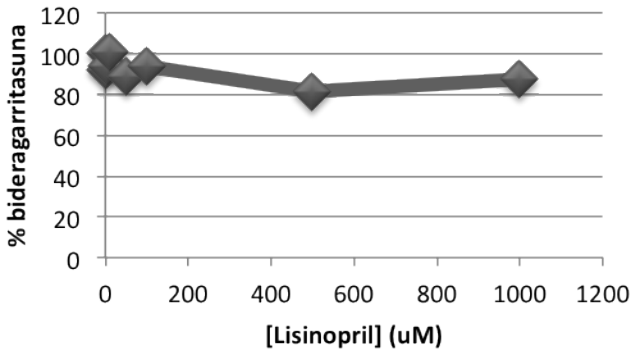
T Dolley-Hitze[1,2,6], F Jouan[1,6], B Martin[1], S Mottier[1], J Edeline[1], O Moranne[5], P Le Pogamp[2], M-A Belaud-Rotureau[1], J-J Patard[3], N Rioux-Leclercq[1,4] and C Vigneau[*,1,2]

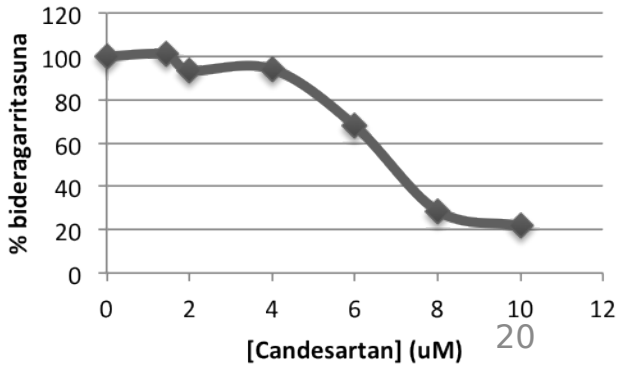
EMAITZAK

II. Ikerketa funtzionala: Kultibo Zelularrak



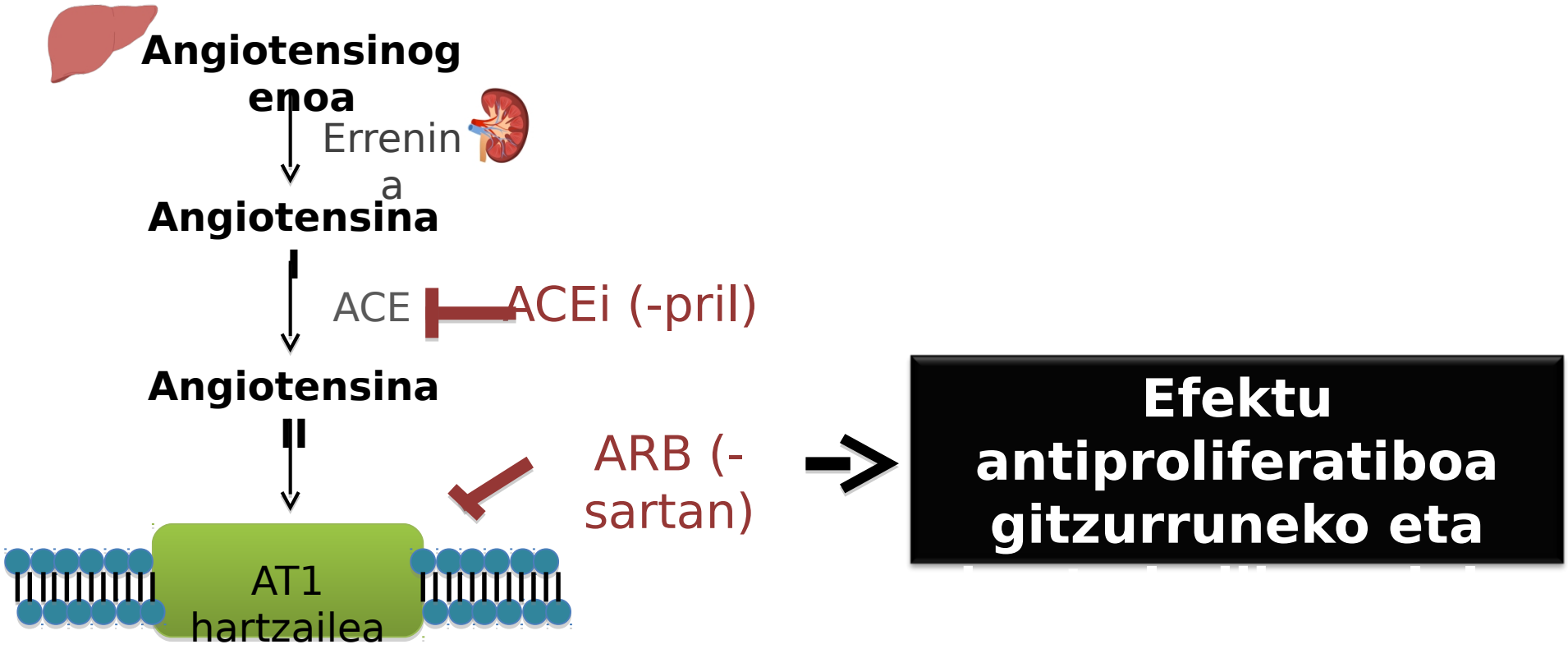






EMAITZAK

II. Ikerketa funtzionala: Kultibo Zelularrak



ONDORIOAK

Errenina-angiotentsina sistema eta minbizia: hipertentsioaren aurkako farmakoak minbiziaren tratamendurako?

Hipertentsioaren tratamendurako klasikoki erabilitako –*sartan*ek giltzurruneko minbizi zelulen proliferazioa murrizten dute, beraz, pentsa daiteke minbizia tratatzeko farmako lagungarri potentzialak izan daitezkeela.

Eskerrik asko!