Enfocaments de recerca clínica i traslacional en melanoma

(Clinical and translational research approaches in melanoma)

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Clinical and translational research approaches in melanoma

Grup de Patologia Oncològica del IRBLLEIDA (Institut de Recerca Biomédica de Lleida)

“Grup de Càncer del Laboratori de Recerca de l’Hospital Universitari Arnau de Vilanova”

Grup de Recerca de Catalunya (Modalitat B)
(2005 SGR 110, 2009 SGR 794)

Grupo regular de la Red Temática de Investigación Cooperativa en Cáncer (RTICC) de las RETICS (Redes Temáticas de Investigación Cooperativa Sanitaria)
(Ref: RD06/0020/1034)

Melanoma research 2003-10

1. Targeted therapies

2. Follow-up of patients with *Dysplastic Nevus Syndrome* employing SIAscopy

3. Analysis of the "Registro Nacional de Melanoma de la AEDV" (1997-2008)

4. Collaboration with the "Xarxa de centres de melanoma de Catalunya i Balears"

Melanoma- 1. Targeted therapies

1.1. Effect of several targeted therapies on *"in vitro"* growth of melanoma cell lines

- STI571 (Imatinib or Glivec®)
- Somatostatin analogues
- Proteasome inhibitors
  (monotherapy or combined therapies)
- Calcium channels inhibitors

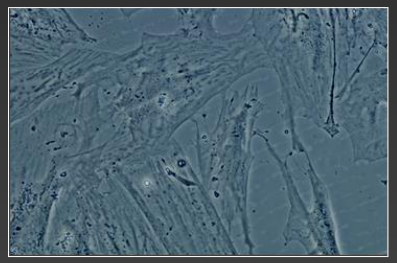
Research agreements: Novartis Farmacéutica SA 2003-05
Grant: FIS PI060832
Predoctoral fellowships: AECC and UdL
Other financial supports: GOTTA

Human cutaneous melanoma-derived cell lines

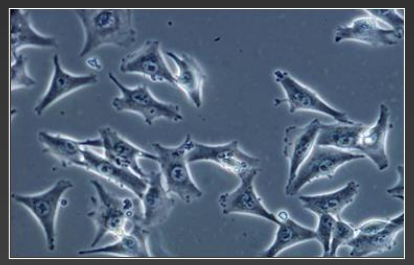
19 cell lines

4 - primary tumors
(Breslow 0,9-12mm)

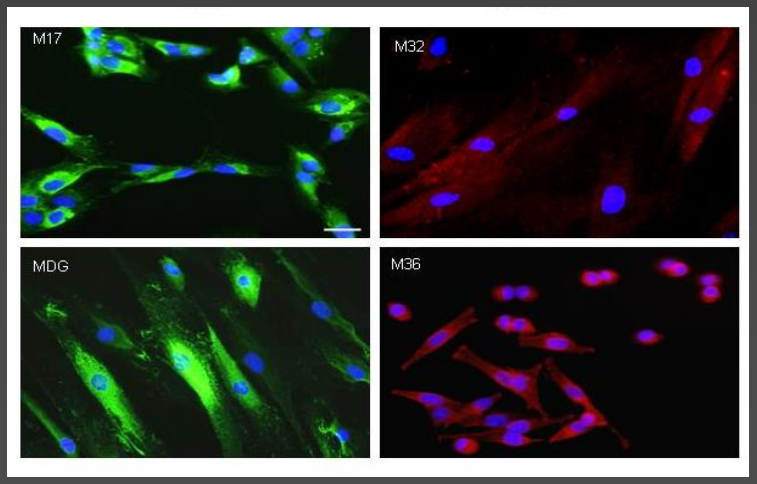
15 – metastatic tumors
12- cutaneous and SC
3 - visceral
1 bone
1 pleural
1 CSF



MDG



TPR-2



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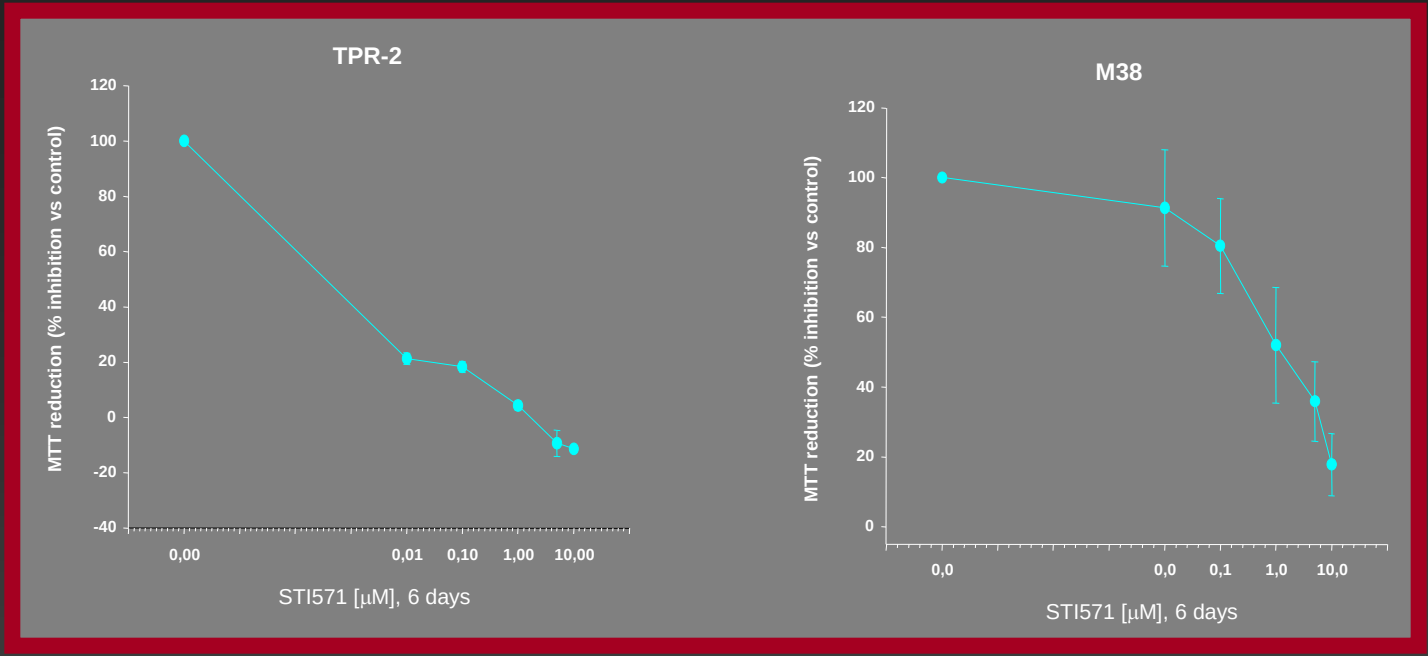
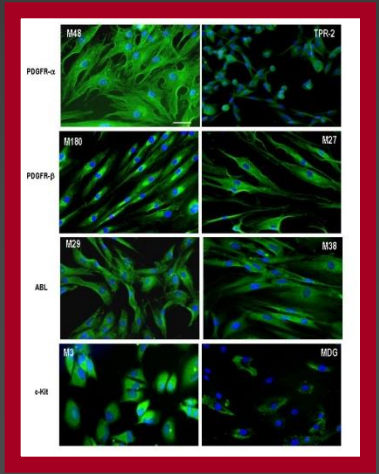
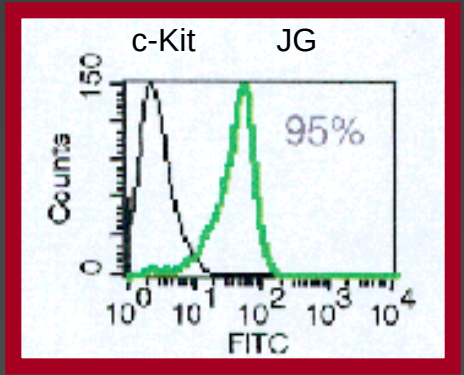
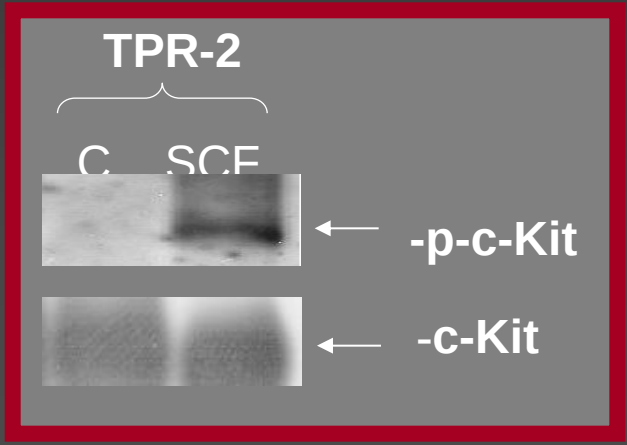
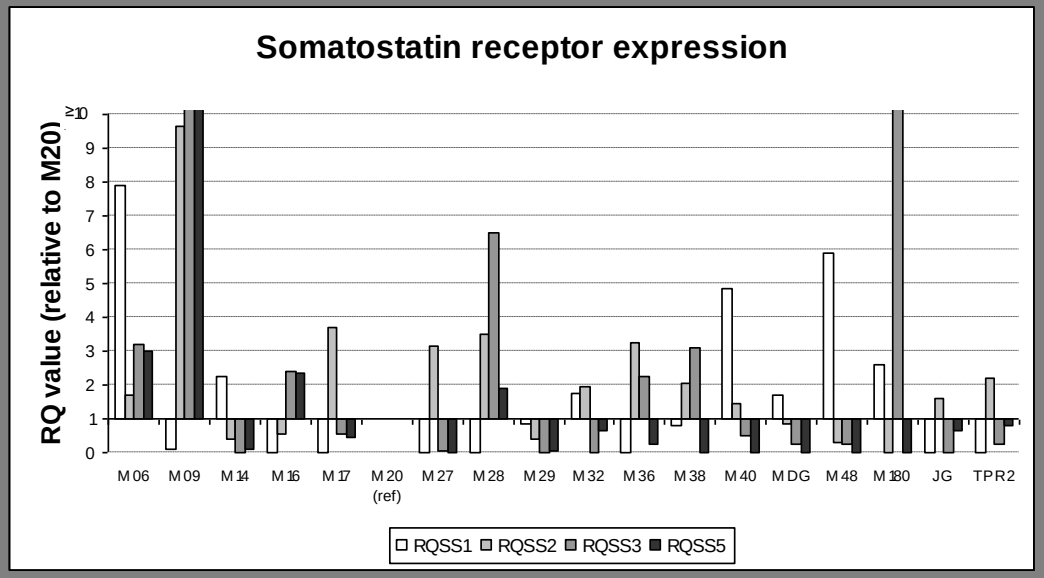


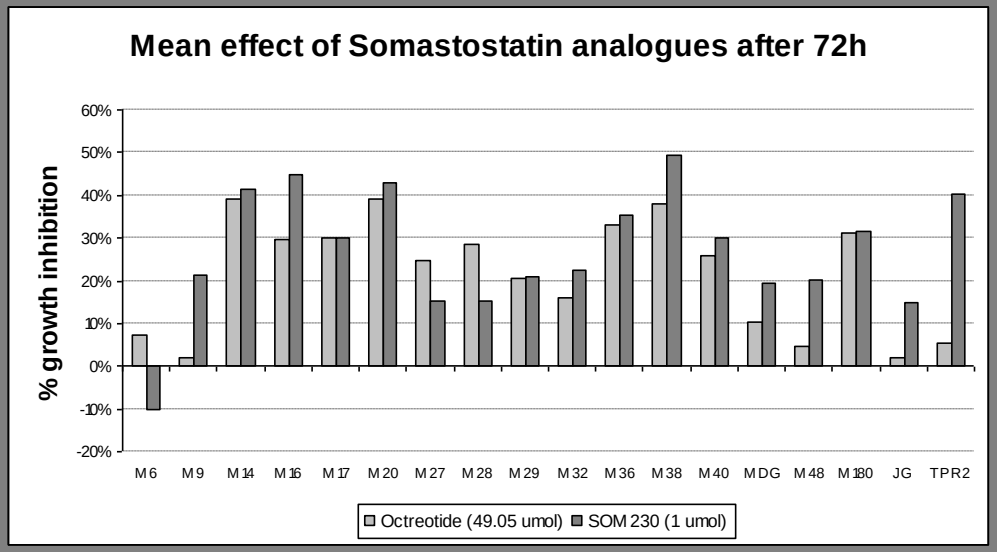






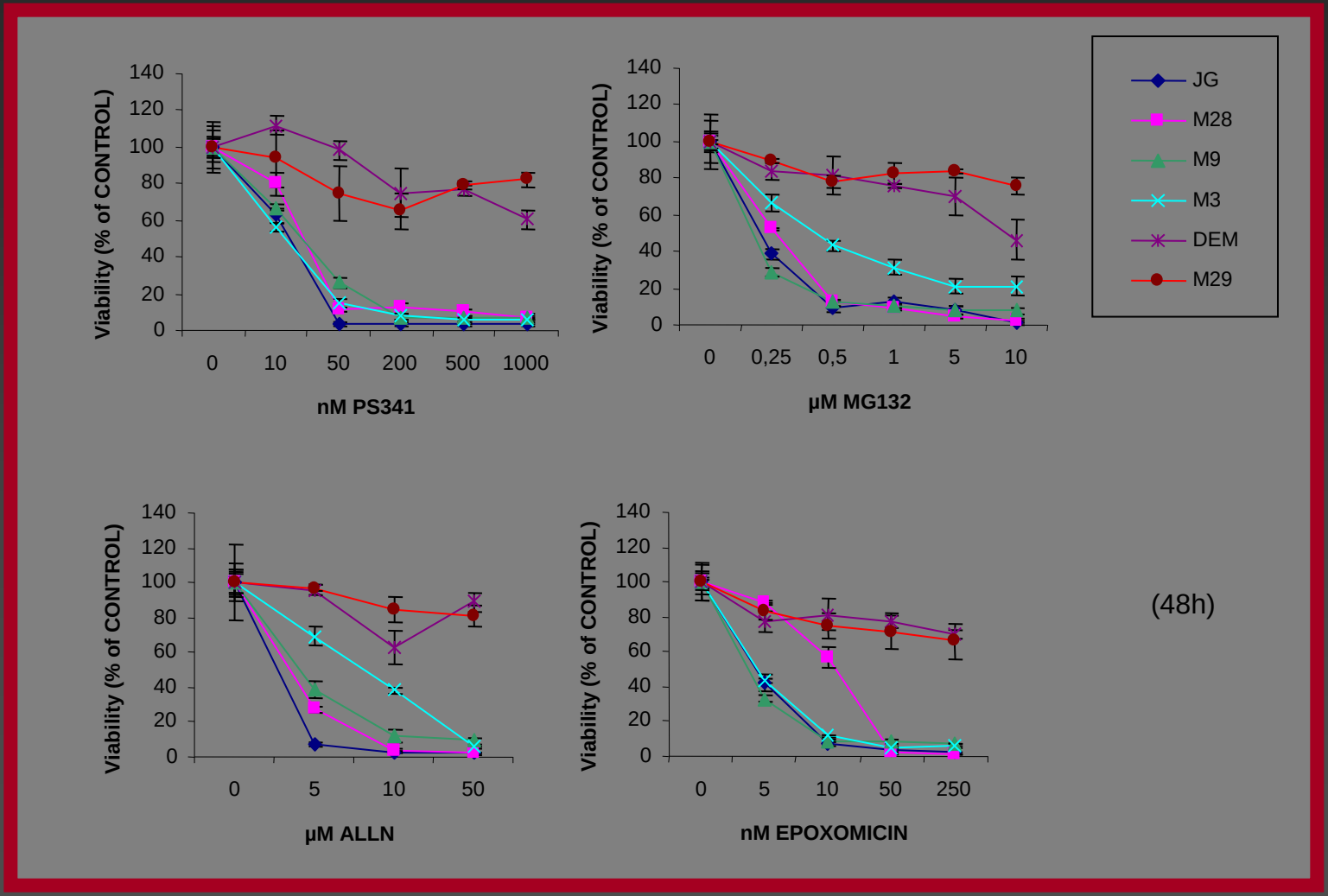
Mayorga ME et al. Antiproliferative effect of STI571 on cultured human cutaneous melanoma-derived cell lines. *Melanoma Research* 2006; 16: 127-135





Martinez M. Expression of somatostatin receptors in melanoma cell lines. Effect of the somatostatin analogues Octreotide and SOM-230 on their proliferation. *J Int Med Res* 2009; 37: 1813-1822

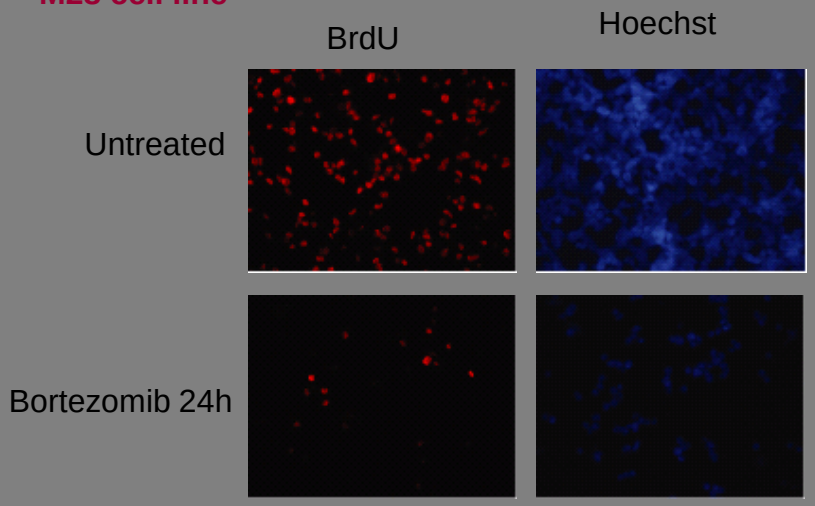
Proteasome inhibitors (Bortezomib, MG132, ALLN, Epoxomicin) induce a decrease in cell viability in a panel of melanoma cell lines

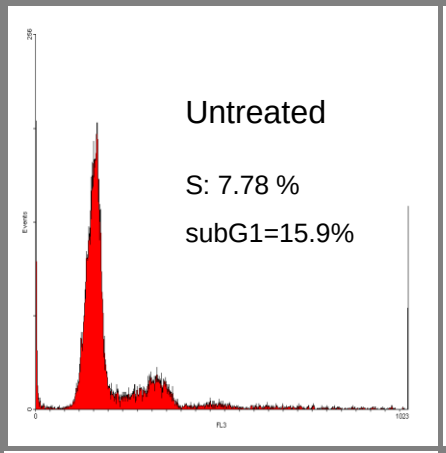


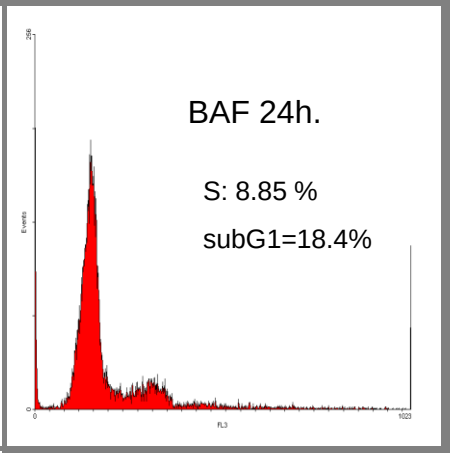
FIS PI060832 2007-2009

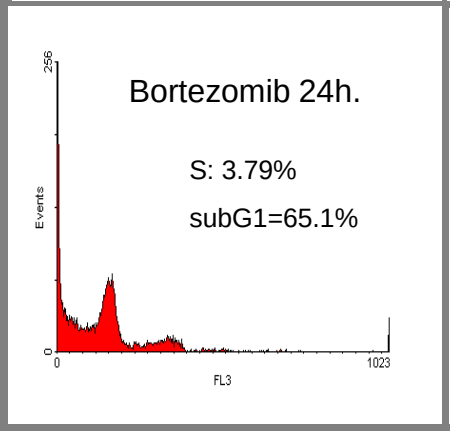
Proteasome inhibitors induce a reduction in cell proliferation rate and a cell cycle arrest

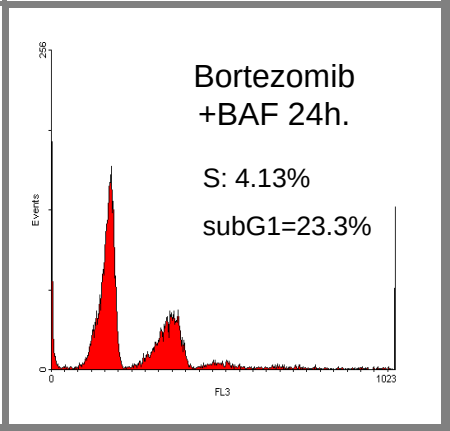
M28 cell line



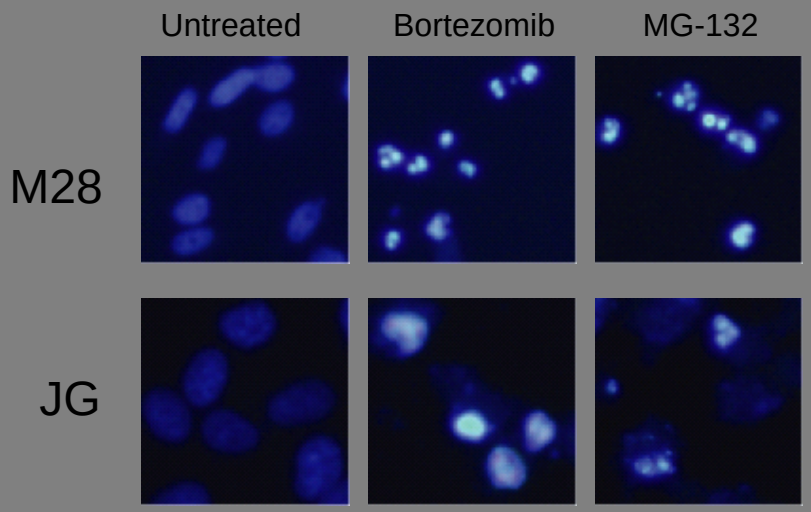


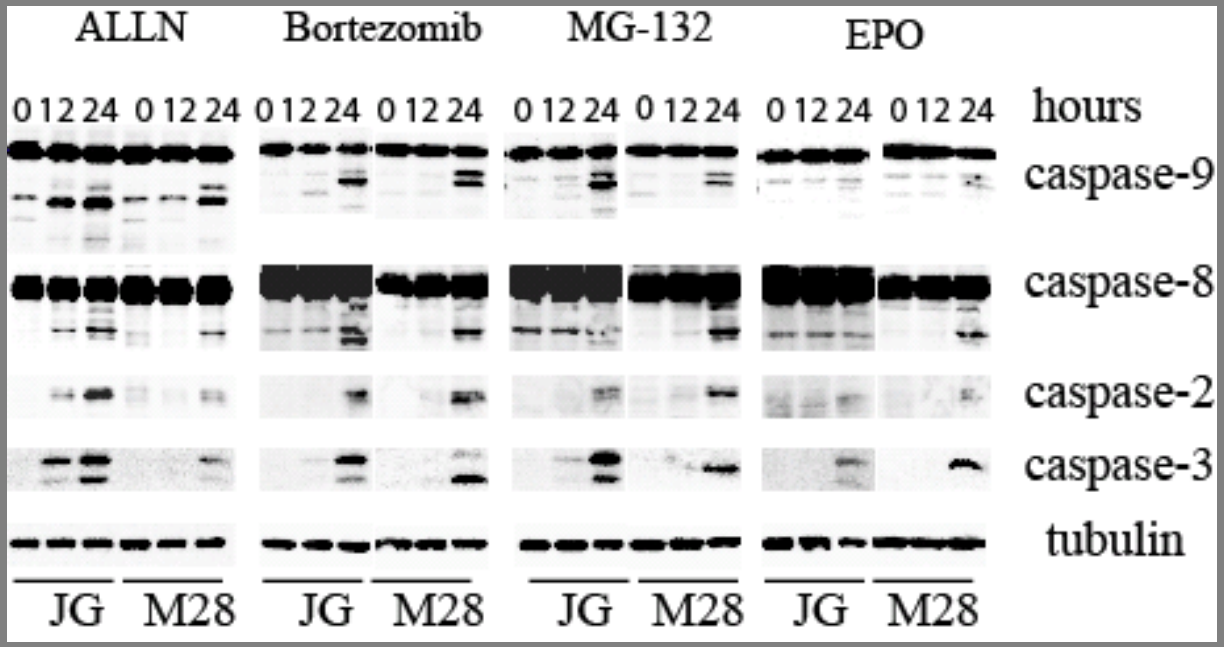




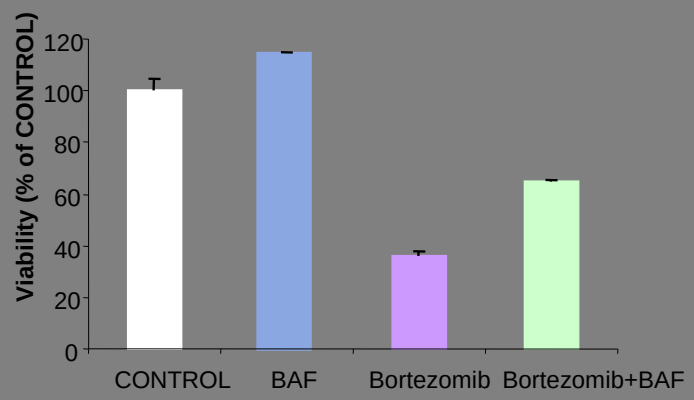


Proteasome inhibitors trigger apoptosis through caspase processing

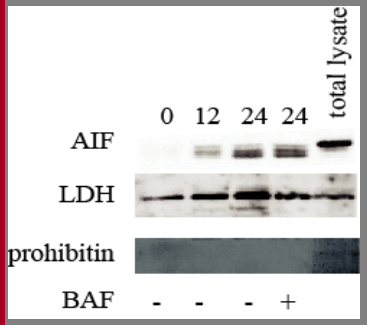


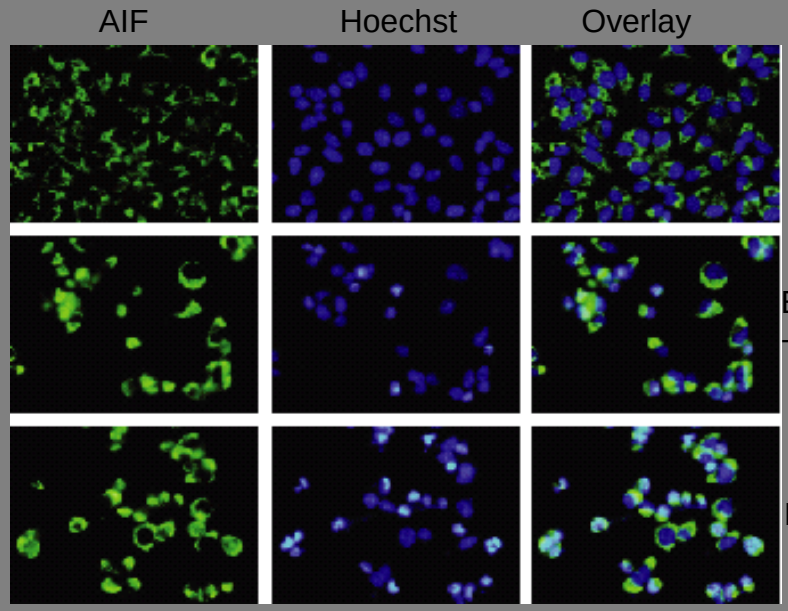


Proteasome inhibitors also induce caspase-independent cell death



Proteasome inhibition induces AIF translocation from mitochondria to the cytosol and nucleus via a caspase independent pathway





- **ME Mayorga et al. Antiproliferative effect of STI571 on cultured human cutaneous melanoma-derived cell lines. *Melanoma Research* 2006; 16: 127-135**

- **M Martinez et al. Expression of somatostatin receptors in melanoma cell lines. Effect of the somatostatin analogues Octreotide and SOM-230 on their proliferation. *J Int Med Res* 2009; 37: 1813-1822**

- **A Sorolla et al. Effect of proteasome inhibitors on proliferation and apoptosis of human cutaneous melanoma-derived cell lines. *Br J Dermatol* 2008; 158: 496-504**

- ME Mayorga et al. Antiproliferative effect of STI571 on cultured human cutaneous melanoma-derived cell lines. *Melanoma Research* 2006; 16: 127-135

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- A Sorolla et al. Effect of proteasome inhibitors on proliferation and apoptosis of human cutaneous melanoma-derived cell lines. *Br J Dermatol* 2008; 158: 496-504

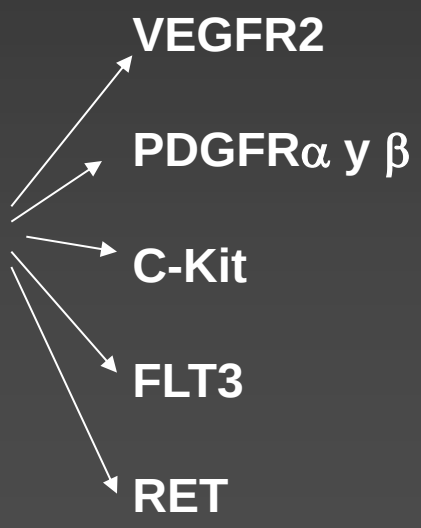
- E Ortega et al. Targeted therapies in gynecologic cancers and melanoma. *Semin Diagn Pathol* 2008; 25: 262-73

Combined therapy with proteasome inhibitors + sunitinib

Bortezomib (PS-341)

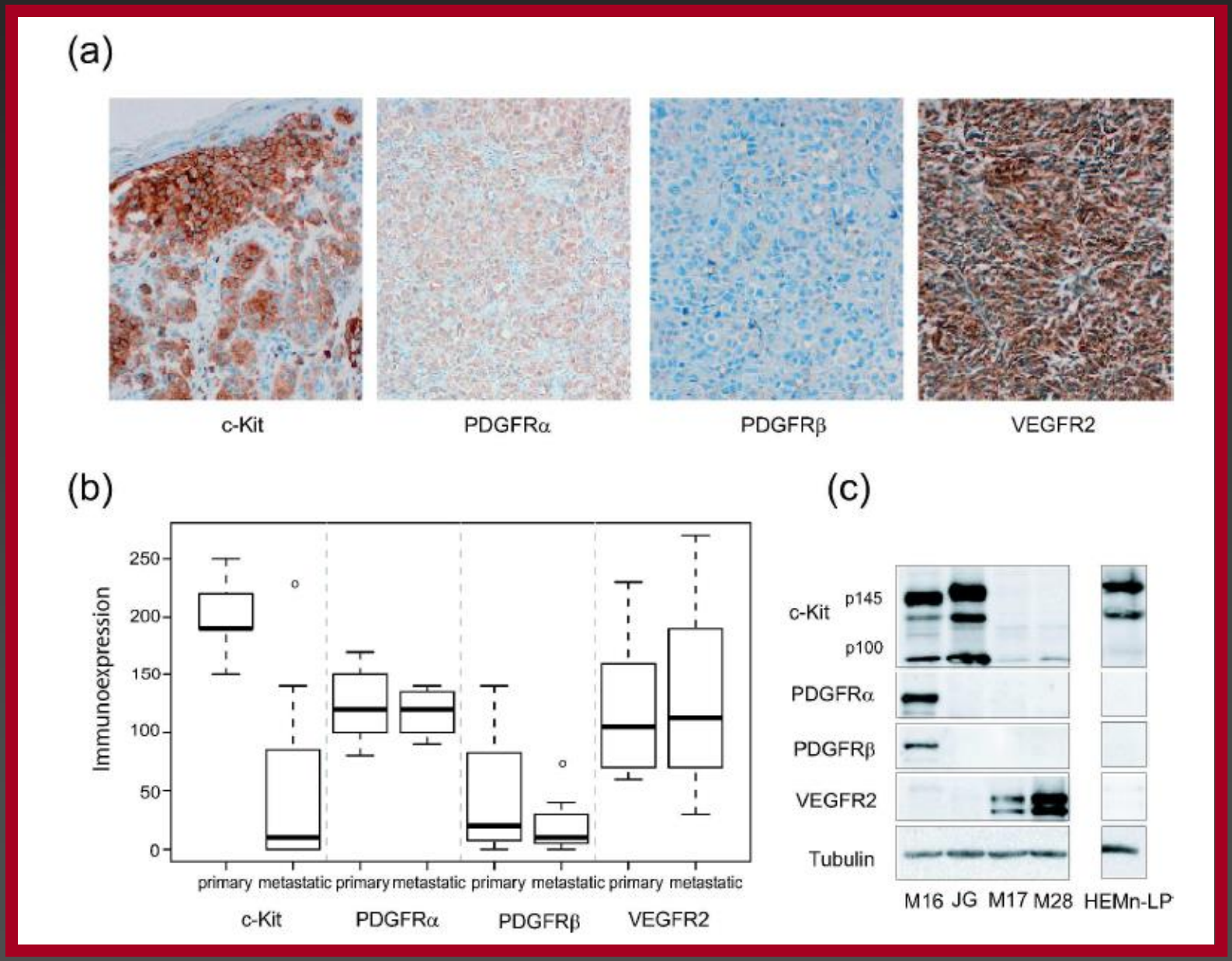
+

Sunitinib (SU11284)



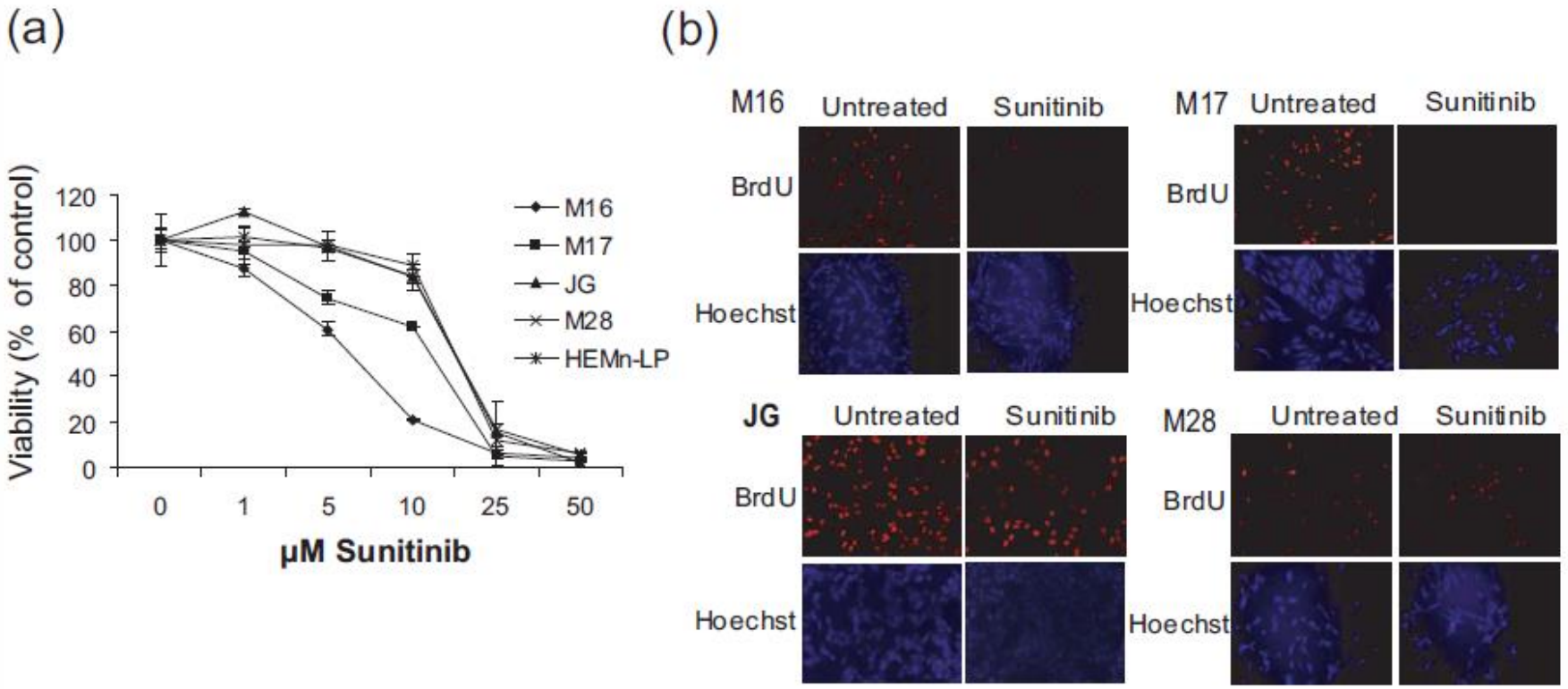
FIS PI060832 2007-2009

Expression of PDGFRα, PDGFRβ, VEGFR2 and c-KIT in a series primary and metastatic melanoma tumor biopsies (a,b) and four metastatic melanoma cell lines (c)

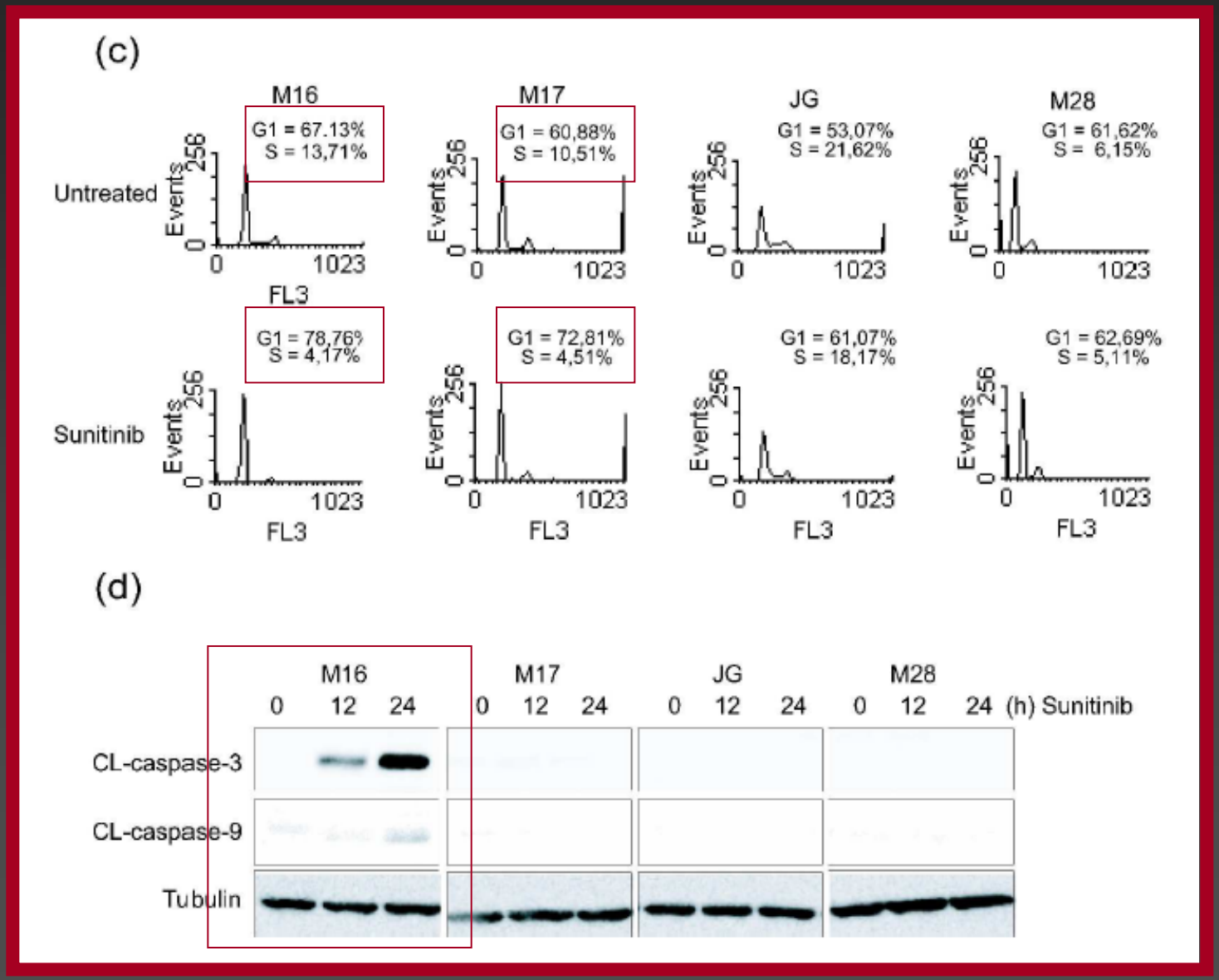


Sunitinib induces different grades of growth inhibition in melanoma cell lines

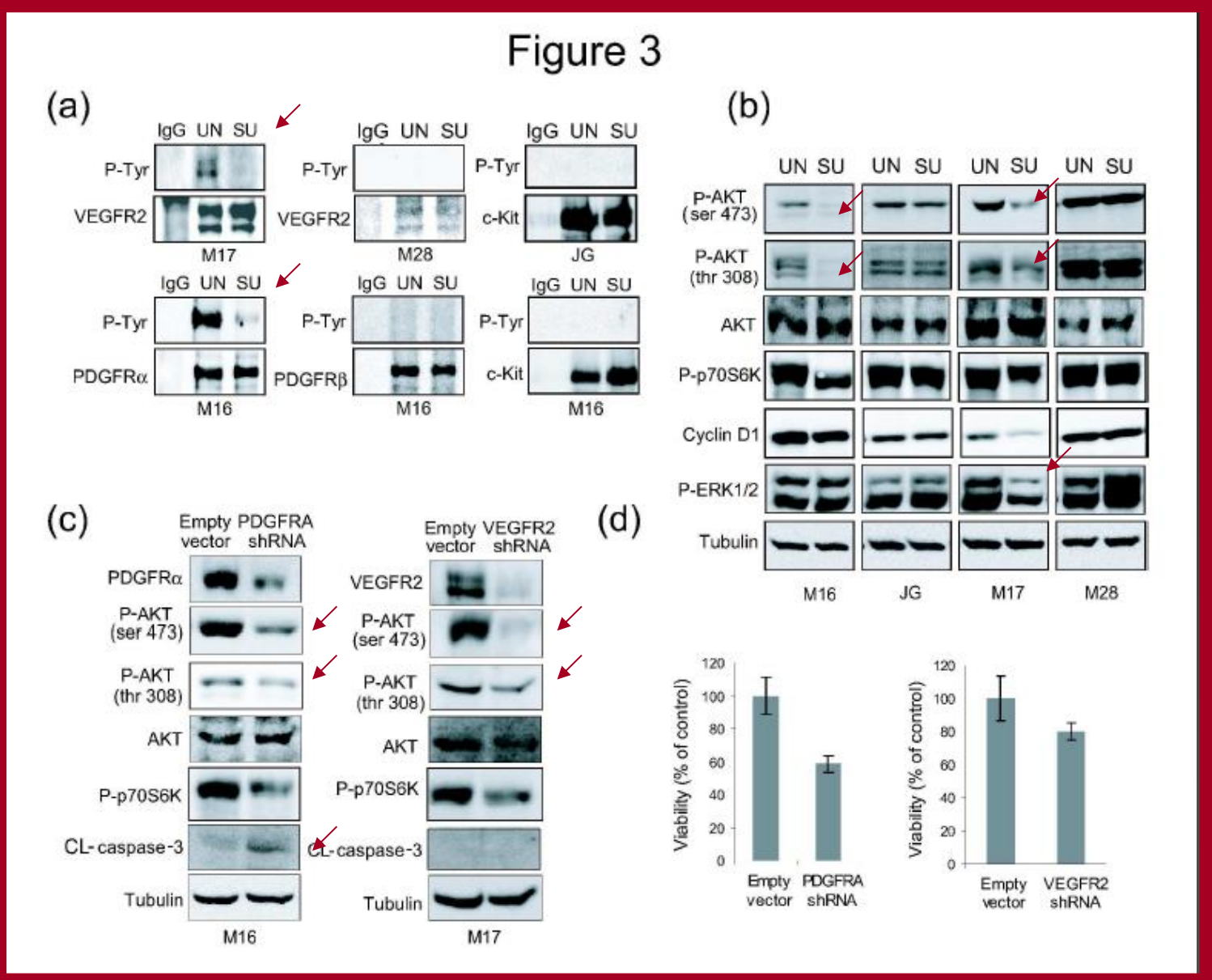
Figure 2



Treatment with Sunitinib induces an arrest of cell cycle in M16 and M17 cell lines and apoptosis in M16



Sunitinib inhibits basal phosphorylation of PDGFRα and VEGFR2 in sensitive M16 and M17 cell lines, respectively, and their downstream signalling pathways (P-AKT and P-ERK)



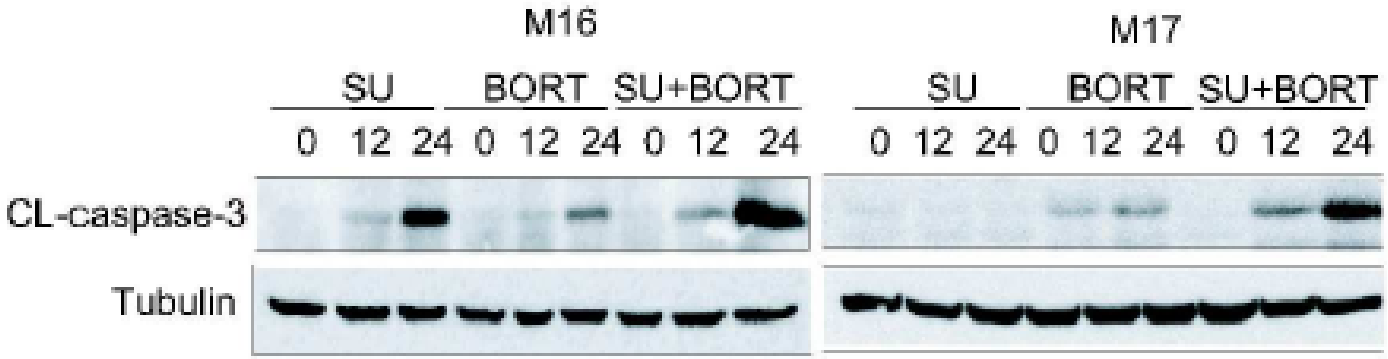
Combined Sunitinib and Bortezomib treatment results in a synergistic increase of cell death in Sunitinib sensitive M16 and M17 cell lines

Figure 4

(a)

	M16	M17	JG	M28
Untreated	5,88%	2,83%	2,97%	1,52%
Sunitinib	11,19%	3,14%	2,61%	2,61%
Bortezomib	15,14%	11,53%	36,96%	1,61%
Sunitinib+ Bortezomib	58,78%	31,73%	33,06%	1,65%

(b)



"Inhibition of activated RTK by Sunitinib induces growth arrest and sensitizes melanoma cells to Bortezomib by blocking Akt pathway"

Description of synergistic effect of sunitinib + bortezomib
and
underlying molecular mechanisms

Could be useful in some metastatic melanoma patients

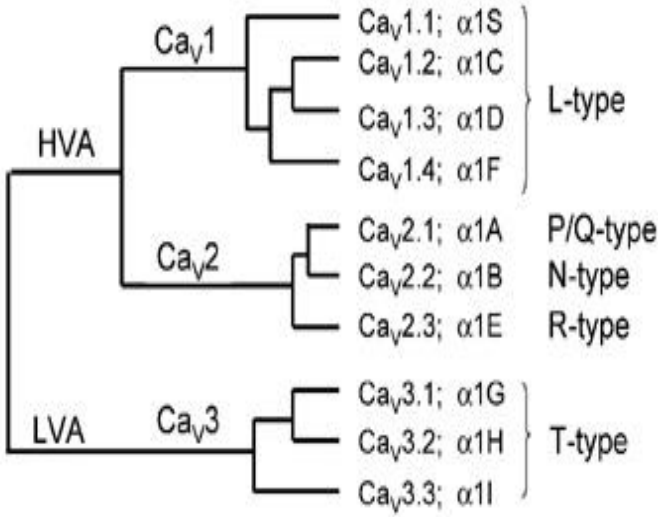
Submitted to Br J Dermatol: BJD-2010-1699

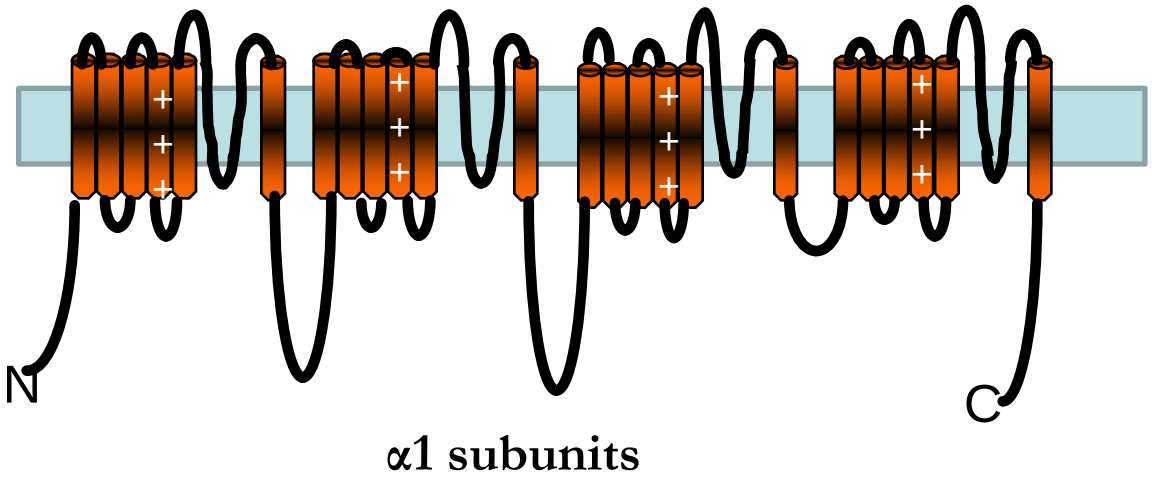
Role of voltage-gated calcium channels in proliferation and viability of human melanoma cells

Arindam Das

Supervisors: Carles Cantí & Rosa Maria Martí

Molecular subtypes of voltage gated calcium channels in mammals





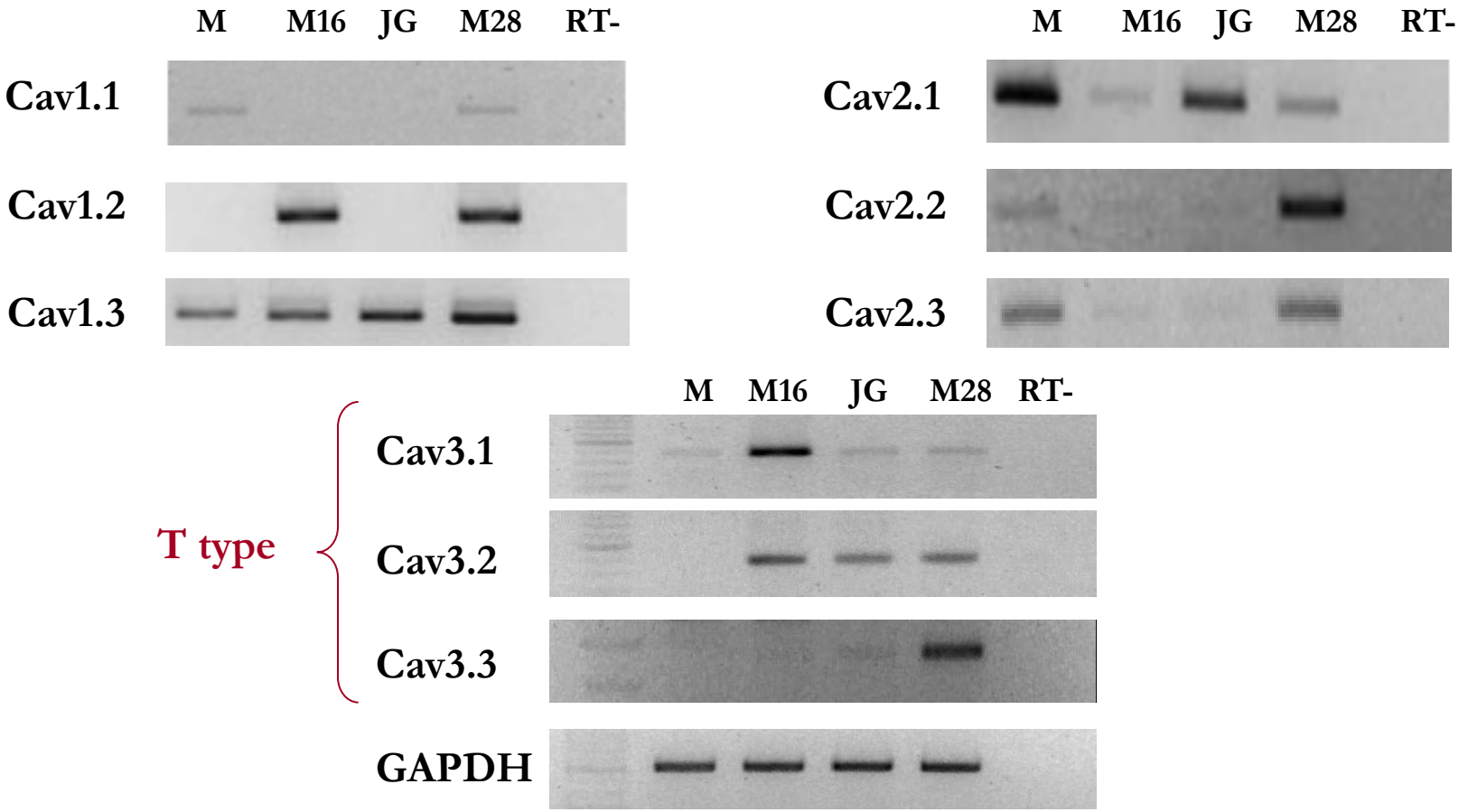
α1 subunits

Annette C. Dolphin, British Journal of Pharmacology 2006

Channel or pump	Cancer type	Channel or pump change in cancer		
		mRNA	Protein	Activity
Voltage-gated channels				
$Ca_V1.2$ (L-type α_{1C})	Colon cancer: patient tissue samples and cell lines	↑	ND	ND
$Ca_V1.1$ (L-type Ca^{2+} channel, exons 41 and 41A)	Colorectal cancer: patient tissue samples and cell lines	↑	ND	ND
$Ca_V3.1$ (T-type α_{1G})	Glioma: patient tissue samples and cell lines	↑	ND	ND
	Colorectal cancer, colorectal adenoma, gastric cancer and acute myeloid leukaemia: patient tissue samples and cancer cell lines (colon, breast, prostate, lung and haematopoietic)	↓	ND	ND
$Ca_V3.3$ (T-type α_{1I})	Colon carcinomas and adenomas: patient tissue samples and cell lines	↓	ND	ND

Monteith et.al, 2009 Nature Reviews

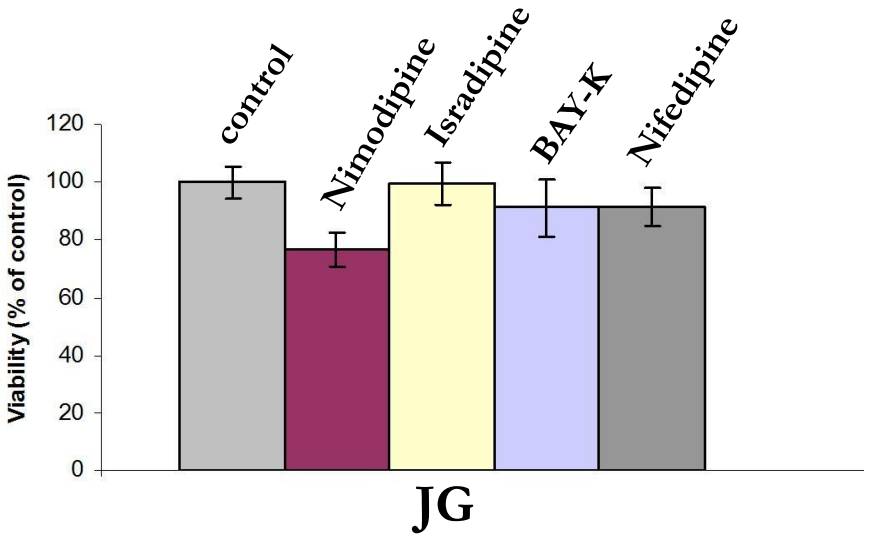
Isoforms of T type calcium channels are highly expressed in melanoma in comparison to melanocytes

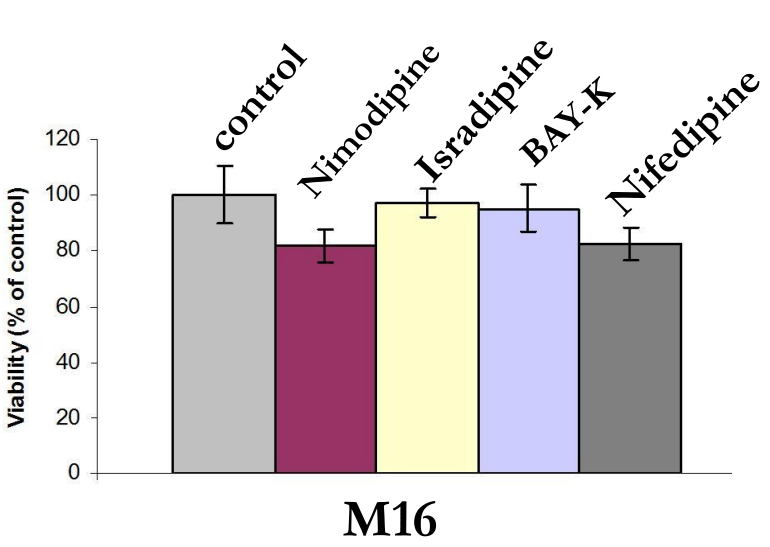


M- epidermal melanocytes isolated from lightly pigmented neonatal foreskin
M16, JG, M28-Melanoma cell lines

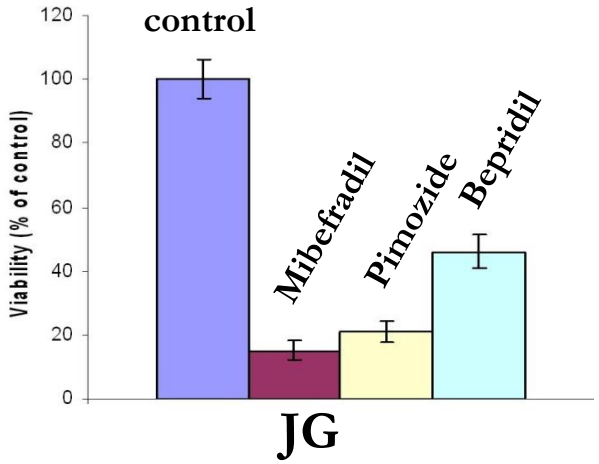
T-type channel blockers reduce the viability of melanoma cell-lines

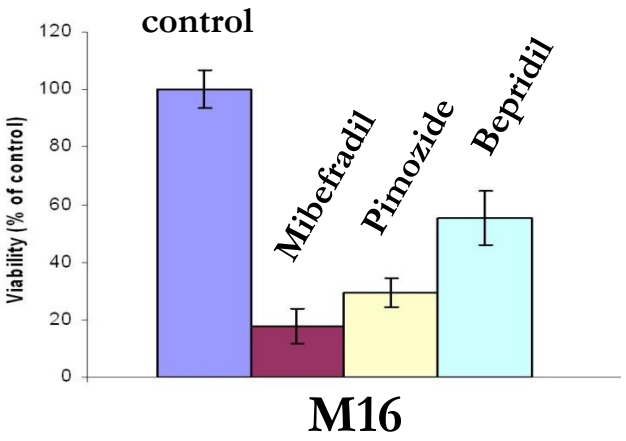
L-type



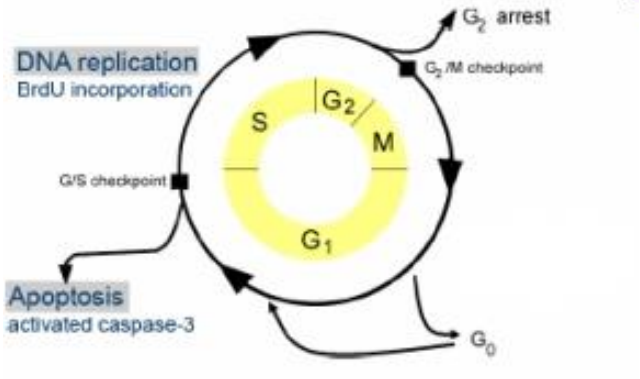


T-type



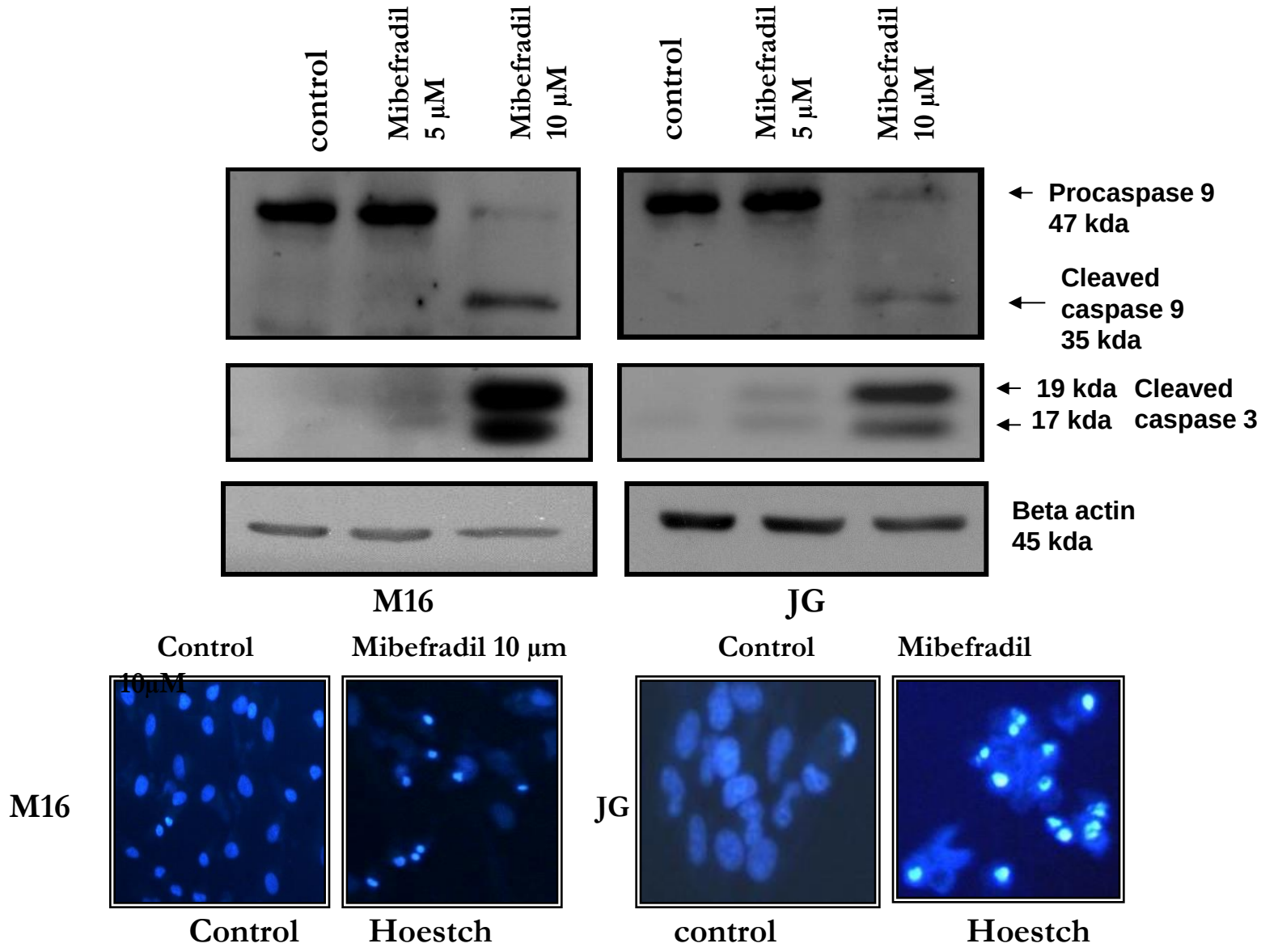


Pharmacological blockage of T-type calcium channel causes cell cycle arrest



	Control	Mibefradil 5 μM	Mibefradil 10 μM
M16	Sub G1-5.22% S-13.59%	Sub G1-24.02% S-7.63%	Sub G0-66.55% S-1.51%
JG	Sub G1-0.78% S-25.37%	Sub G1-34.02% S-10.82%	Sub G1-58.66% S-8.91%

Pharmacological blockage of T-type calcium channel induces caspase-dependent apoptosis of melanoma cells



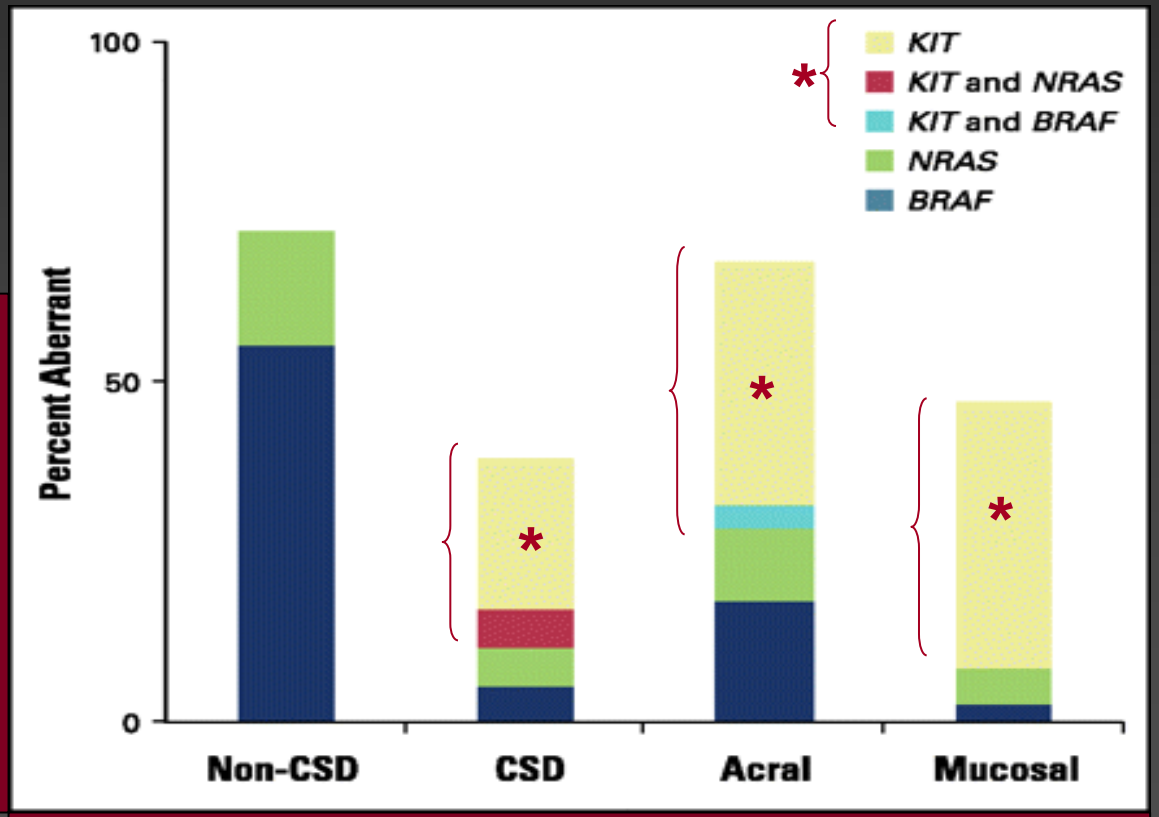
Melanoma- 1. Targeted therapies

1.2. "Expression analysis and mutational study of the c-KIT gene in LENTIGINOUS MELANOMAS" (LMM, ALM, Mucosal M)

Leandro Abal Díaz

IRBLLEIDA: Ajut a la Recerca adreçat al Personal en Formació Sanitària Especialitzada de l'Hospital Universitari Arnau de Vilanova de Lleida

Genetic aberrations of the c-Kit gene in some melanoma types



Curtin JA et al. J Clin Oncol 2006; 24: 4340-4346

Melanoma research 2003-10

2. Digital follow-up of patients with *Dysplastic Nevus Syndrome* employing SIAscopy

supported by

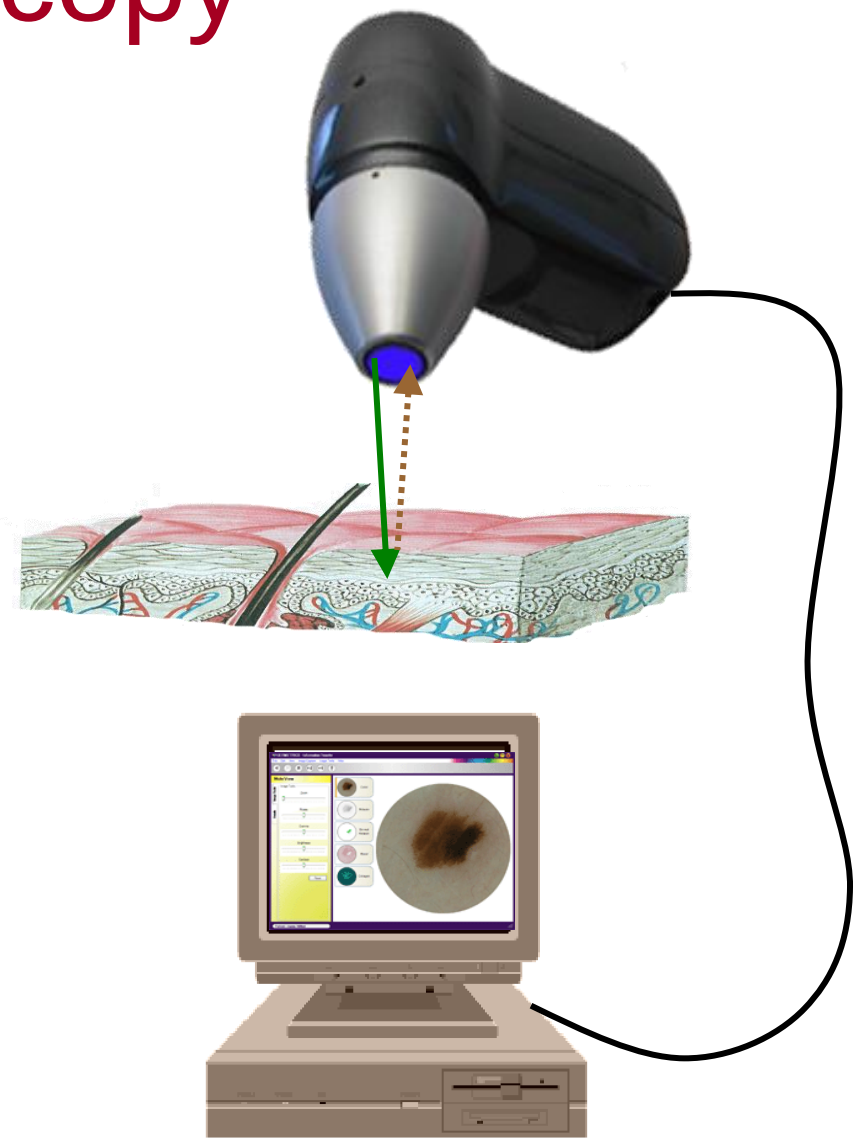
“Lliga contra el càncer de les comarques de Lleida” *(enero 2007)*

SIAscopy

Spectrophotometric

Intracutaneous

Analysis



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Mole View

Image Tools

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Contrast

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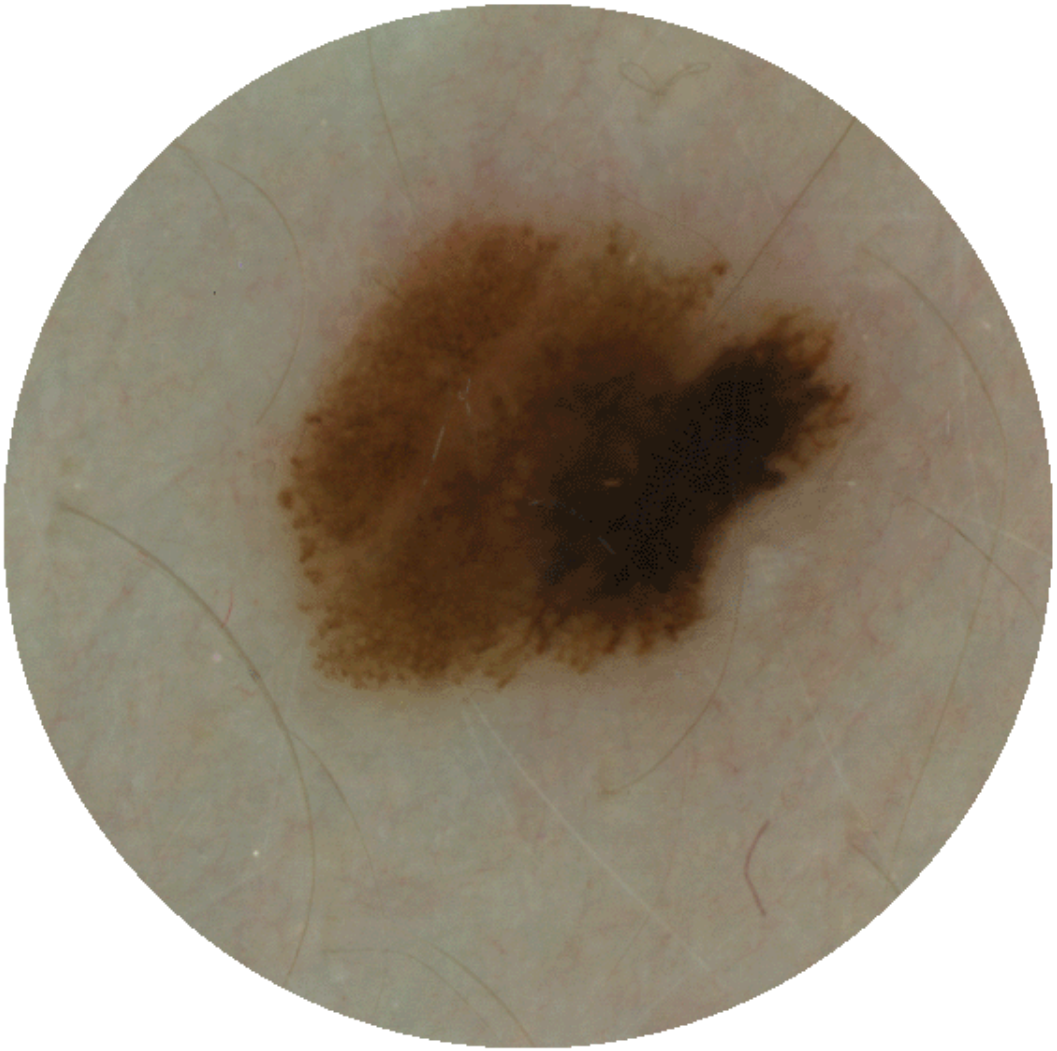
Color

Melanin

Dermal Melanin

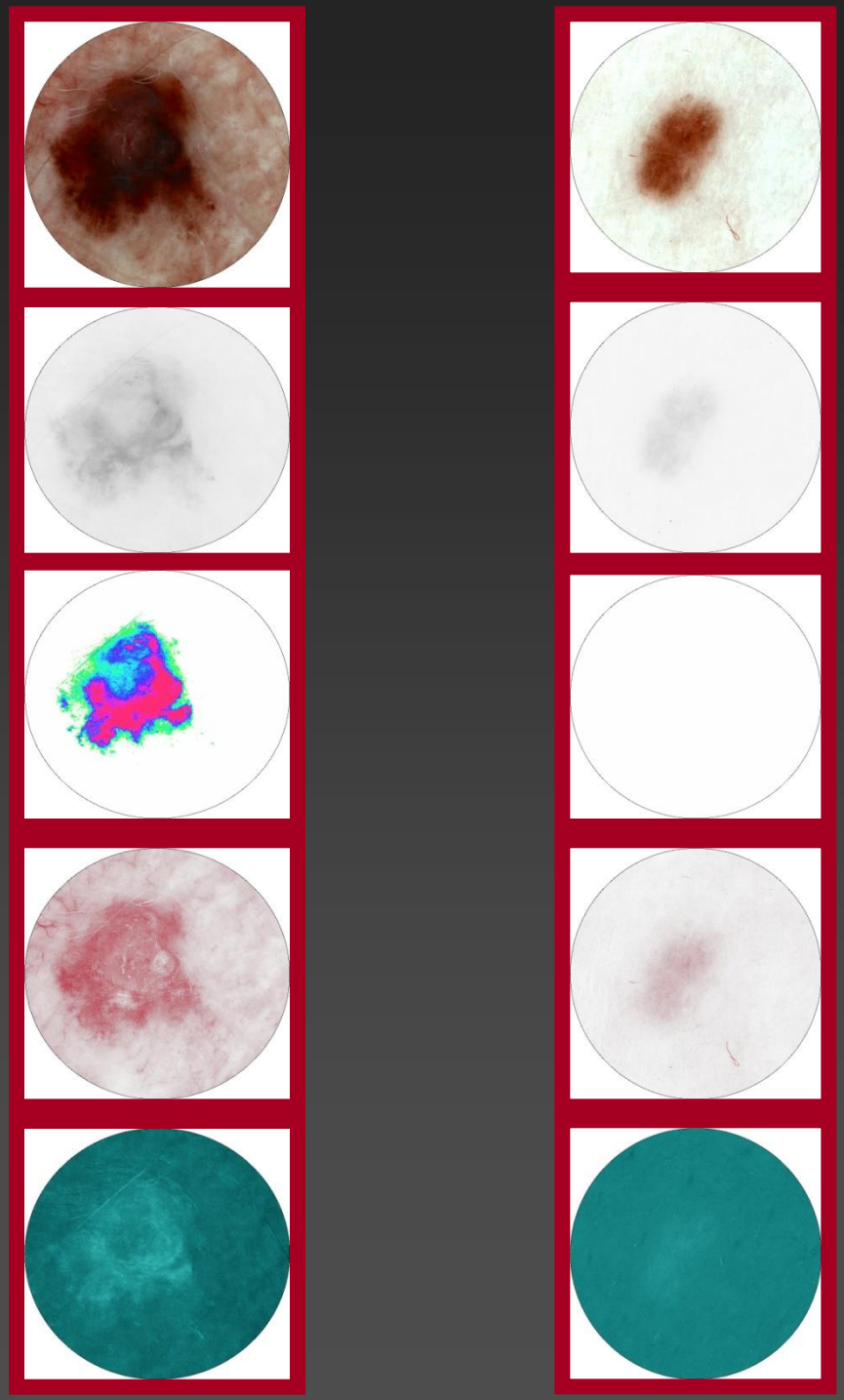
Blood

Collagen



Patient : Melvyn Arthur Nomer

Malignant melanoma



Melanocytic nevus

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Mole Manager

Last Visit Lesion Details

Lesion ID

Notes

Save

Status on :

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Filter

Filter By Status

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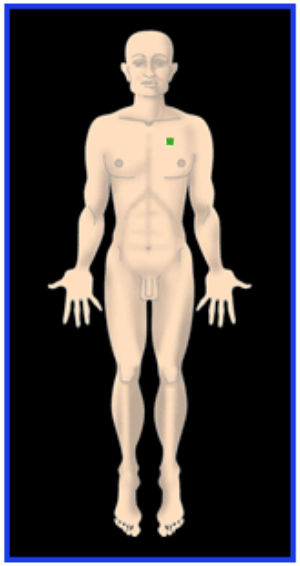

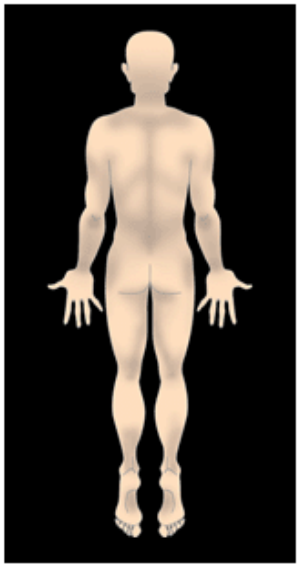

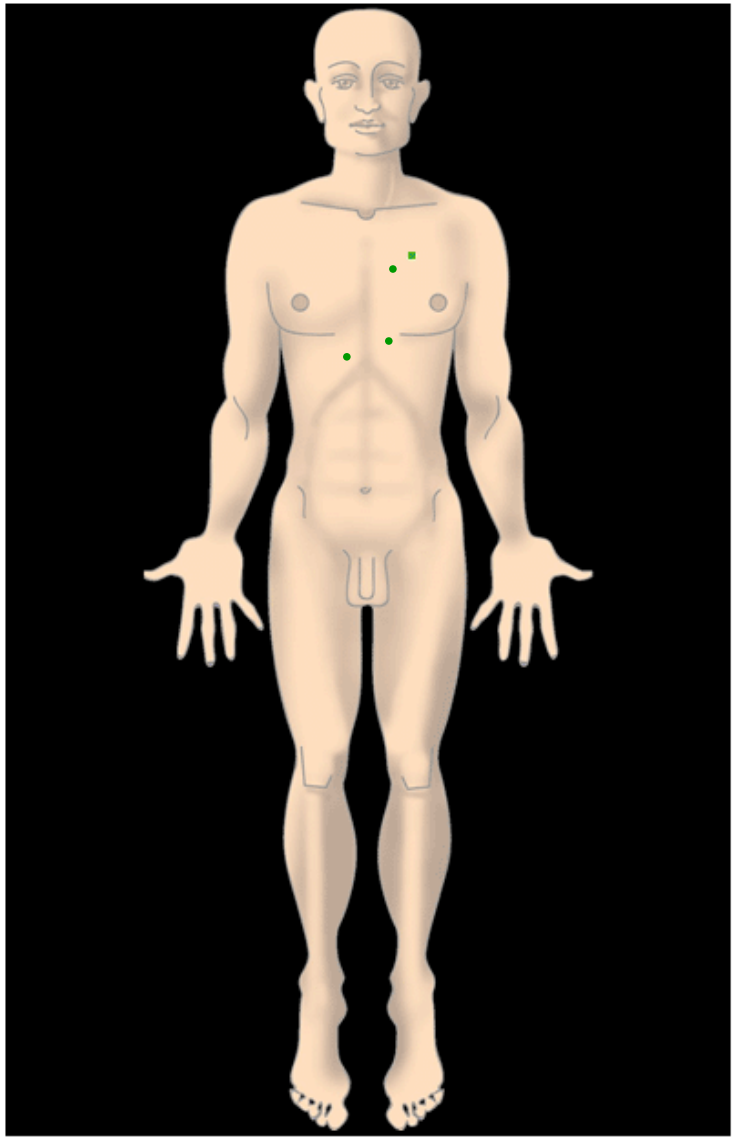

Patient : Melvyn Arthur Norner

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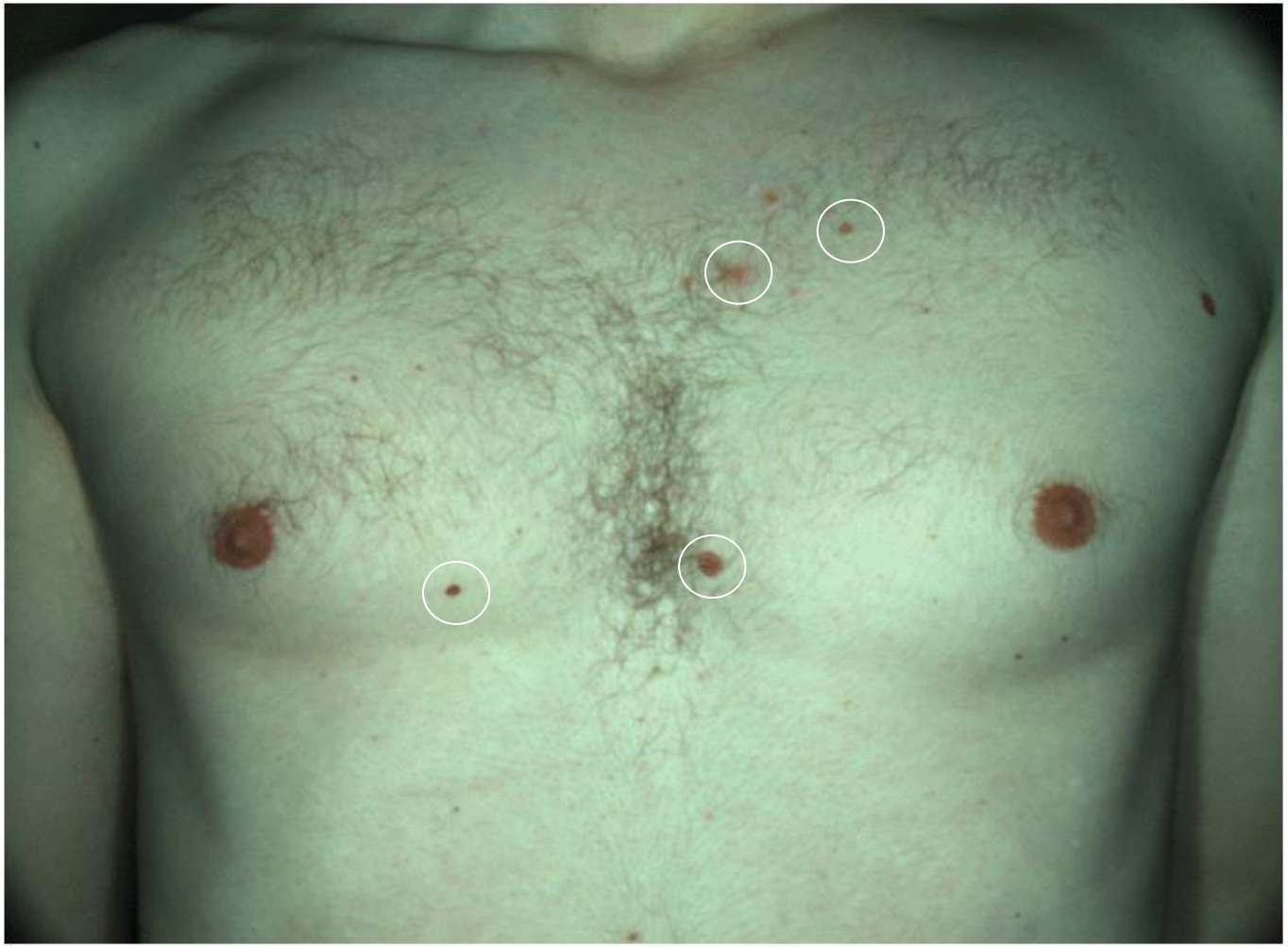
Fade

Display bottom image in black and white

Display circles

Display lesion IDs

Match



Patient : Joe Bloggs

2. Digital follow-up of patients with Dysplastic Nevus Syndrome employing SIAscopy (april 2007-october 2010)

Number of patients: 96

Follow-up: 2– 42 months

Diagnostics: 1 pigmented basal cell carcinoma
23 melanocytic nevi: 11 dysplastic, 5 junctional, 4 compound, 4 intradermal

Risk factors for melanoma:

Familiar history of dysplastic nevus syndrome: 59
Familiar history of melanoma: 14
Familiar history of familiar melanoma: 0

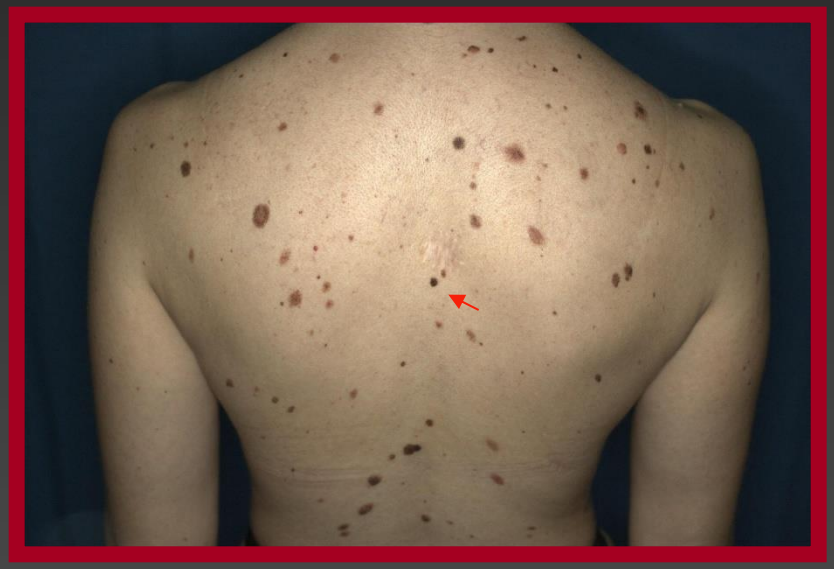
Personal history of melanoma: 8 **Personal history of multiple melanoma: 1**

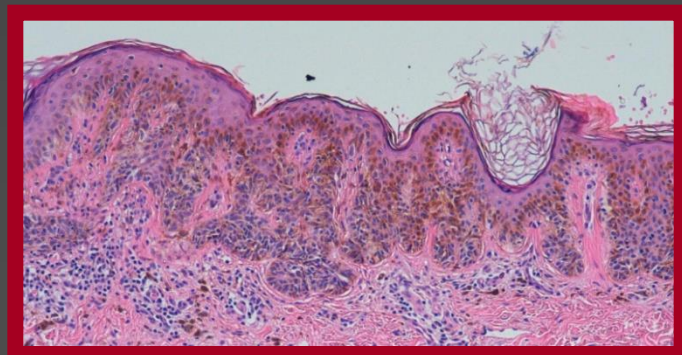
Personal history of non-melanoma skin cancer: 6
Personal history of other malignancies: 1

Personal history of immunodeficiency / immunosupressed therapies: 2

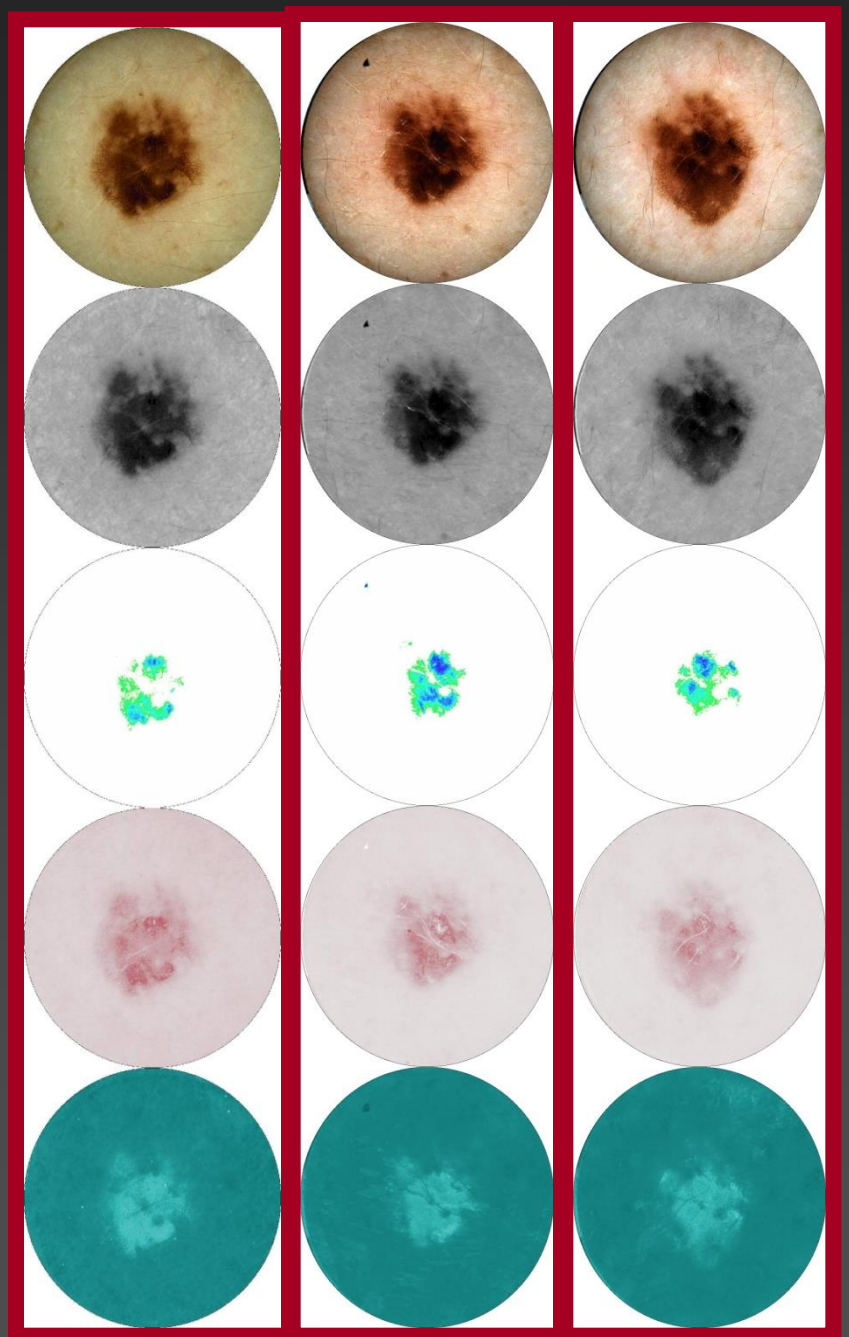
36 year-old woman

- Dysplastic nevus syndrome
- 1 relative with MM (cousin)



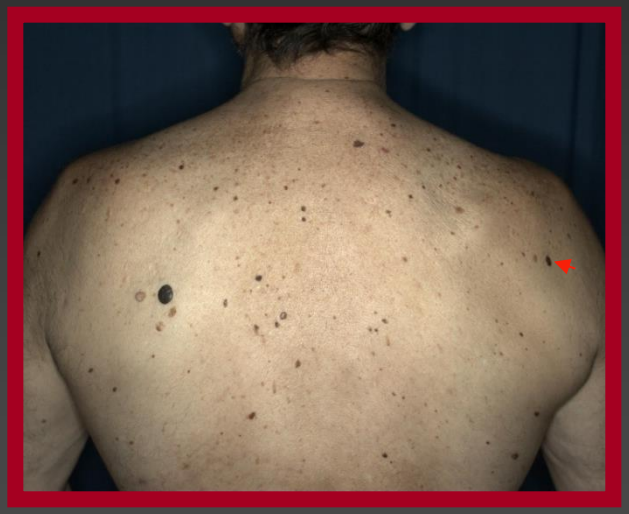


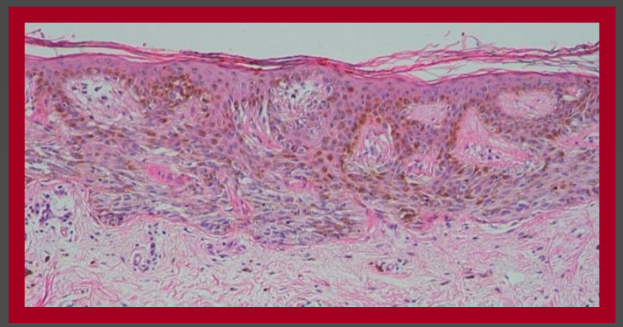
Dysplastic nevus



67 year-old man

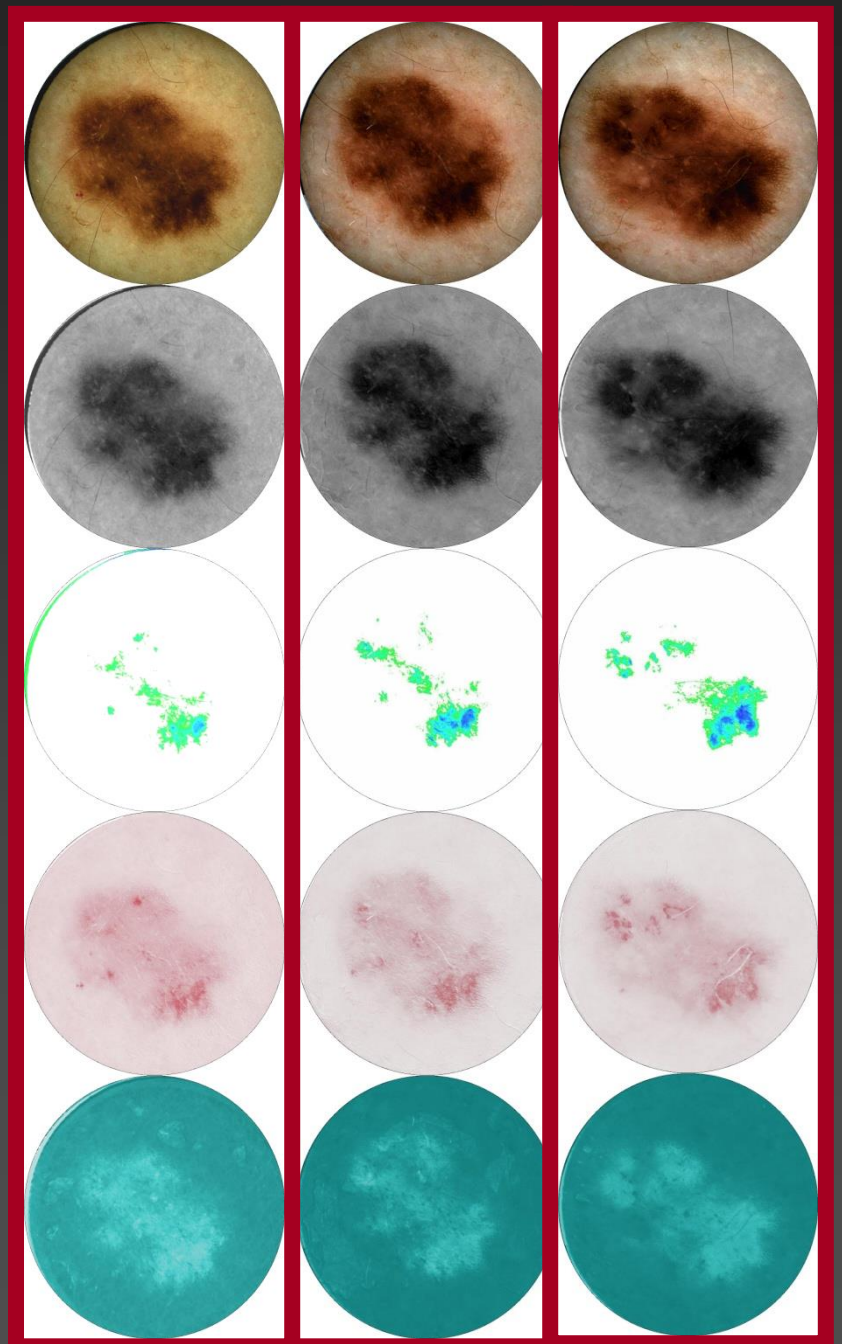
- Dysplastic nevus sd
- Personal history of
  - MM
  - Renal cell carcinoma
  - Paratesticular liposarcoma
  - Soft tissue sarcoma
  - Chronic T cell lymphocytosis
- 2 siblings with haematological and CNS malignancies





Dysplastic nevus

18-10-07 17-01-08 16-04-09



Melanoma research 2003-10

1. Targeted therapies

2. Follow-up of patients with *Dysplastic Nevus Syndrome* employing SIAscopy

3. Analysis of the "Registro Nacional de Melanoma de la AEDV" (1997-2008)

4. Collaboration with the "Xarxa de centres de melanoma de Catalunya i Balears"

Registro Nacional de Melanoma Cutáneo de la AEDV

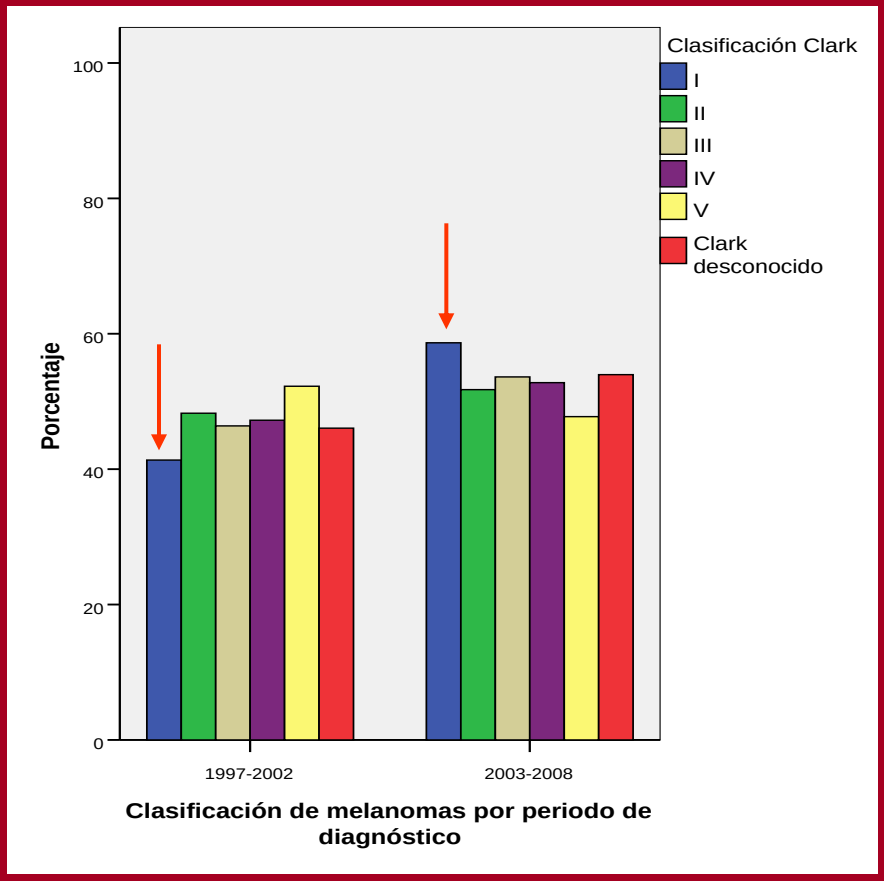
1997-diciembre 2008

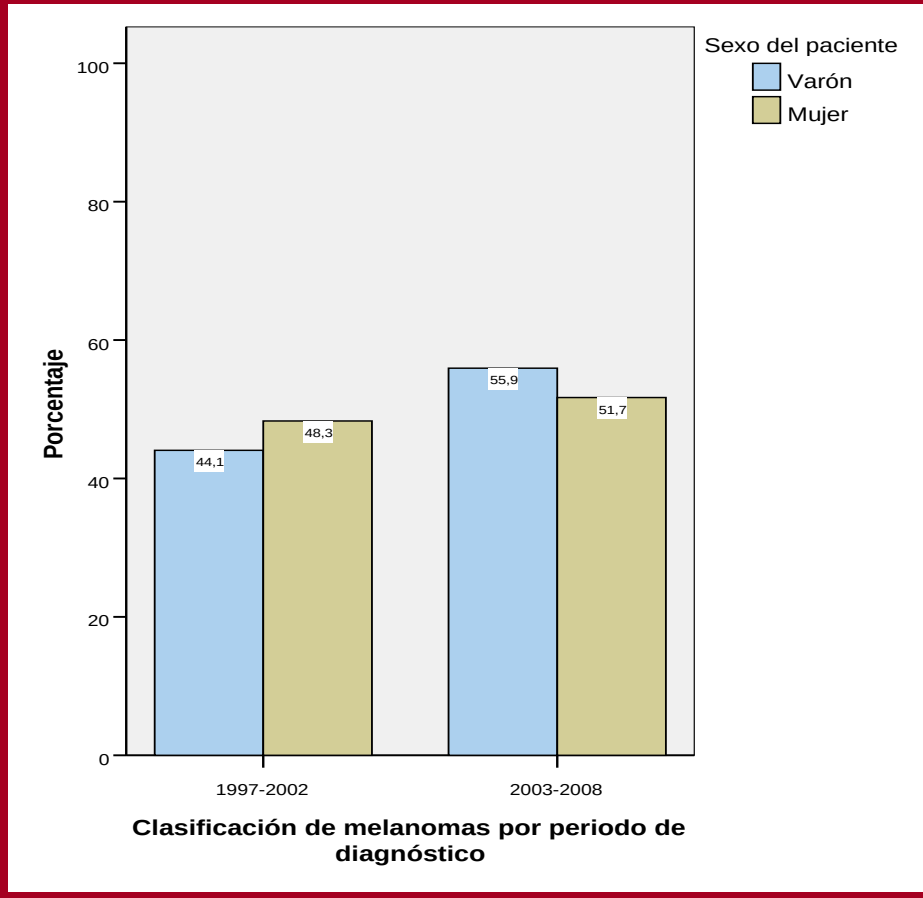
10.370 casos incluidos

Schering - Plough, S.A.
BIOTECH

E-C-BIO, ESTUDIOS CIENTÍFICOS

Comparative analysis of the features of malignant melanoma cases diagnosed in 1997-2002 vs 2003-2008





Melanoma research 2003-10

1. Targeted therapies

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4. Collaboration with the "Xarxa de centres de melanoma de Catalunya i Balears" (22 hospitals)

- **Clinical practice guidelines for cutaneous melanoma management**

DOCUMENTO DE CONSENSO

Valoración inicial, diagnóstico, estadificación, tratamiento y seguimiento de los pacientes con melanoma maligno primario de la piel. Documento de consenso de la "Xarxa de Centres de Melanoma de Catalunya i Balears"

C. Mangas[a,*], C. Paradelo[a], S. Puig[b], F. Gallardo[c], J. Marcoval[d], A. Azon[e], R. Bartralot[f], S. Bel[g], X. Bigatà[h], N. Curcó[i], J. Dalmau[j], L.J. del Pozo[k], C. Ferrándiz[a], M. Formigón[l], A. González[m], M. Just[n], A. Llambrich[o], E. Llistosella[p], J. Malvehy[q], R.M. Martí[r], M.E. Nogués[s], R. Pedragosa[t], V. Rocamora[u], M. Sàbat[v] y M. Salleras[w]

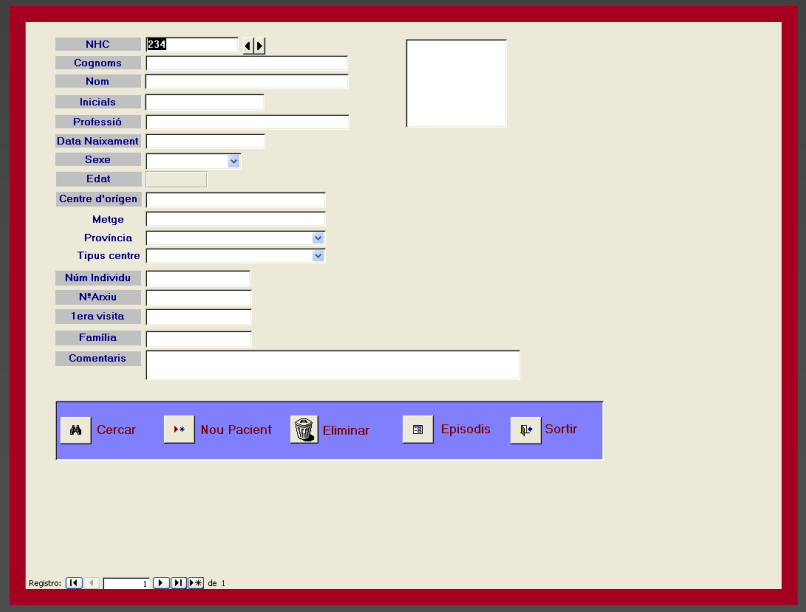
Actas Dermosifiliogr. 2010;101(2):129–142

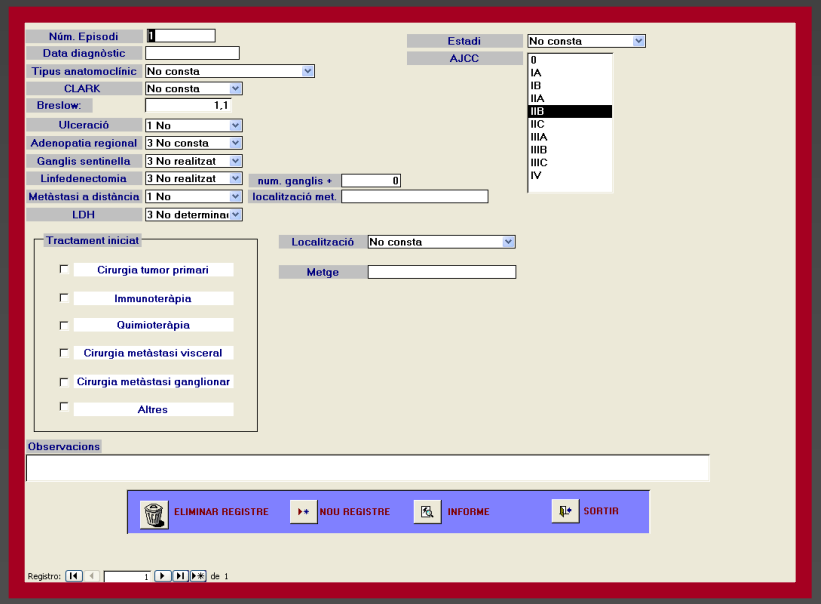
4. Collaboration with the "Xarxa de centres de melanoma de Catalunya i Balears" (22 hospitals)

- **Clinical practice guidelines for cutaneous melanoma management**

- **Cutaneous melanoma registry** (Catalonia and the Balearic Islands)

  . Development of a database





4. Collaboration with the "Xarxa de centres de melanoma de Catalunya i Balears" (22 hospitals)

- **Clinical practice guidelines for cutaneous melanoma management**

- **Cutaneous melanoma registry (Catalonia and the Balearic Islands)**

  . Development of a database
  . 2000-2007 data collection and analysis
  (currently being drafted for publication)

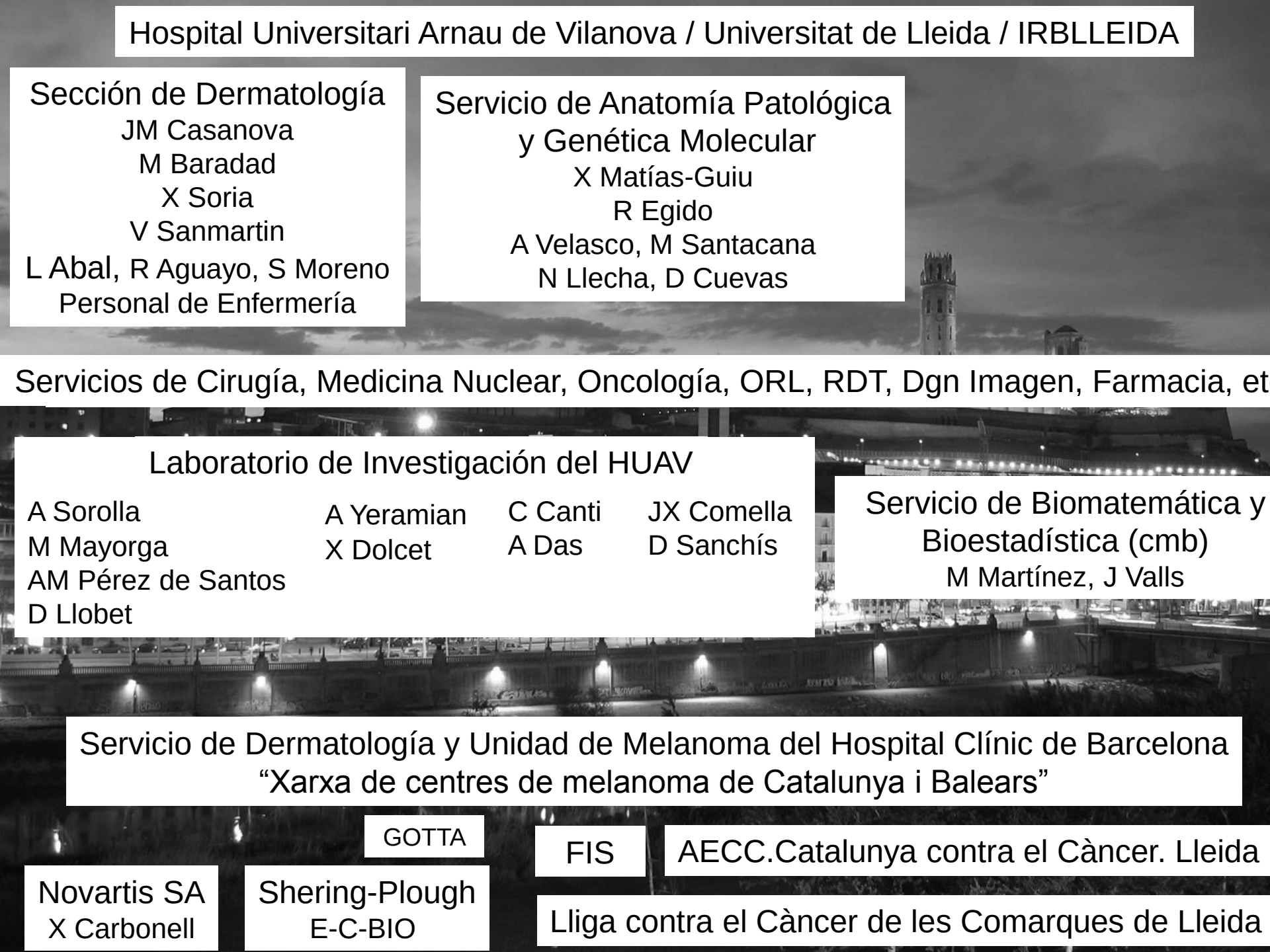
- **Other common projects (multidisciplinary scenario)**

Melanoma research

FUTURE AIMS

- To end current studies and to continue our participation in multicentric projects
- Targeted therapy: *In vitro* invasion and migration assays, murine models (xenografts)
- Analysis and extension of SIAscope studies
- Other


ricard@lleida



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Servicio de Dermatología y Unidad de Melanoma del Hospital Clínic de Barcelona
"Xarxa de centres de melanoma de Catalunya i Balears"

GOTTA

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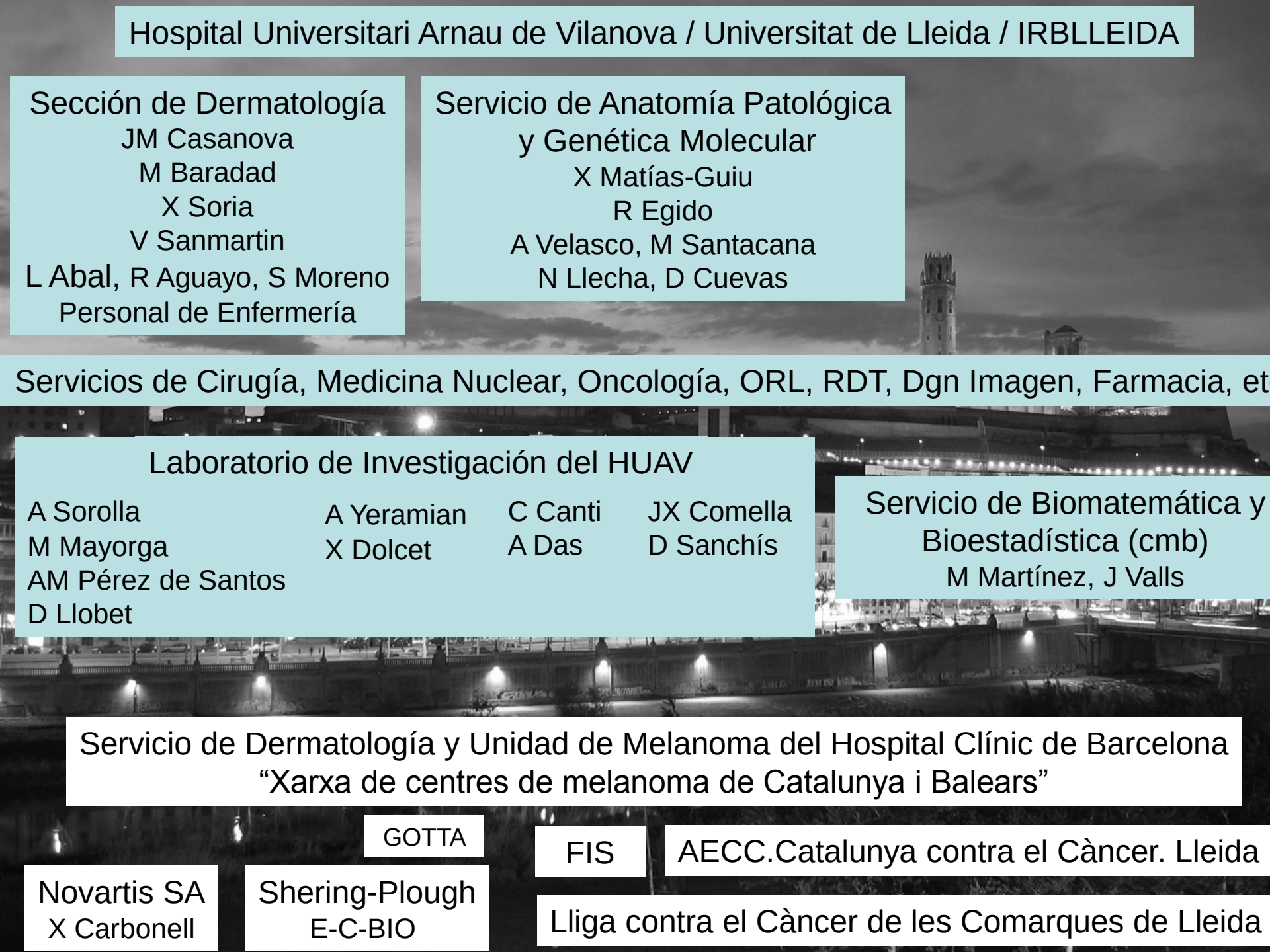
AECC.Catalunya contra el Càncer. Lleida

Novartis SA
X Carbonell

Shering-Plough
E-C-BIO

Lliga contra el Càncer de les Comarques de Lleida



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