Genetics and Genomics: Identifying Disease Causing Genes

CELLULAR AND MOLECULAR MARKERS IN THE DEVELOPMENT AND PROGNOSIS OF LYMPHOPROLIFERATIVE DISORDERS

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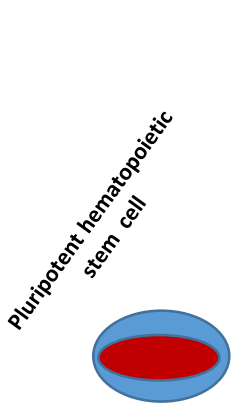
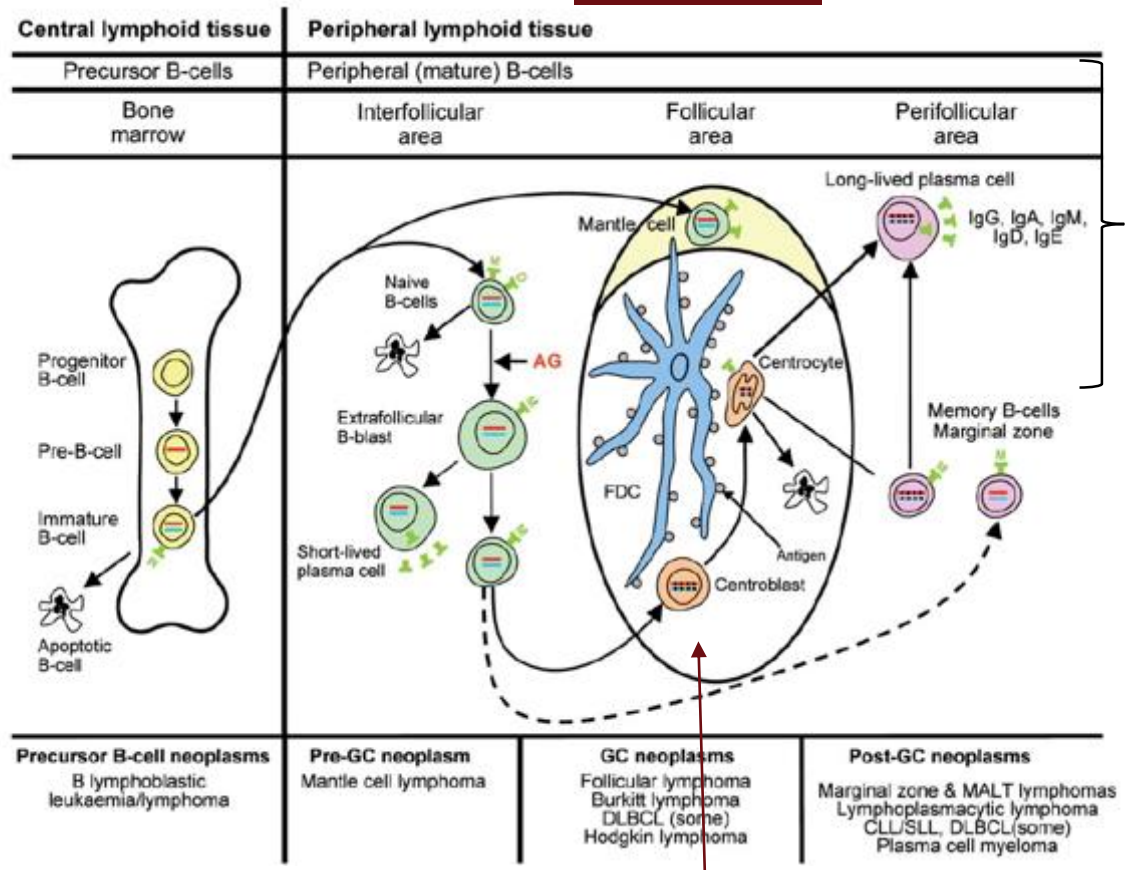
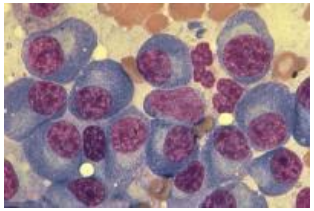
LYMPHOPROLIFERATIVE DISORDERS

- **Lymphoproliferative disorders are a set of malignant diseases characterized by abnormal proliferation of lymphocytes, also called B and T cells, which are derived from pluripotent hematopoietic stem cells in the bone marrow**

Lymph node







MM = a clonal plasma cells malignant disease

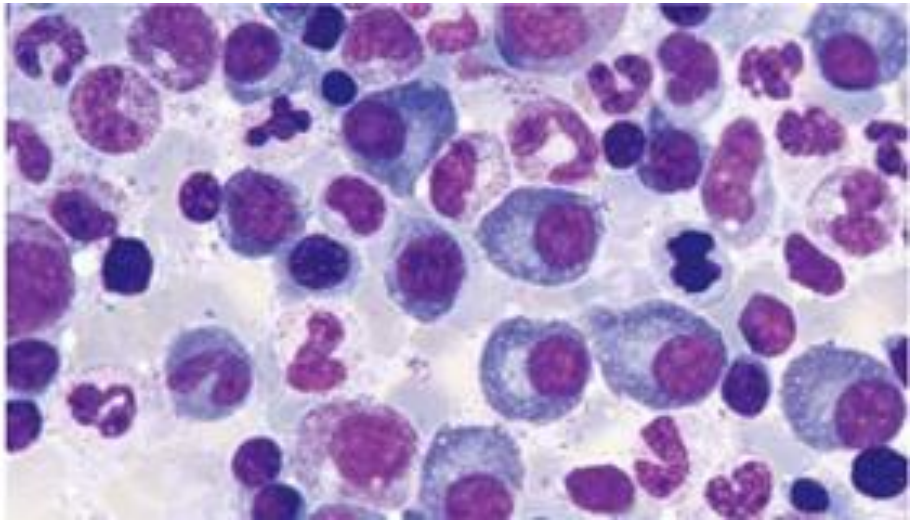
Bone marrow

Genomic instability

WHO, 2008

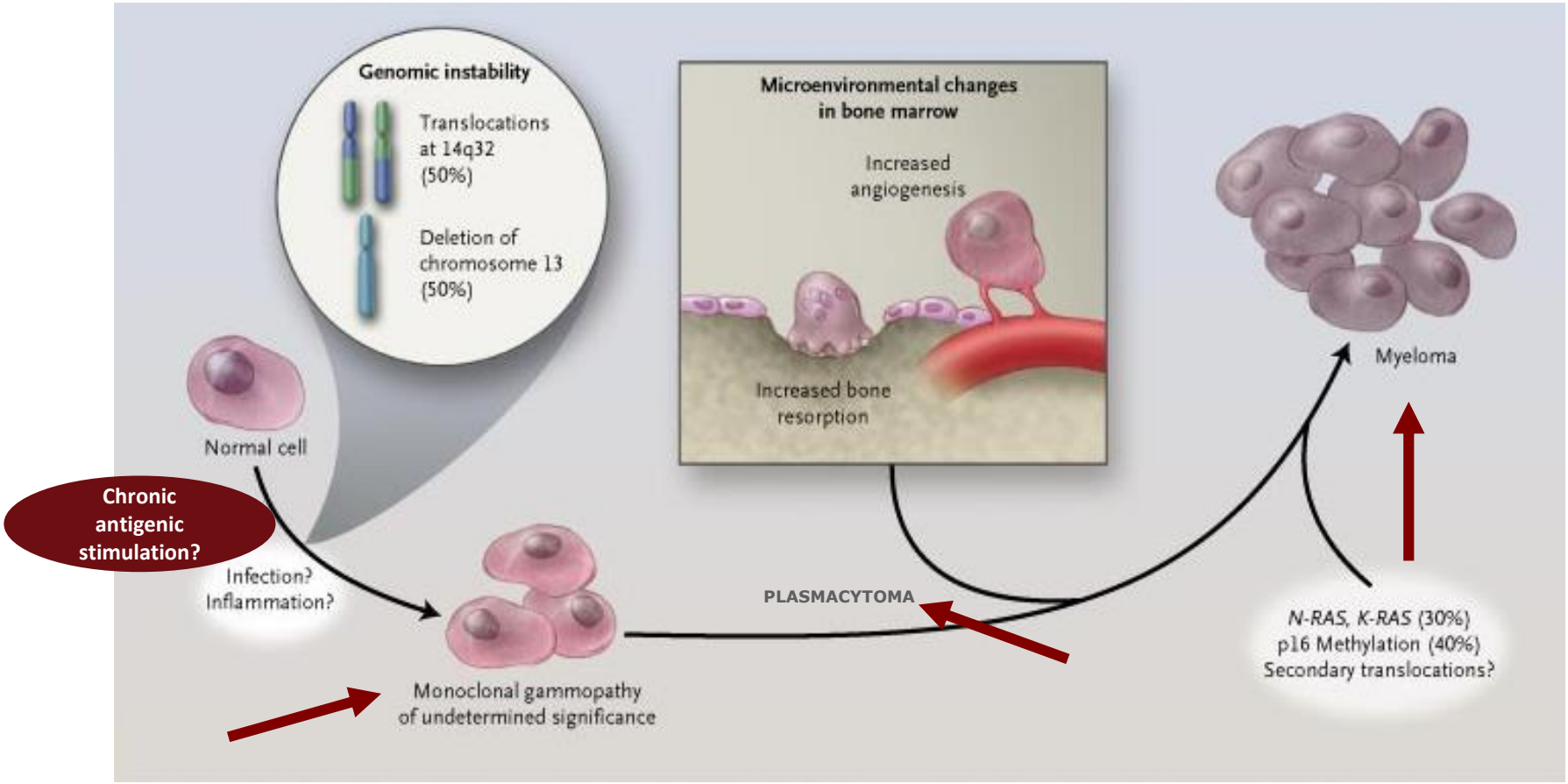
EPIDEMIOLOGY

- ✓ MM accounts for 1% of all malignancies and 10% of hematological malignancies
- ✓ MM is the second most frequent lymphoproliferative disorder
- ✓ Incidence:
  - ✓ ~15,000 new cases/year in the USA
  - ✓ No oficial information in Brazil



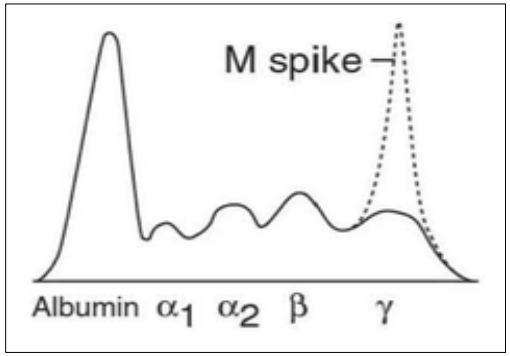
Bone marrow aspirate, 1000X

MULTIPLE MYELOMA



Kyle & Rajkumar, 2004

MULTIPLE MYELOMA

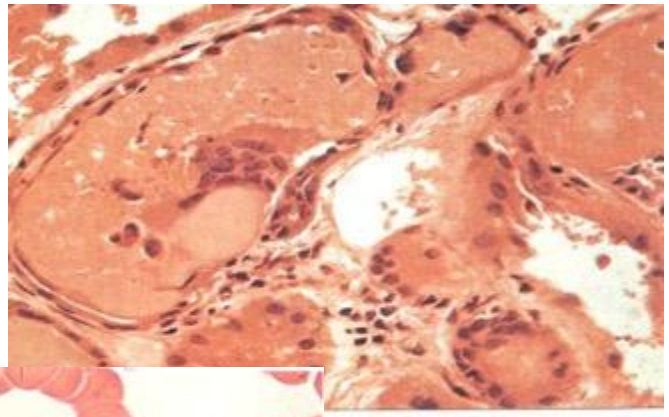


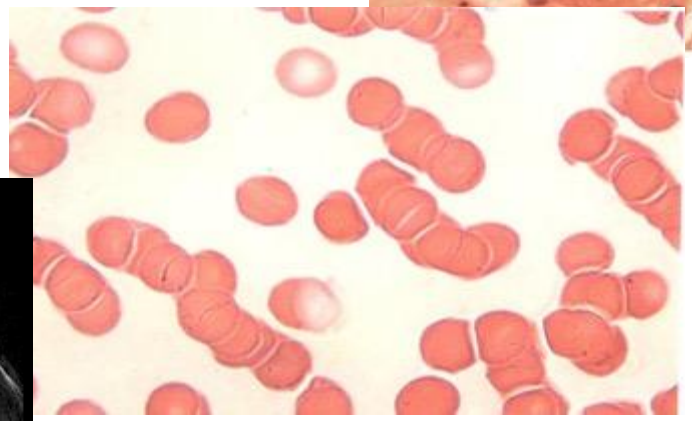
New Diagnostic Criteria International Myeloma Working Group

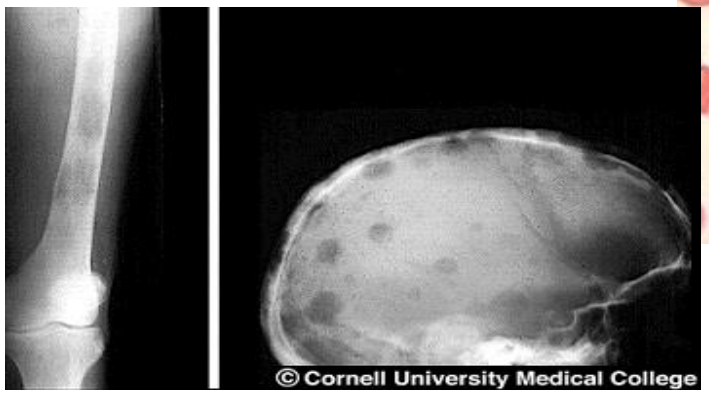
- Plasma cells >=10% or plasmacytoma in biopsy

and

- At least one end-organ disfunction (CRAB):
  - ✓ HyperCalcemia
  - ✓ Renal insufficiency
  - ✓ Anemia
  - ✓ Bone lesions



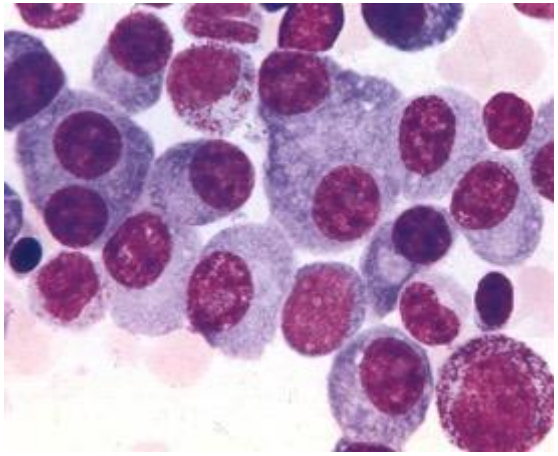




Rajkumar et al, IMWG, Lancet Oncology, 2014

CURRENT SITUATION

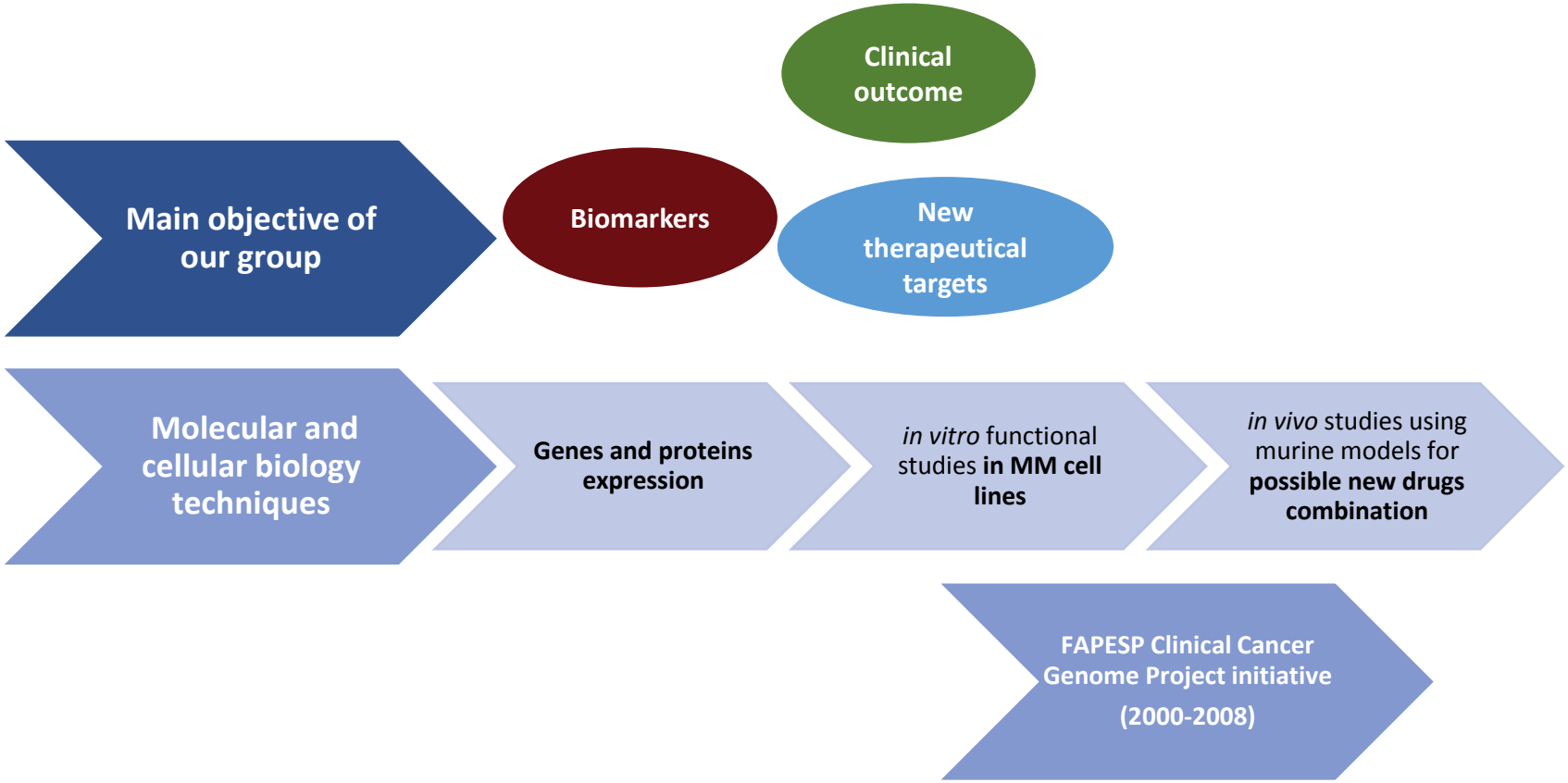
- ✓ Approval schemes with proteasome inhibitors (bortezomib, carfilzomib, ixazomib) and lenalidomide by the FDA
  - ✓ MM = chronic, incurable disease
  - ✓ The five-year survival rate is around 35 percent
- ✓ This situation highlights an urgent need for novel therapies for the treatment of multiple myeloma



Bone marrow aspirate, 1000X

Cho, CRI, 2015

CELLULAR AND MOLECULAR MARKERS IN THE DEVELOPMENT AND PROGNOSIS OF LYMPHOPROLIFERATIVE DISORDERS



Clinical Genomics Project in Multiple Myeloma (2000-2008)

GENE EXPRESSION IN MULTIPLE MYELOMA: IDENTIFICATION OF TUMOR MARKERS AND POSSIBLE THERAPEUTIC TARGETS

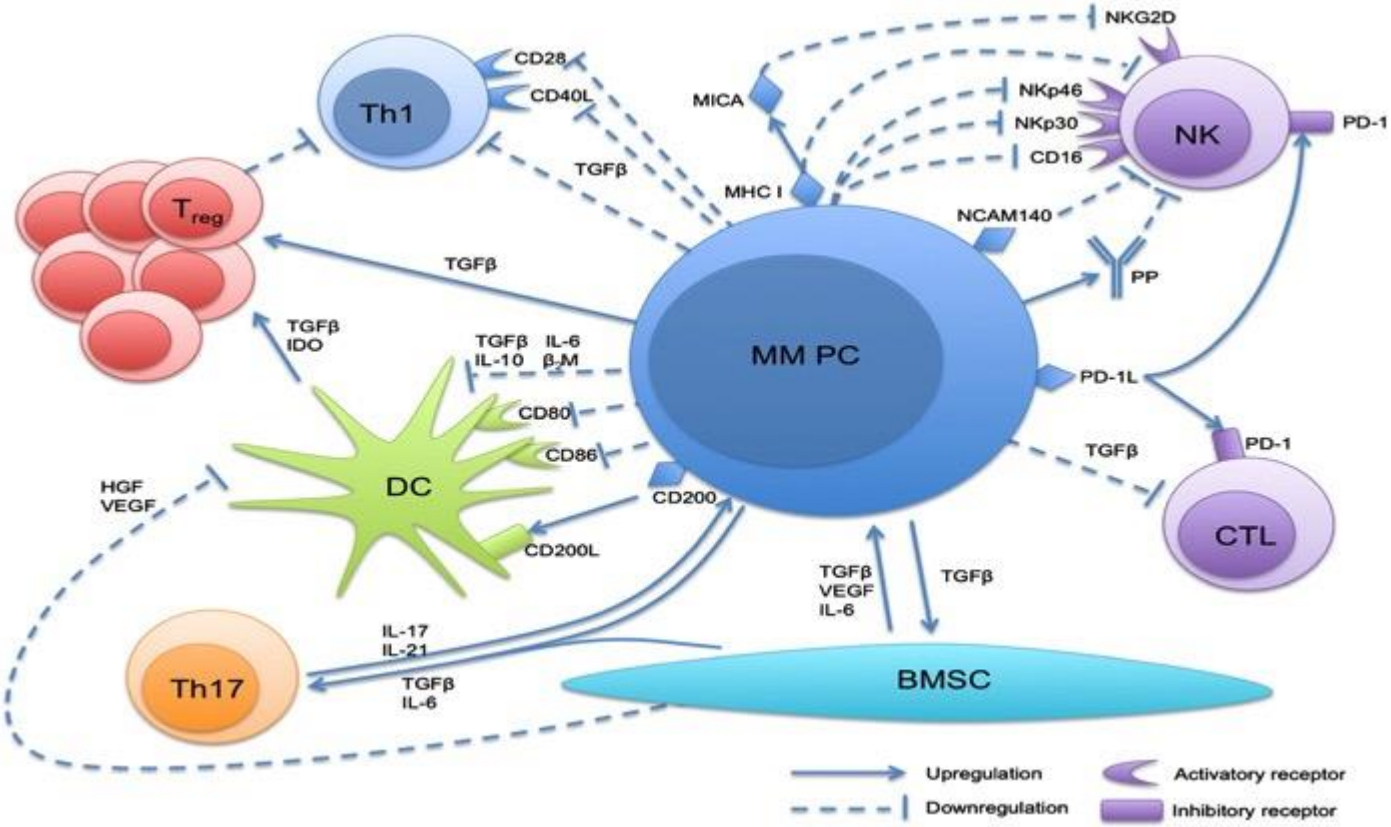
1. Discipline of Hematology and Hemotherapy, Universidade Federal de São Paulo, UNIFESP, São Paulo, Brazil

2. Ludwig Institute for Cancer Research, São Paulo Branch, Brazil

3. Faculdade de Medicina de Ribeirão Preto/USP, Brazil

Presenting 5 Players in Multiple Myeloma

- ✓ *Tumor proteins*
- ✓ *Dendritic cells*
- ✓ *T-cells*
- ✓ *BMSC (bone marrow stromal cells)*
- ✓ *Cancer stem cells*



Feyler, Blood Reviews, 2013

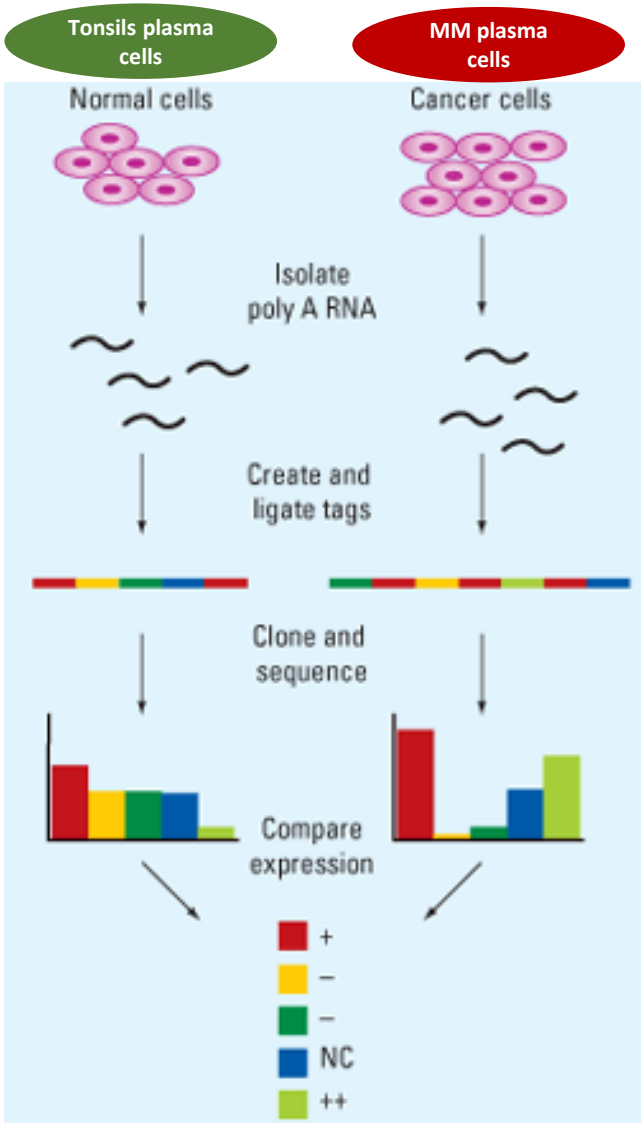
✓ *Tumor proteins*

NEW POSSIBLE TARGETS IN MM?

CANCER LETTERS

SAGE analysis highlights the importance of *p53csv*, *ddx5*, *mapkapk2* and *ranbp2* to multiple myeloma tumorigenesis☆

Roberta S. Felix[1], Gisele W.B. Colleoni[1], Otavia L. Caballero[1], Mihoko Yamamoto, Manuella S.S. Almeida, Valéria C.C. Andrade, Maria de Lourdes L.F. Chauffaille, Wilson A. da Silva Jr., Maria Dirlei Begnami, Fernando Augusto Soares, Andrew J. Simpson, Marco Antonio Zago, André L. Vettore
[1] These authors contributed equally for this paper.



Adapted from Augen, Modern Drug Discovery, 2004

SERIAL ANALYSES OF GENE EXPRESSION: MM LIBRARY AND NORMAL PLASMA CELL LIBRARY

12 overexpressed genes in MM
(> 10 times than in normal plasmacytes)

Gene symbol	Gene name	Function
ZFHX1B	Zinc finger homeobox 1b	Transcription Cell metabolism
*XBP1**	X box binding protein 1	Immune response Transcription
*PIM2**	Pim 2 oncogene	Transcription Signaling Cell metabolism Apoptosis
LGALS1	Lectin, galactoside-binding soluble 1 (galectin 1)	Signaling Apoptosis Cell proliferation
*RANBP2**	Ran binding protein 2	Transcription
TRIAP1/ P53CSV	P53 inducible cell-survival factor	Cell Cycel control Apoptosis
*DDX5**	DEAD (Asp-Glu-Ala-Asp) box polypeptide 5	Transcription
LSM5	LSM5 homolog u6 small nuclear RNA associated	Transcription
*JUND**	Jun D proto-oncogene	Transcription Signaling Apoptosis
*MAPKAPK2**	Mitogen-activated protein kinase 2	Signaling
*SP140**	SP140 nuclear body protein	Immune response Transcription
*NTN-1**	Nitrin 1	Cell metabolism

*MoAb available for immunohistochemistry

Real-time PCR validation of gene expression in 31 MM cases and 3 normal controls

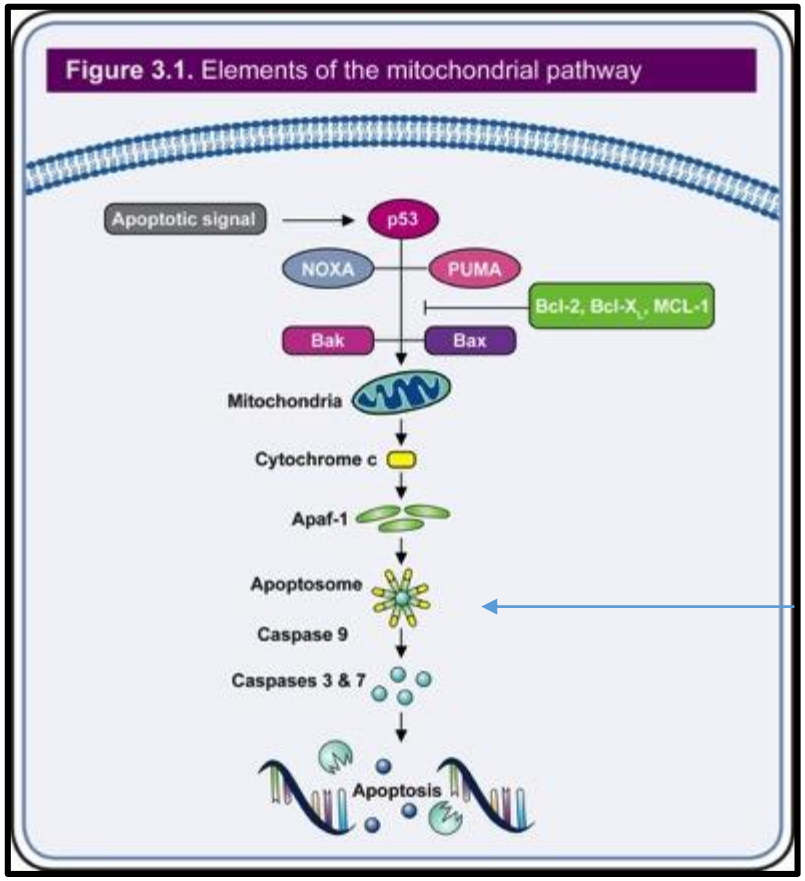
	Overexpression	Hypoexpression	Normoexpression
XBP1	**64.5%**	0%	35.5%
SP140	25.8%	3.2%	71%
TRIAP1/P53CSV	**90%**	0%	10%
RANBP2	**58%**	0%	42%
DDX5	**67.7%**	0%	32.3%
MAPKAPK2	**58%**	0%	42%
ZHFX1B	6.4%	25.8%	67.8%
LGALS1	32.2%	0%	67.8%
LSM5	45%	0%	55%
PIM2	25.8%	3.2%	71%

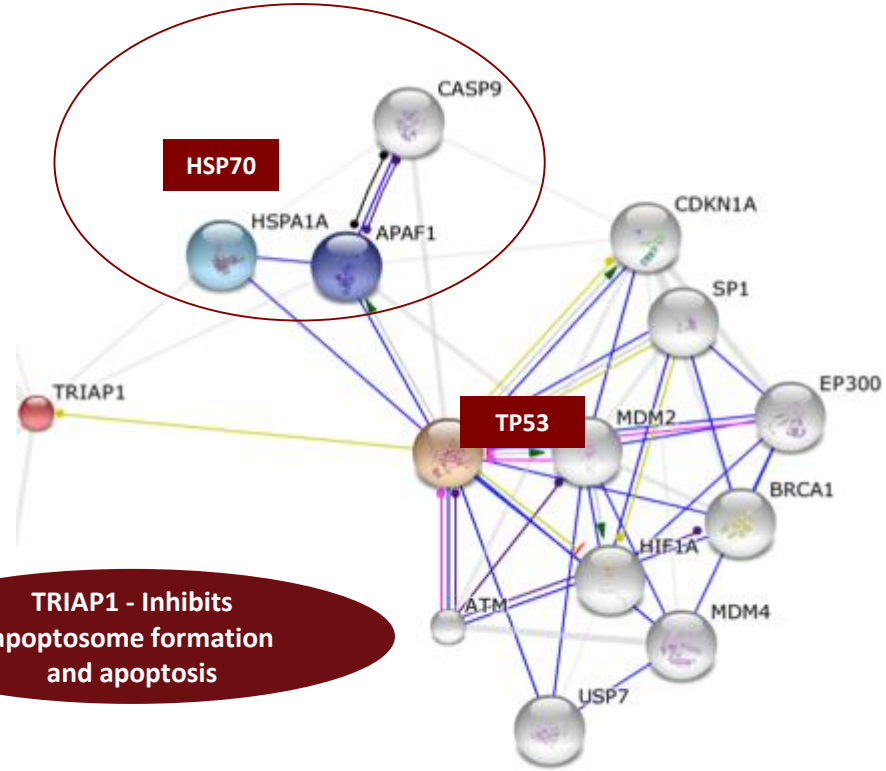
Genes** were considered **differentially expressed** in tumor samples when their expression levels showed at least a **4-fold increment or decrease in comparison to normal samples.

Felix et al, Cancer Letters, 2009

Guardian of cell cycle
TP53 Tumor supressor gene

TRIAP1 - TP53 regulated inhibitor of apoptosis

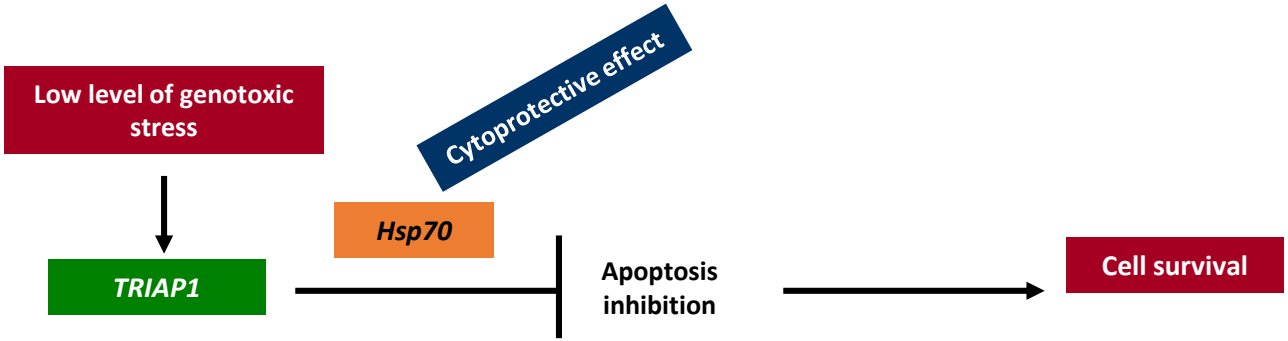




TRIAP1 - Inhibits apoptosome formation and apoptosis

http://www.biooncology.com/research-education/apoptosis/pathways
http://string-db.org/

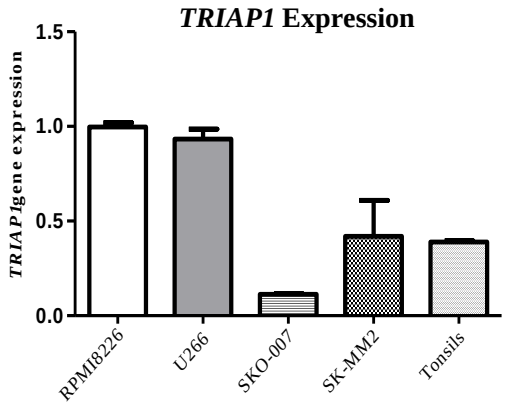
Normal Cells



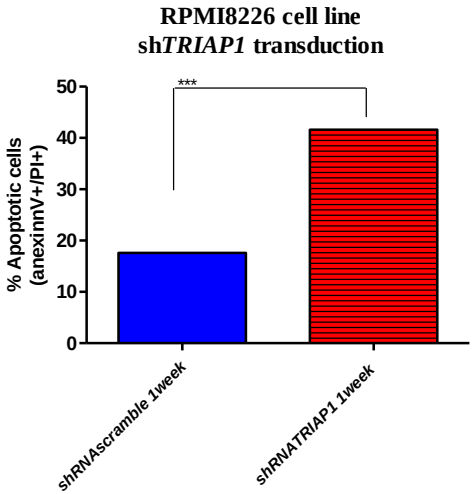
Cancer Cells

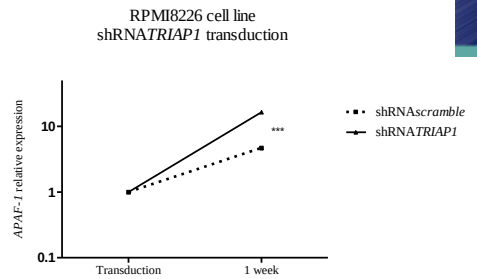
Alves, Felix, Vettore, Colleoni, http://atlasgeneticsoncology.org//Genes/TRIAP1ID44577ch12q24.html

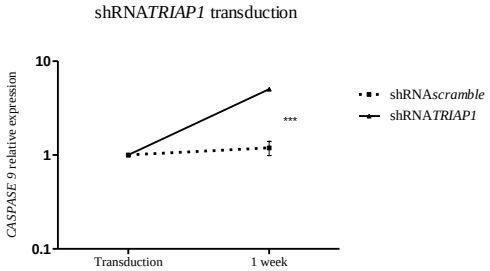
TP53 REGULATED INHIBITOR OF APOPTOSIS 1 (TRIAP1) STABLE SILENCING INCREASES LATE APOPTOSIS BY UPREGULATION OF CASPASE 9 *AND APAF1* IN RPMI8226 MULTIPLE MYELOMA CELL LINE



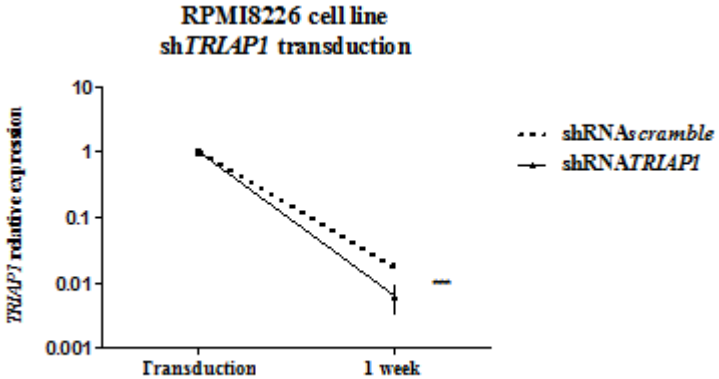
Problem
Validation in animal model



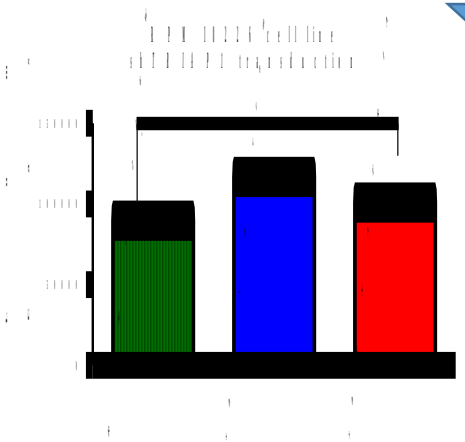


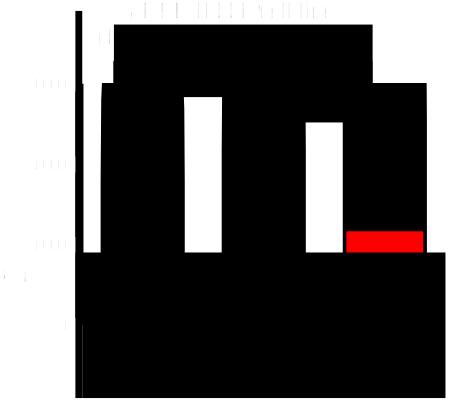


Stable silencing



No good antibody available for WB





U266 cell line: resistance to cell death after shRNA*TRIAP1* transduction

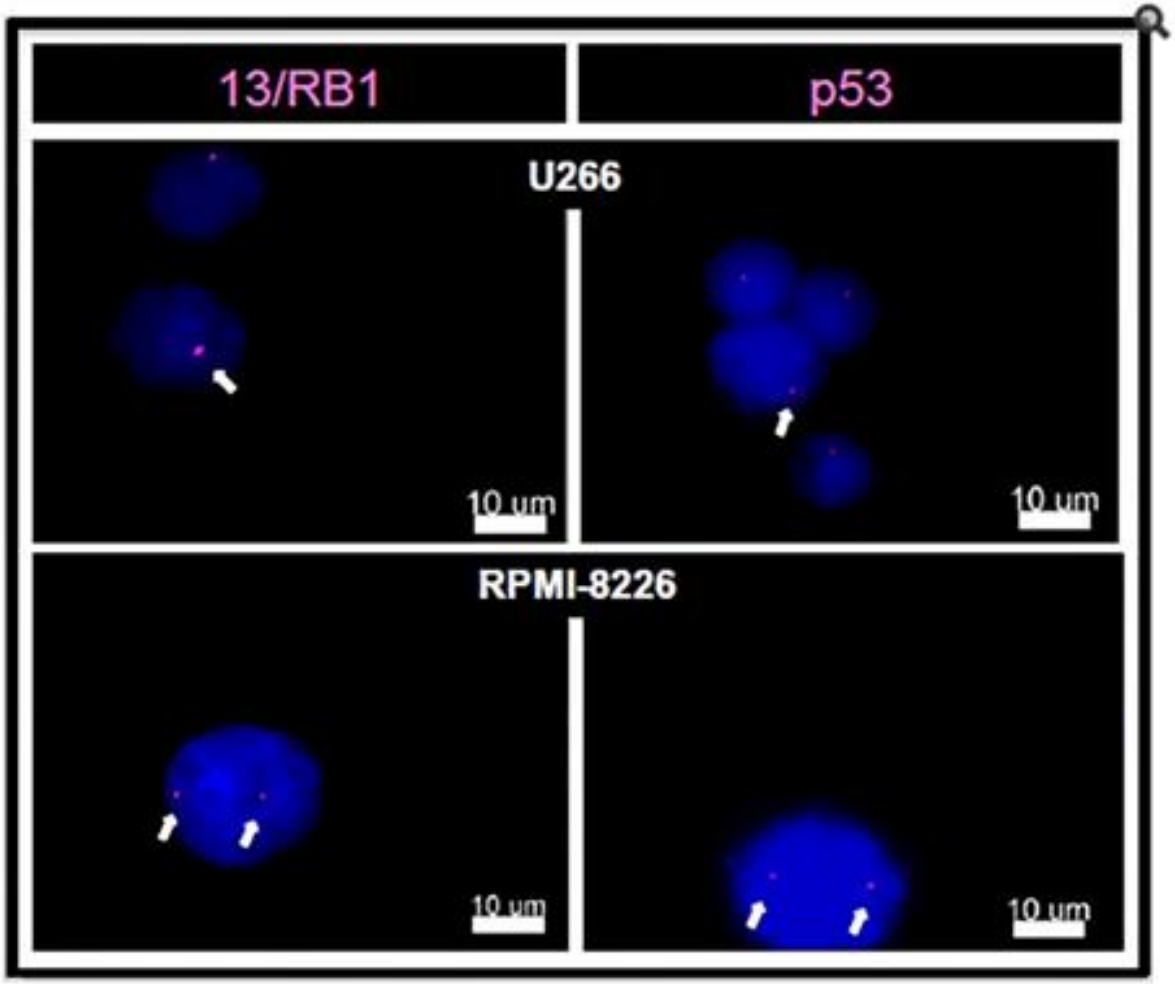
Fook-Alves et al , BBA Molecular Basis of Disease, 2016

Genes & Cancer

Genes Cancer. 2015 Nov; 6(11-12): 462–471. PMCID: PMC4701225

Multiple myeloma cell lines and primary tumors proteoma: protein biosynthesis and immune system as potential therapeutic targets

Rodrigo Carlini Fernando,[#1] Fabricio de Carvalho,[#1] Diego Robles Mazzotti,[2] Adriane Feijó Evangelista,[3] Walter Moisés Tobias Braga,[1] Maria de Lourdes Chauffaille,[1] Adriana Franco Paes Leme,[4] and Gisele Wally Braga Colleoni[1]



Cytogenetic analyses of MM cell lines (U266, RPMI-8226) by FISH technique

U266 cell line has **t(11;14)**, **E419X missense mutation on *RB1* gene, A161T missense mutation on *TP53* gene** and has **shown deletions of chromosome 13 and 17p**, which involve, respectively, *RB1* and *TP53* genes http://www.keatslab.org/myeloma-cell-lines/common-genetics

RPMI8226 cell line presents the t(14;16) translocation, ***TP53* point mutation** [located in exon 7 (c.853G>A) resulting in a *TP53* missense mutation (p.E285K)] and **no Rb1 or *TP53* deletion by FISH**. http://www.keatslab.org/myeloma-cell-lines/common-genetics

U266 = del 13 + del 17p

RPMI8226= no 13 or 17p deletions

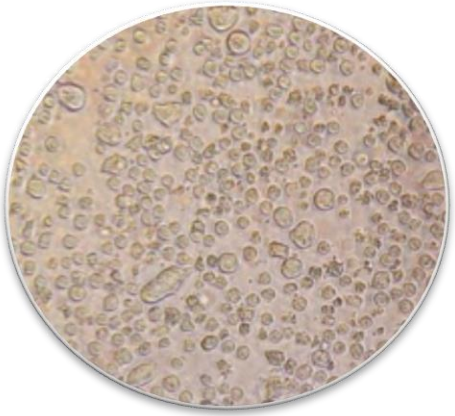
Fernando et al , Genes & Cancer, 2015

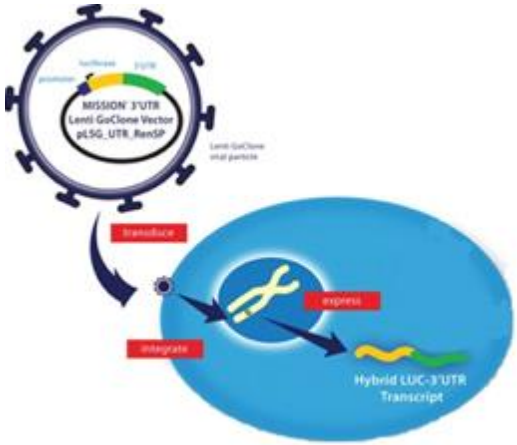
HEAT SHOCK PROTEIN 70 (HSP70) AS THERAPEUTIC TARGET IN MULTIPLE MYELOMA: *IN VITRO* AND *IN VIVO* ANALYSES

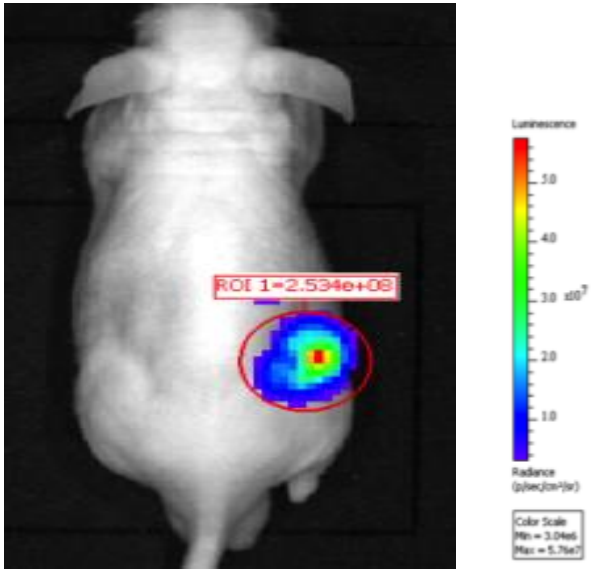
AIMS:

- ✓ Development of a xenograft model of bioluminescent cell lines in immunodeficient mice.
- ✓ To explore the role of the inhibition of HSP70 (VER155008), with or without the proteasome inhibitor bortezomib, *in vitro* and *in vivo*.

RPMI8226 cell line → **Transduction with vetor containing luciferase gene** → **Bioluminescent RPMI8226-LUC-PURO cell line xenotrasplanted in immunodeficient NOS/SCID mice**





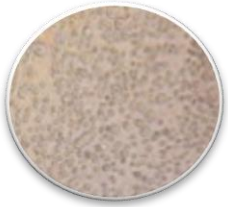


http://www.springerimages.com/Images/Biomedicine/1-10.1007_s10585-007-9083-9-1

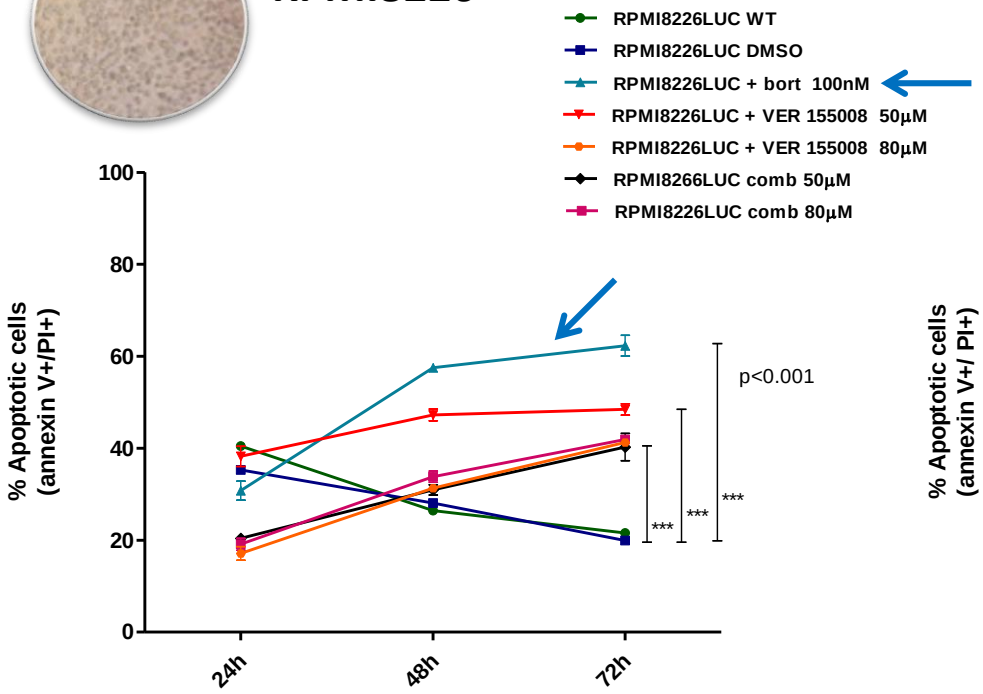
Eugenio et al, 2016, unpublished data

HEAT SHOCK PROTEIN 70 (HSP70) AS THERAPEUTIC TARGET IN MULTIPLE MYELOMA: *IN VITRO* APOPTOSIS ANALYSES

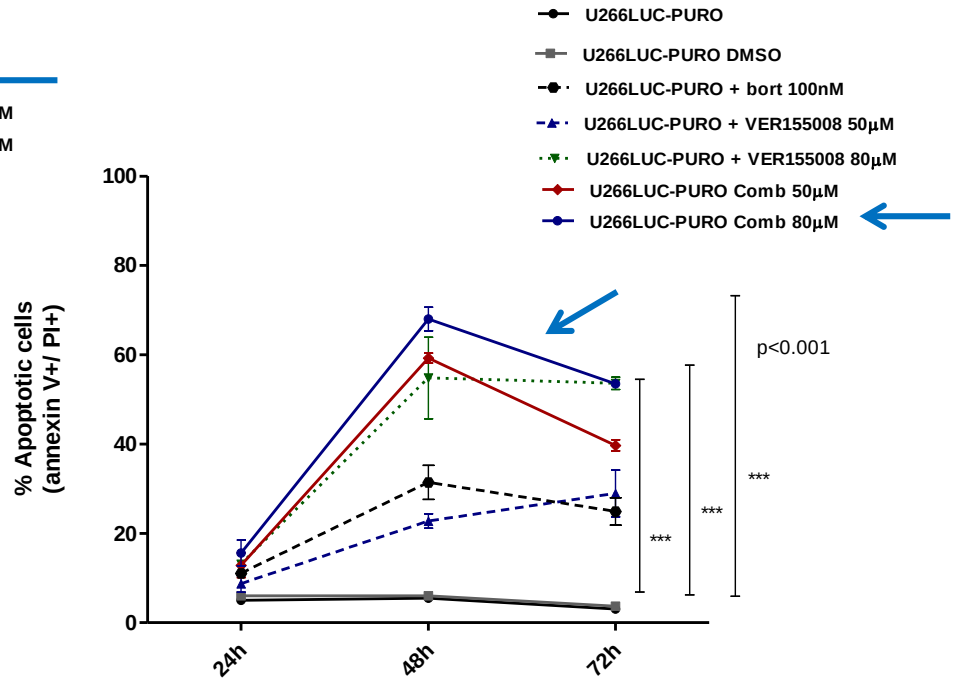
RPMI8226- LUC-PURO cell line



RPMI8226



U266



U266 Combo = >60% of late apoptosis induction after 48hs

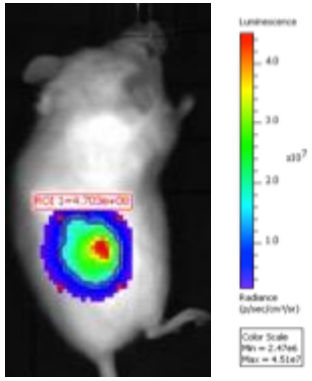
Bortezomib - Proteasome inhibitor
VER 155008 - HSP70 inhibitor

Eugenio et al, 2016, unpublished data

HEAT SHOCK PROTEIN 70 (HSP70) AS THERAPEUTIC TARGET IN MULTIPLE MYELOMA: *IN VIVO* ANALYSES

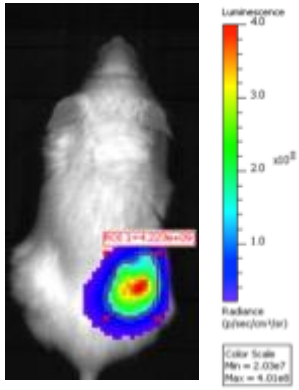
RPMI8226-LUC-PURO cell line

VER15508



ROI = 4.703e+08 p/s

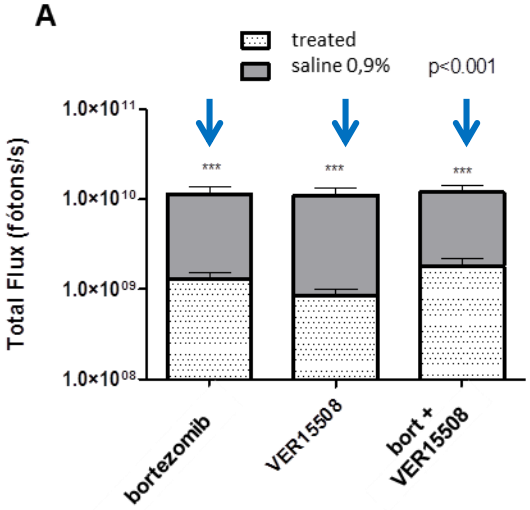
SALINE 0,9%

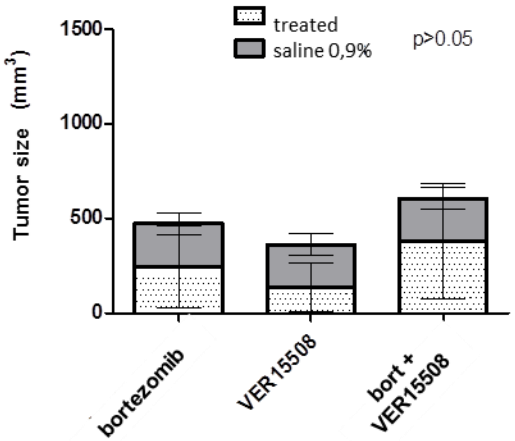


ROI = 4.223e+09 p/s

NOD.Cg-Prkdc^{scid}Il2rg^{tm1Wjl}/SzJ **mice treated with VER155008 (40mg/kg)** ***versus*** **mice treated with saline sodium chloride injection after one week**

Emission of bioluminescence of mice treated with bortezomib , VER155008 and combination *versus* untreated mice after one week of treatment



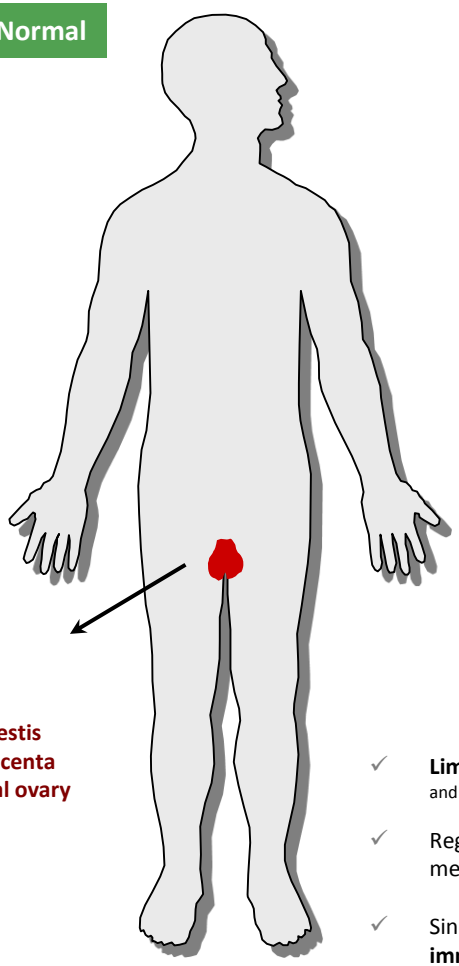


Next step - U266 mice model

Eugenio et al, 2016, unpublished data

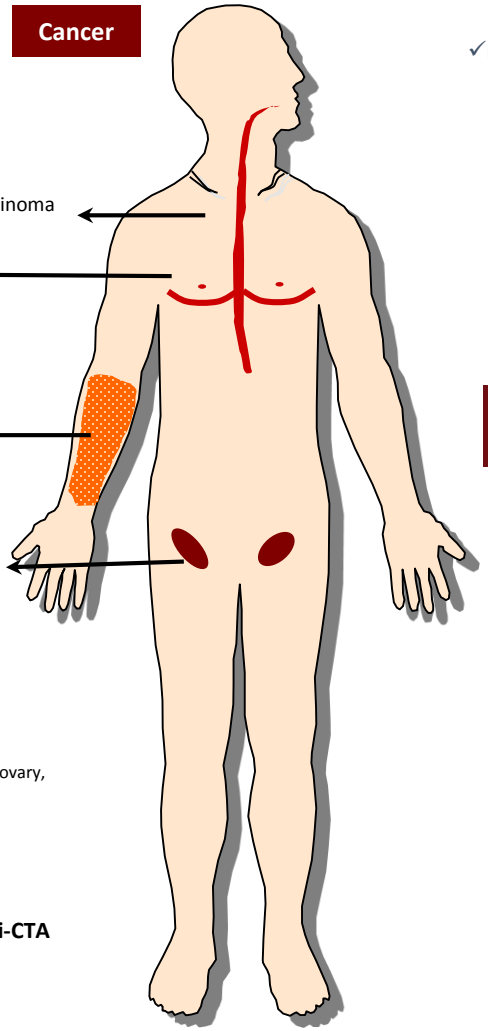
Cancer/Testis Antigens (CTAs)

Normal



Testis
Placenta
Fetal ovary

Cancer



Esophagus carcinoma

Breast cancer

Melanoma

"MAGE"

Ovary Carcinoma

- ✓ **Limited expression in somatic tissues** (testis, fetal ovary, and placental cells)
- ✓ Regulation of CTAs expression by epigenetic mechanisms (methylation)
- ✓ Since gonads are **immune privileged organs**, **anti-CTA immune response** could be **tumor-specific**

✓**Highly immunogenic** protein inducing:

✓specific **cellular immune** response

✓specific **humoral immune** response

CTAs are attractive targets for immunotherapy in cancer

Adapted, Albert & Darnell, 2004

Article

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Abstract | Introduction | Results | Discussion | Abbreviations | Acknowledgements | References | Materials and methods | Contact

Cancer Immunity, Vol. 8, p. 2 (1 February 2008) Submitted: 5 September 2007. Accepted: 8 October 2007.

Prognostic impact of cancer/testis antigen expression in advanced stage multiple myeloma patients

Valéria C. C. Andrade[1], André L. Vettore[2,3], Roberta S. Felix[1], Manuella S. S. Almeida[1], Fabrício de Carvalho[1], José Salvador R. de Oliveira[1], Maria de Lourdes Lopes Ferrari Chauffaille[1], Adagmar Andriolo[4], Otavia L. Caballero[5], Marco Antonio Zago[6] and Gisele W. B. Colleoni[1]

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[2]Ludwig Institute for Cancer Research, São Paulo Branch, Brazil
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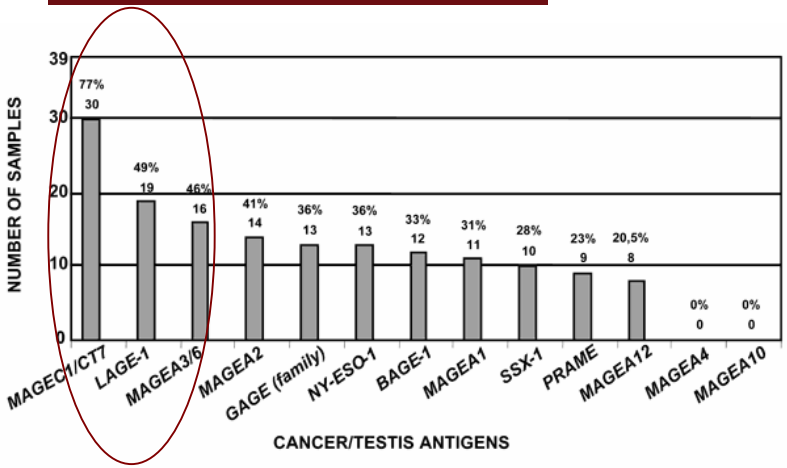
[5]Ludwig Institute for Cancer Research, New York Branch, USA
[6]Faculdade de Medicina de Ribeirão Preto/USP, Brazil

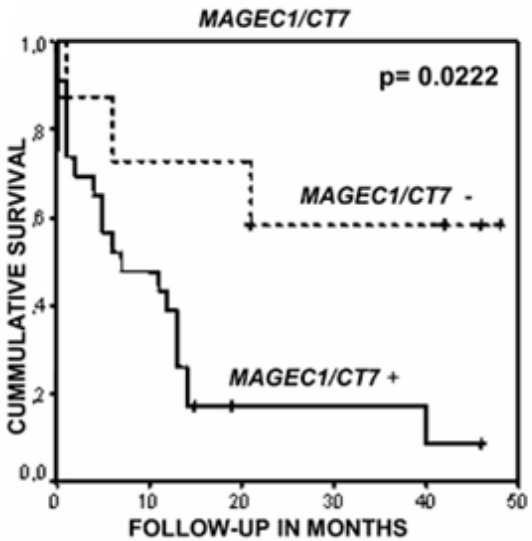
Communicated by: LJ Old

Keywords: human, multiple myeloma, CT antigens, mRNA, tissue distribution, prognosis

3 CTAs expressed in 85% of newly diagnosed MM



Number and percentage of MM patients with positive expression of the 13 CT antigens analyzed.



***MAGE C1/CT7* – independent prognostic fator**

Andrade et al, Cancer Immunity, 2008

Clinical and Developmental Immunology
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Clin Dev Immunol. 2012; 2012: 257695.
Published online 2012 Mar 11. doi: 10.1155/2012/257695
PMCID: PMC3310219

Cancer/Testis Antigen MAGE-C1/CT7: New Target for Multiple Myeloma Therapy

Fabricio de Carvalho,[1,*] André L. Vettore,[2] and Gisele W. B. Colleoni[1]

Author information ▶ Article notes ▶ Copyright and License information ▶

What have we learned about MAGE-C1/CT7 in MM ?

- ✓ **Frequently expresed in MM (~70% cases)**
- ✓ **Nuclear and cytoplasmic expression – no plasmatic membrane expression**
- ✓ **Sometimes focal tumor expession**
- ✓ **Low spontaneous humoral response**
- ✓ **Homology with *MAGE-C2/C10***
- ✓ **Independent prognostic factor in MM**

Carvalho et al, Clinical and Developmental Immunology, 2012

✓ ***Tumor antigens***

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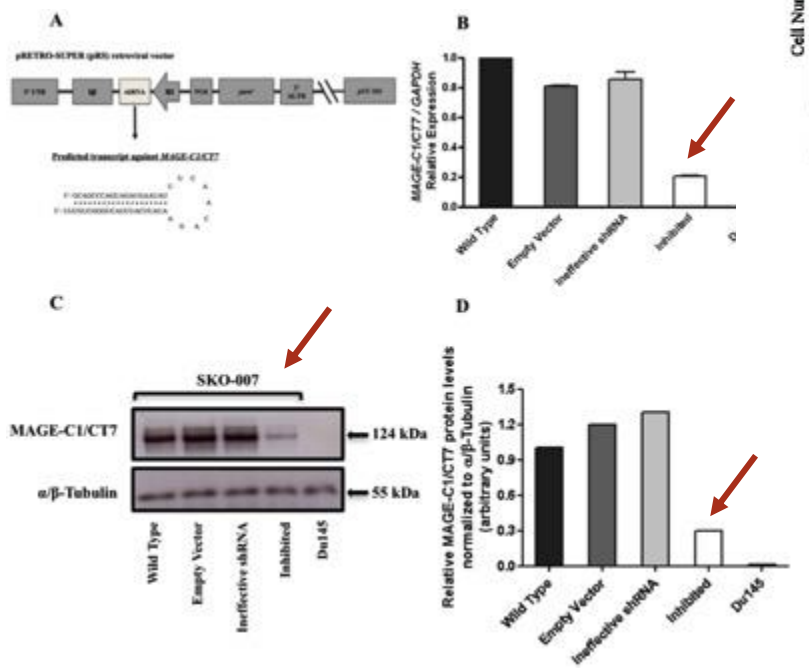
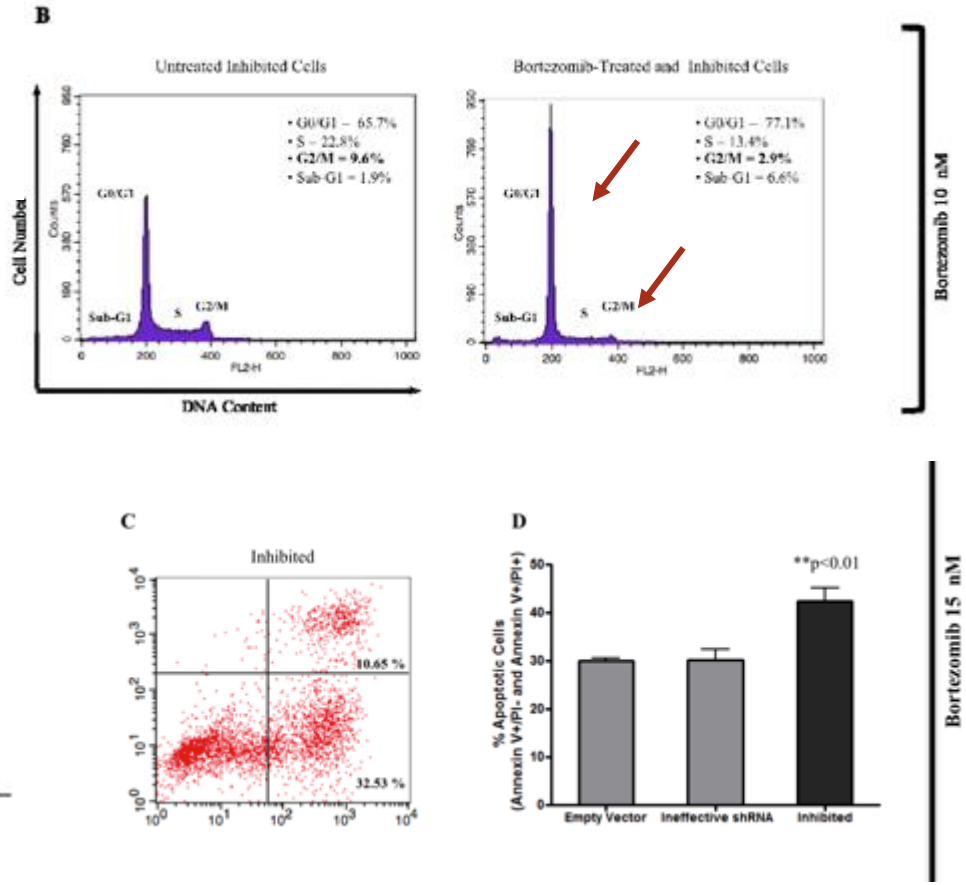
RESEARCH ARTICLE

Targeting MAGE-C1/CT7 Expression Increases Cell Sensitivity to the Proteasome Inhibitor Bortezomib in Multiple Myeloma Cell Lines

Fabricio de Carvalho, Erico T. Costa, Anamaria A. Camargo, Juliana C. Gregorio, Cibele Masotti, Valeria C.C. Andrade, Bryan E. Strauss, Otavia L. Caballero, Djordje Atanackovic, Gisele W.B. Colleoni

Published: November 16, 2011 • DOI: 10.1371/journal.pone.0027707





shRNA*MAGEC1/CT7*

shRNA*MAGEC1/CT7* + bortezomib

Carvalho et al, Plos One, 2011

Article

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Abstract | Introduction | Results | Discussion | Abbreviations | Acknowledgements | References | Materials and methods | Contact

Cancer Immunity, Vol. 8, p. 2 (1 February 2008) Submitted: 5 September 2007. Accepted: 8 October 2007.

Prognostic impact of cancer/testis antigen expression in advanced stage multiple myeloma patients

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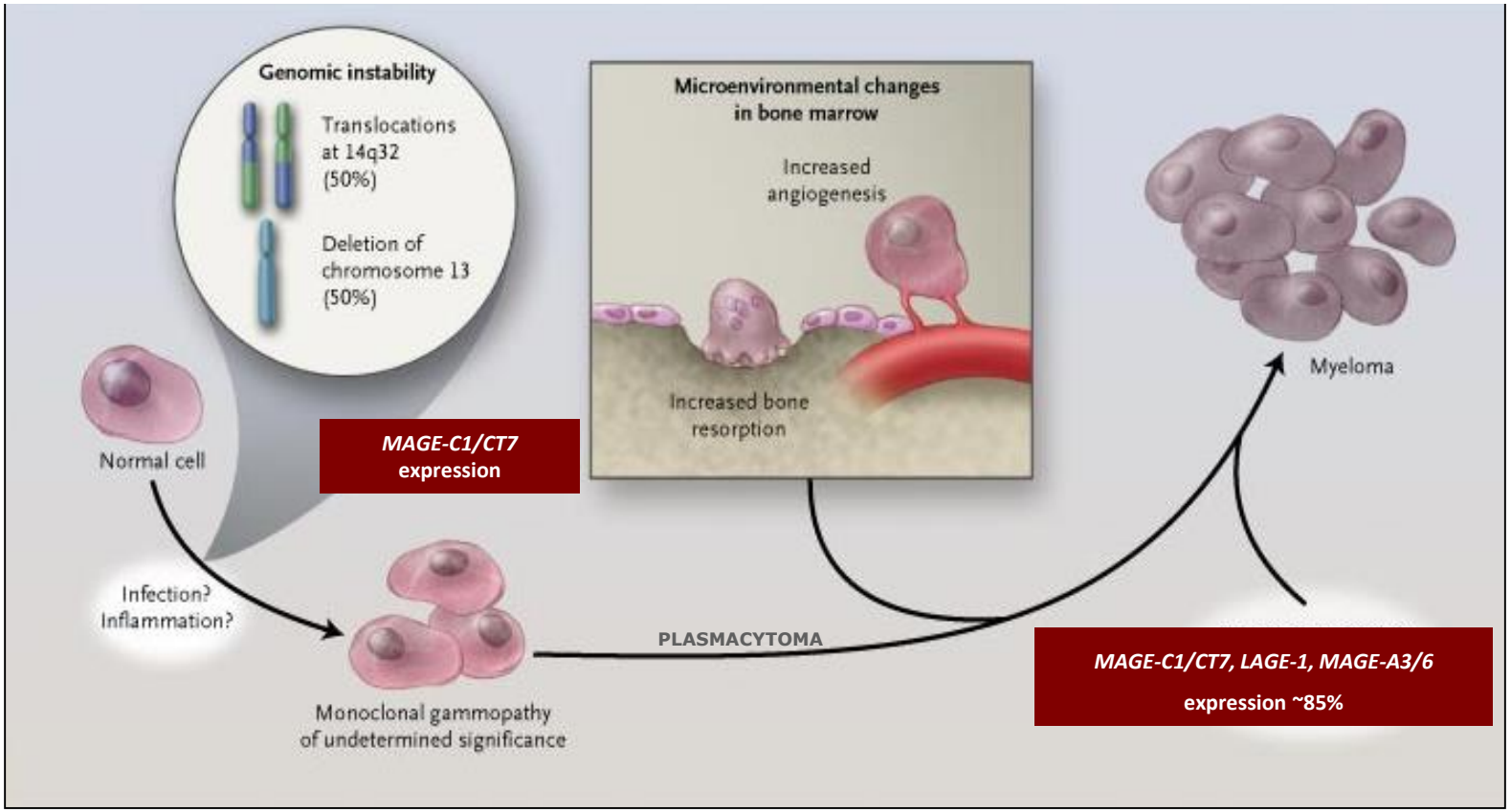
Communicated by: LJ Old

Keywords: human, multiple myeloma, CT antigens, mRNA, tissue distribution, prognosis

***MAGEC1/CT7* has biological role in early stages of MM and may contribute to plasma-cell proliferation**



Are they possibly good targets for polyvalent vaccines?

Andrade et al, Cancer Immunity, 2008

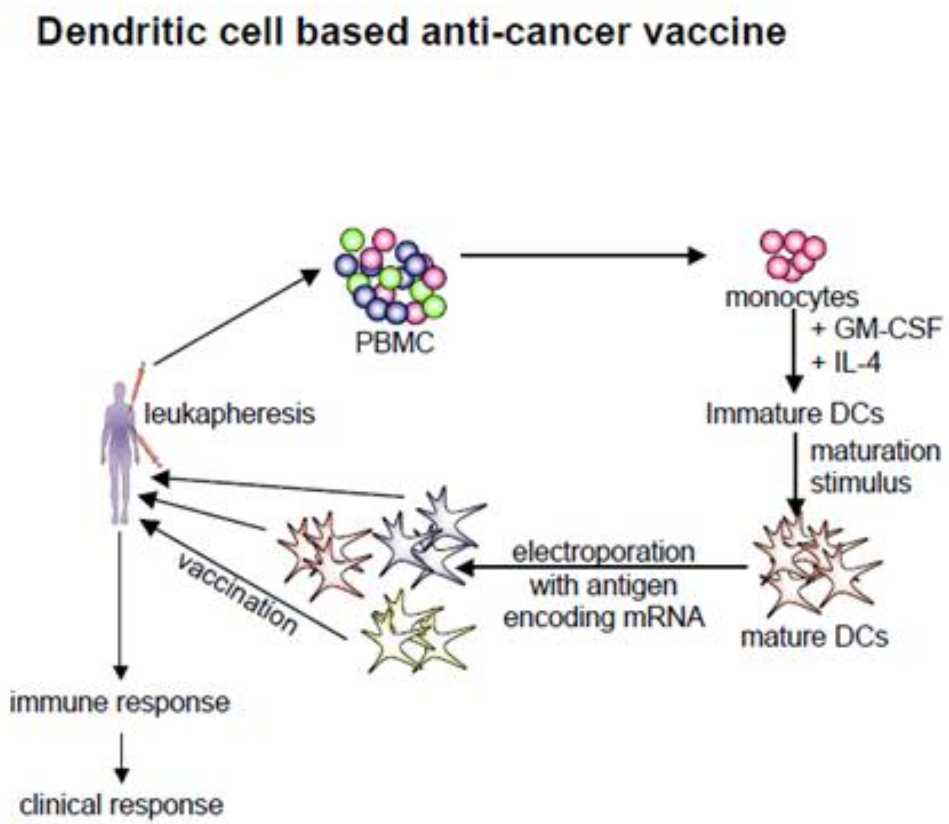
Vrije Universiteit Brussel

Universitair Ziekenhuis Brussel

✓ *Tumor antigens*
✓ *Dendritic cells*

Phase I/II clinical trial to investigate vaccination with CTA-loaded DCs in MM patients on LEN maintenance therapy

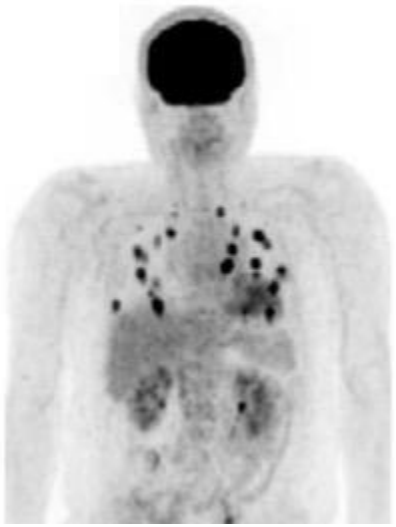
- **VUB proposed to vaccinate MM patients on *LEN maintenance therapy with DCs matured* by electroporation with TriMix and co-electroporated with mRNA encoding the CTAs *MAGE-C1* and *MAGE-A3***

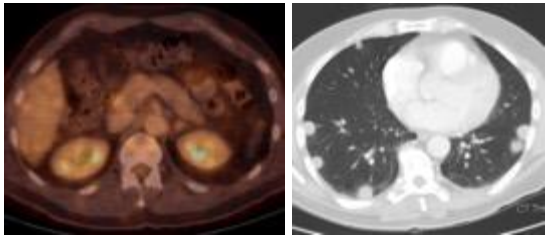


Courtesy Prof. Kris Thielemans, VUB

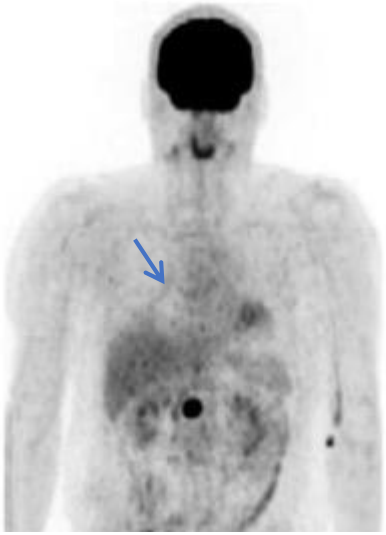
Ilustration – TriMixDC-MEL + Ipi

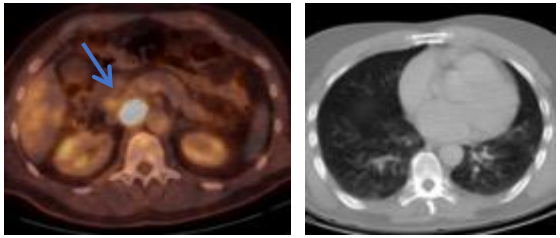
58y male
Stage IV-M1c
BRAFwt
Refractory to temozolomide



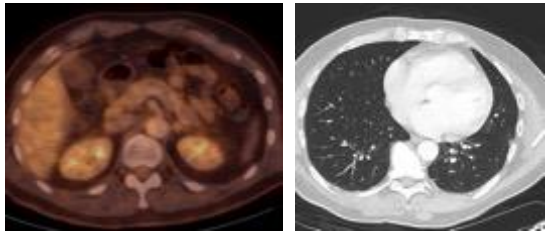


6 Jul 2011, Baseline





18 Oct 2011, +14 Weeks



16 Jan 2012, +27 Weeks

Courtesy Prof. Kris Thielemans, VUB

✓ *Tumor antigens*
✓ *Dendritic cells*

ClinicalTrials.gov
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Trial record **2 of 4** for: myeloma vaccine MAGE
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Study of MAGE-A3 and NY-ESO-1 Immunotherapy in Combo With DTPACE Chemo and Auto Transplantation in Multiple Myeloma

This study has been completed.

Sponsor:
University of Arkansas

Information provided by (Responsible Party):
University of Arkansas

ClinicalTrials.gov Identifier:
NCT00090493

First received: August 26, 2004
Last updated: May 16, 2013
Last verified: May 2013
History of Changes

ClinicalTrials.gov
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Trial record **4 of 4** for: myeloma vaccine MAGE
◂ Previous Study | Return to List | Next Study

MAGE-A3 Protein + AS15 as Consolidation for Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation

This study is ongoing, but not recruiting participants.

Sponsor:
Ludwig Institute for Cancer Research

Collaborator:
GlaxoSmithKline

Information provided by (Responsible Party):
Ludwig Institute for Cancer Research

ClinicalTrials.gov Identifier:
NCT01380145

First received: June 20, 2011
Last updated: April 29, 2015
Last verified: April 2015
History of Changes

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Trial record **22 of 65** for: myeloma vaccine
◂ Previous Study | Return to List | Next Study ▸

CT7, MAGE-A3, and WT1 mRNA-electroporated Autologous Langerhans-type Dendritic Cells as Consolidation for Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation

This study is currently recruiting participants. (see Contacts and Locations)

Verified September 2015 by Memorial Sloan Kettering Cancer Center

Sponsor:
Memorial Sloan Kettering Cancer Center

Collaborator:
Rockefeller University

Information provided by (Responsible Party):
Memorial Sloan Kettering Cancer Center

ClinicalTrials.gov Identifier:
NCT01995708

First received: November 20, 2013
Last updated: September 10, 2015
Last verified: September 2015
History of Changes

MSKCC - Autologous dendritic cell vaccine after autologous stem cell transplant

✓ *T-cells*

FOXP3 and *CTLA4* Overexpression in Multiple Myeloma Bone Marrow as a Sign of Accumulation of CD4+ T Regulatory Cells

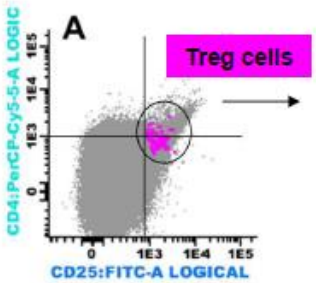
Original Article
Cancer Immunology, Immunotherapy
November 2014, Volume 63, Issue 11, pp 1189-1197

First online: 07 August 2014
Open Access

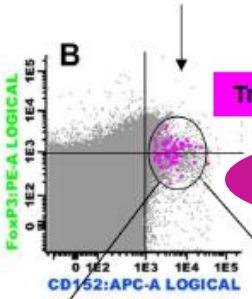
FOXP3 and *CTLA4* overexpression in multiple myeloma bone marrow as a sign of accumulation of CD4+ T regulatory cells

Walter Moises Tobias Braga, Bruna Raphaell da Silva, Ana Carolina de Carvalho, Yumi H. Maekawa, Adriana Bruscato Bortoluzzo, Edgar Gil Rizzatti, Djordje Atanackovic, Gisele Wally Braga Colleoni

Article Metrics
Citations 5
Social Mentions 3



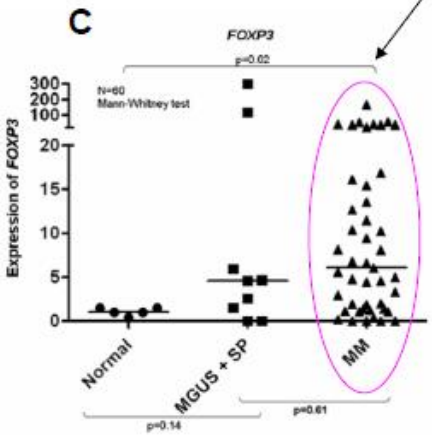
Flow cytometry showing in pink CD4+CD25high population in MM bone marrow aspirate sample

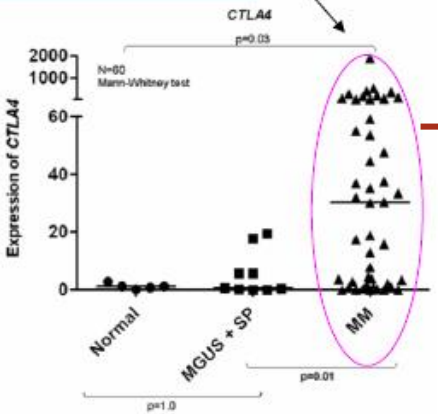


Flow cytometry showing in pink FOXP3+CD152/CTLA4+ population in MM bone marrow aspirate sample

FOXP3+/CTLA4+

FOXP3 and *CTLA4* gene expression by qPCR in normal, MGUS/solitary Plasmacytoma and MM bone marrow aspirates





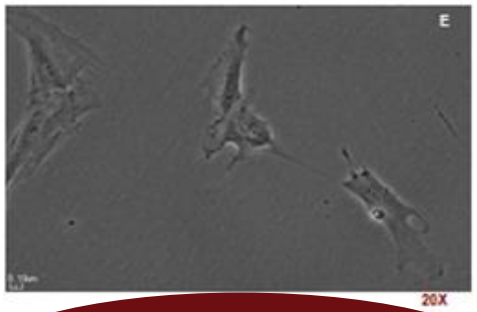
Nivolumab (anti-PD-1 antibody) and ipilimumab (anti-CTLA-4) antibody, are in a phase I trial testing in blood cancers, including multiple myeloma (NCT01592370)

Braga et al, Clinical and Developmental Immunology, 2014

IMMUNOPHETOYPIC AND FUNCTIONAL CHARACTERIZATION AND GENE EXPRESSION PROFILING OF MULTIPLE MYELOMA PATIENTS AND HEALTHY INDIVIDUALS BONE MARROW STROMAL CELLS

MM Cases
N = 20

Newly diagnosed and untreated multiple myeloma patients



Early death in cell culture without malignant plasma cells support

Bone marrow aspiration

Bone marrow stromal cells isolation and expansion

Immunophenotypic characterization by flow cytometry

RNA extraction and gene expression profling by microarray

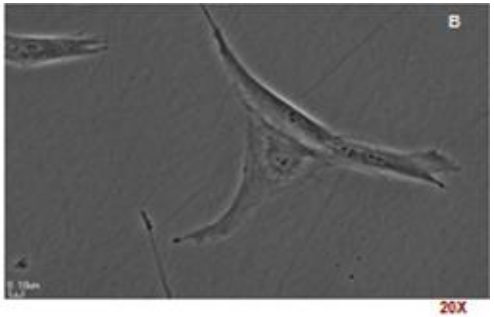
GeneChip® Human Exon 1.0 ST Array (Affymetrix)
4 cases vs. 4 controls (both in triplicates)

Bionformatics analysis and candidate genes selection

Protein Expression Validation

Healthy Controls
N = 10

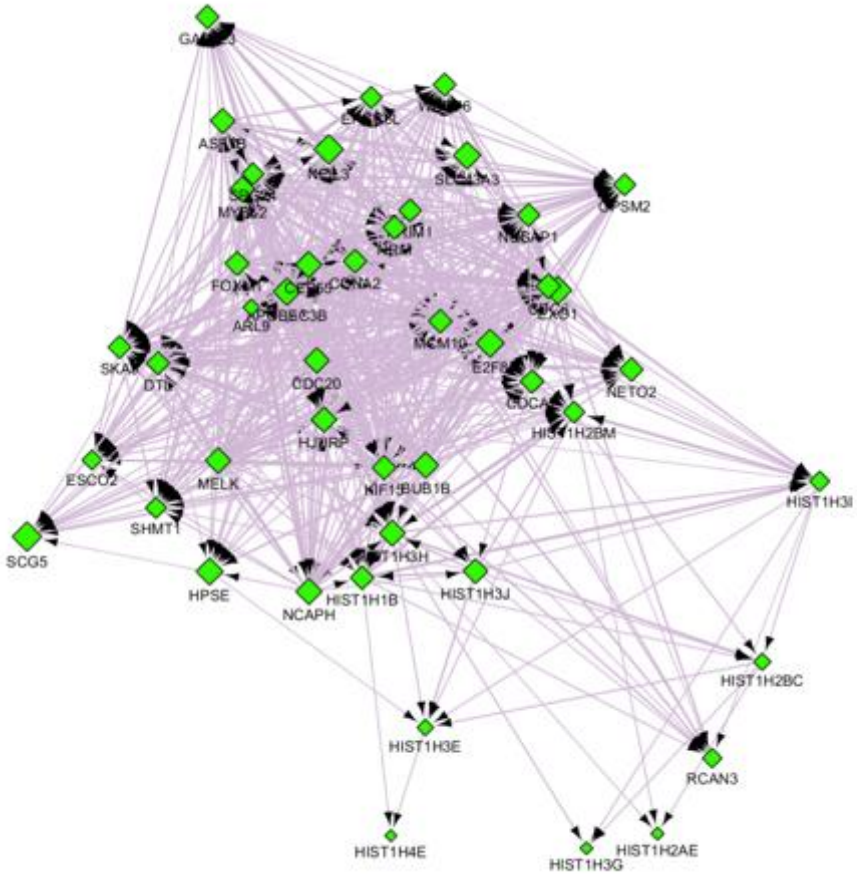
Healthy bone marrow donors for allogeneic transplantation



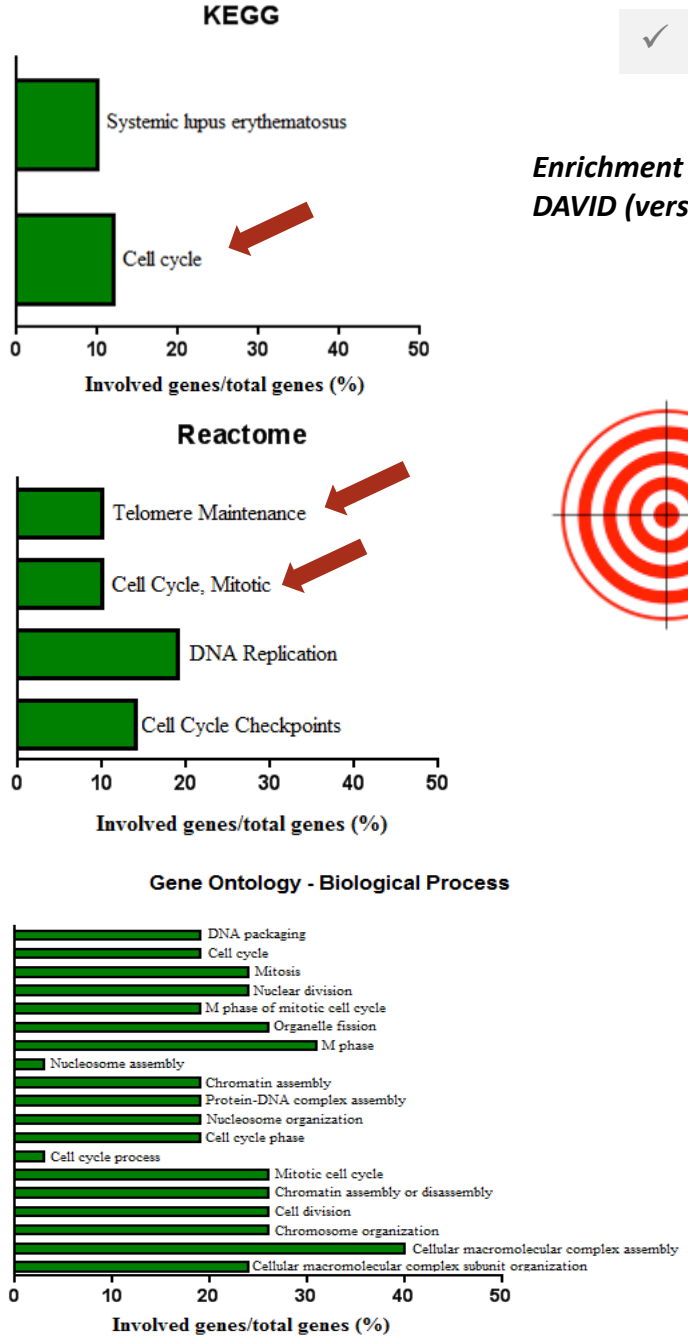
Fernando, 2016, unpublished data

✓ BMSC

Network analysis of differentially expressed genes in BMSCs – Cytoscape (version 3.3.0)

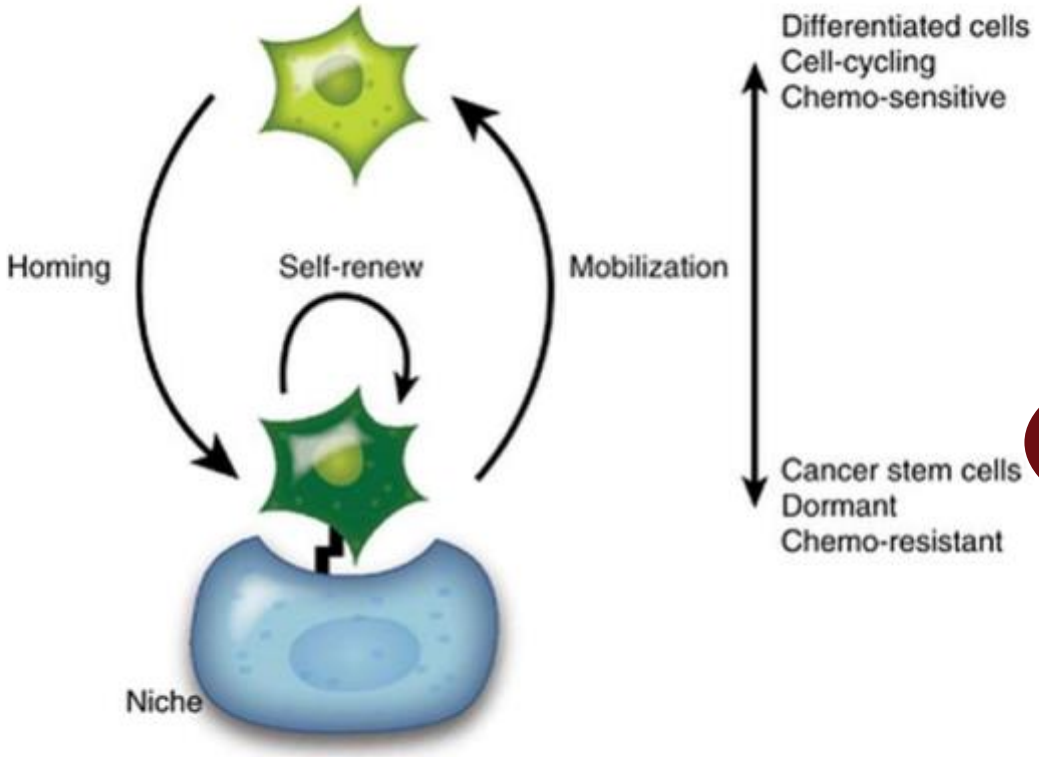


Enrichment analysis DAVID (version 6.7)



Fernando, 2016, unpublished data

Cancer Stem Cell



MM relapses despite:
Immunomodualtory drugs
Proteasome inhibitors
Autologous transplant

www.nature.com

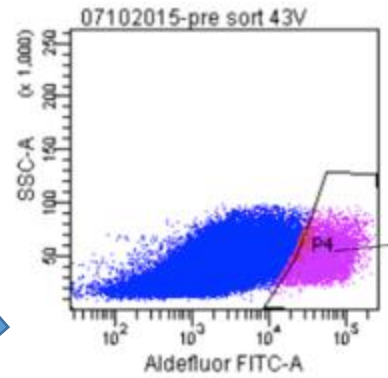
MM-CSCs: controversy about the existence and cell phenotype

Boucher *et al*, 2012 - ALDH+/CD19+/CD34+/ CD138-
Matsui *et al*, 2008 - ALDH+/CD20+/CD27+/CD34-/CD138-

ISOLATION AND CHARACTERIZATION OF CANCER STEM CELLS FROM BONE MARROW SAMPLES OF NEWLY DIAGNOSED PATIENTS WITH MYELOMA

Pilot study: FACS Aria analysis in MGUS case

- Aldefluor™

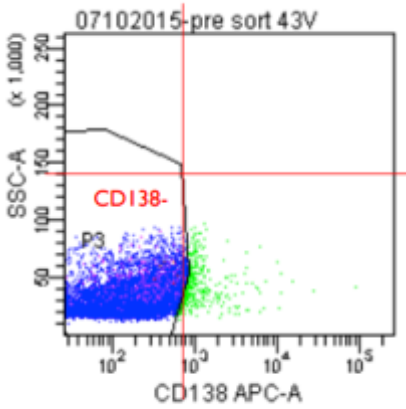


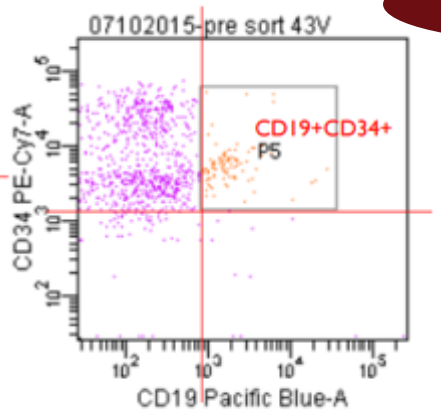
ALDH: stemness marker

ALDH+

FACS ARIA cell sorting

RNA extraction





Possible MM-CSC

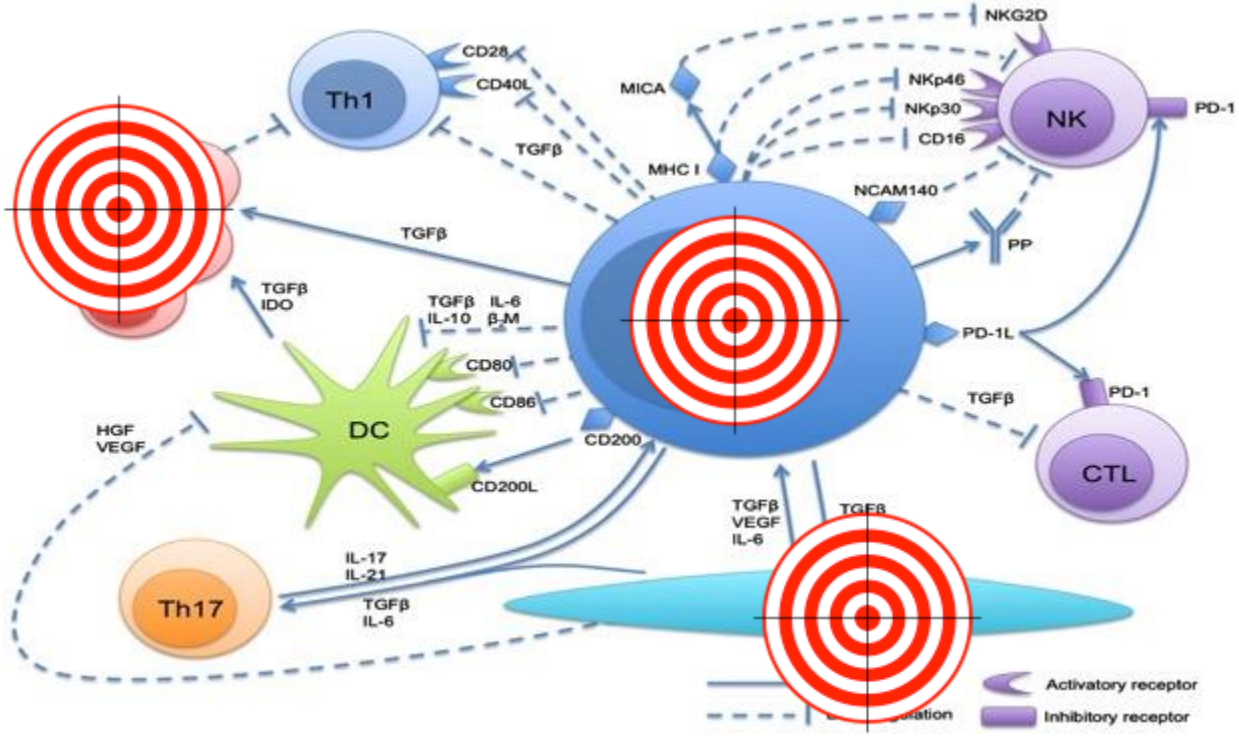
RT² Profiler™ PCR Array Human Cancer Stem Cells (Qiagen, Hilden , Germany) - 84 genes related to CSCs

The genes are envolved in various processes such as cell proliferation , self-renewal, asymmetric division, cell migration and signal transduction, among which are: *NANOG, Oct4, SOX2 , ALDH1A1 , CD34* stemness-related genes

Fook-Alves and Dantonio, 2016, unpublished data

5 Players in Multiple Myeloma

- ✓ *Tumor proteins/antigens*
- ✓ *Dendritic cells*
- ✓ *T-cells*
- ✓ *BMSC* (bone marrow stromal cells)
- ✓ *Cancer stem cells*



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