# Cytokine pathways: which one to target?

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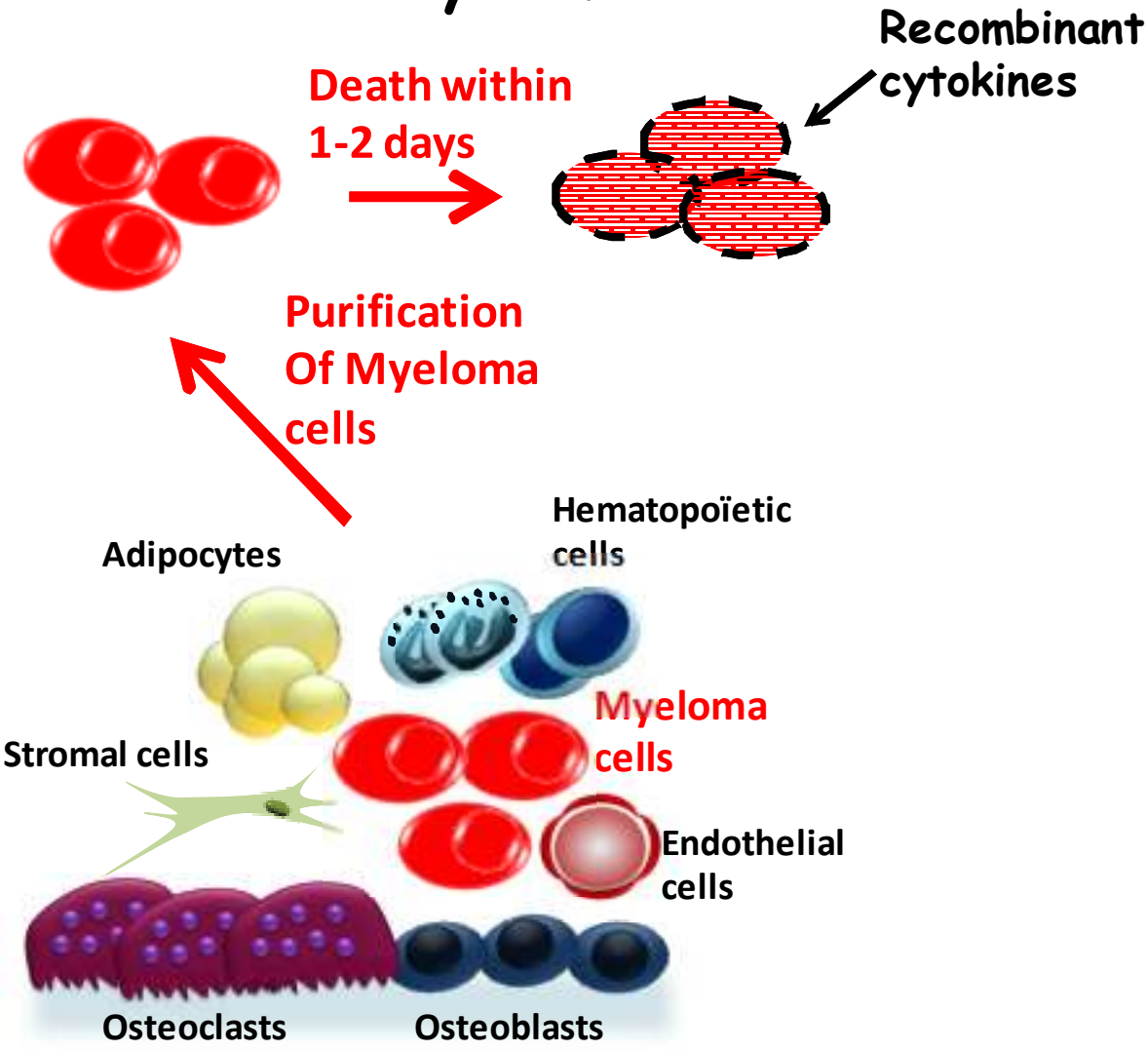
No conflict of interest

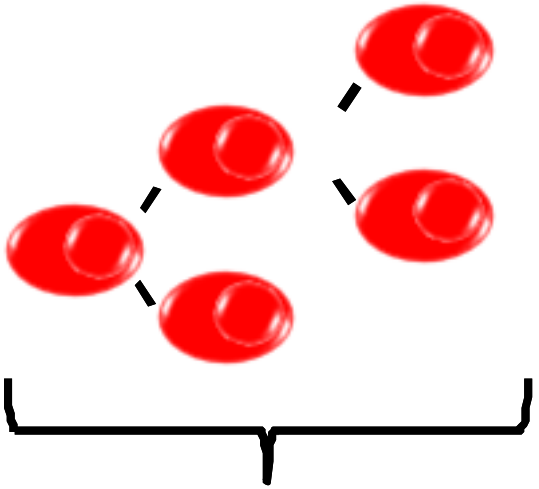
# Primary Myeloma cells of patients with intramedullary Myeloma are dependent on the environment for their survival

## Patients with intramedullary Myeloma




## Patients with extramedullary Myeloma

In vitro growing cell lines can be obtained



IGF-1, IL-6, IL-21, BAFF/APRIL, IFNα, IL-10, HGF, EGF, VEGF, Jagged/Notch

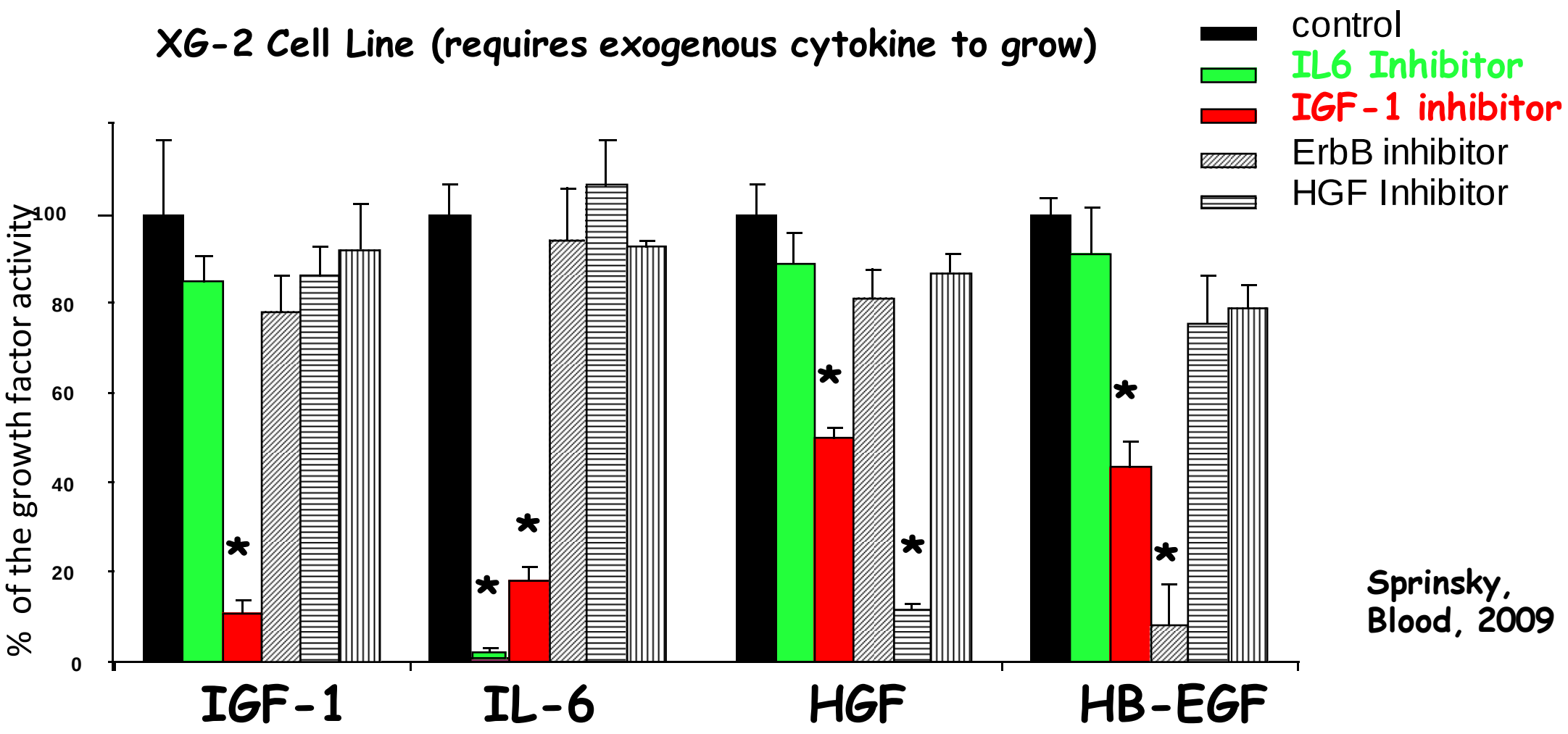
# Hierarchy of myeloma cell growth factors using cell lines

1. IGF-1 is essential (particularly as an autocrine growth factor)
2. IL-6 is a major myeloma cell growth factor in all myeloma cell lines
3. HGF, and EGF members, are less important (1/3 and ¼ of cell lines)
4. APRIL, triggers the growth of ¼ of cell lines
5. Other growth factors: IL-21, IFNa, VEGF, Chemokines, Jagged, …

Sprynski, Blood, 2009

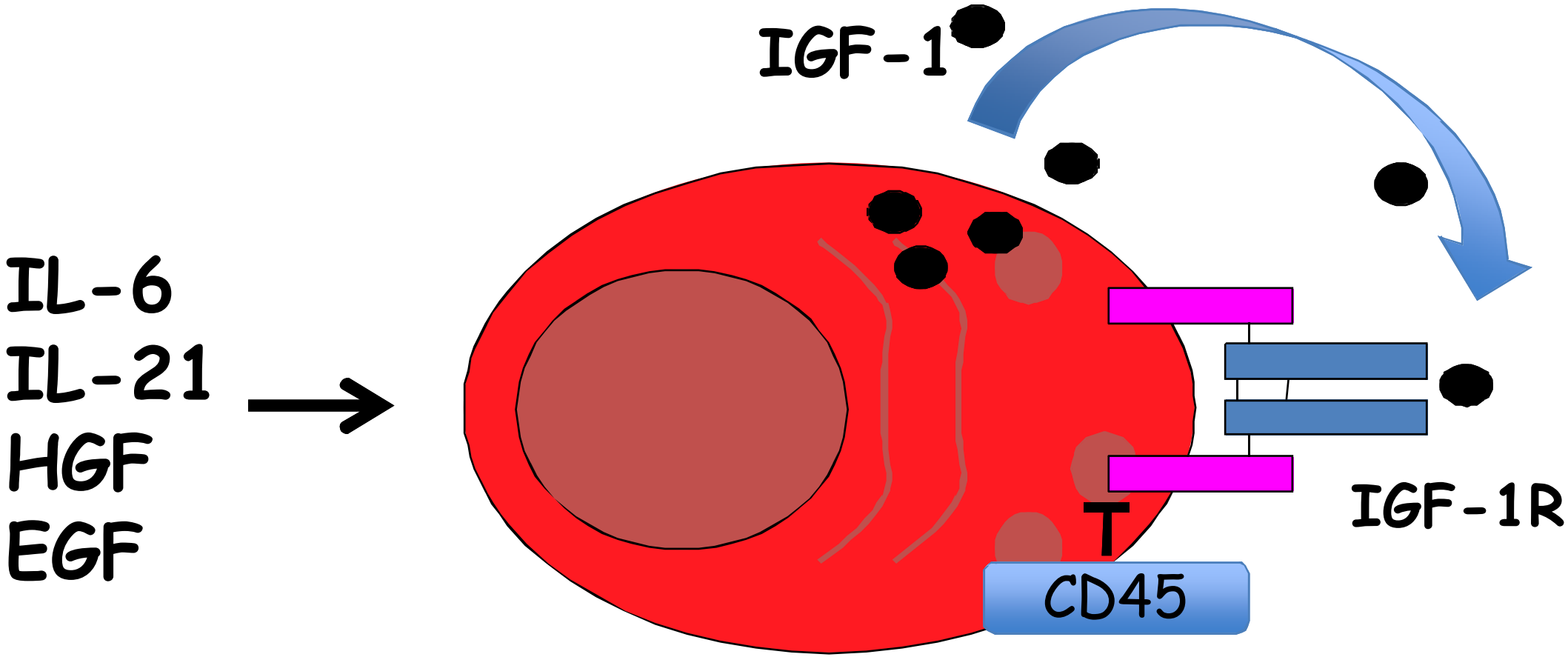
# IGF-1 is the main myeloma cell growth factor

(particularly as an autocrine growth factor), the other growth factors being partly dependent on an autocrine IGF-1/IGF-1R loop




Sprinsky, Blood, 2009

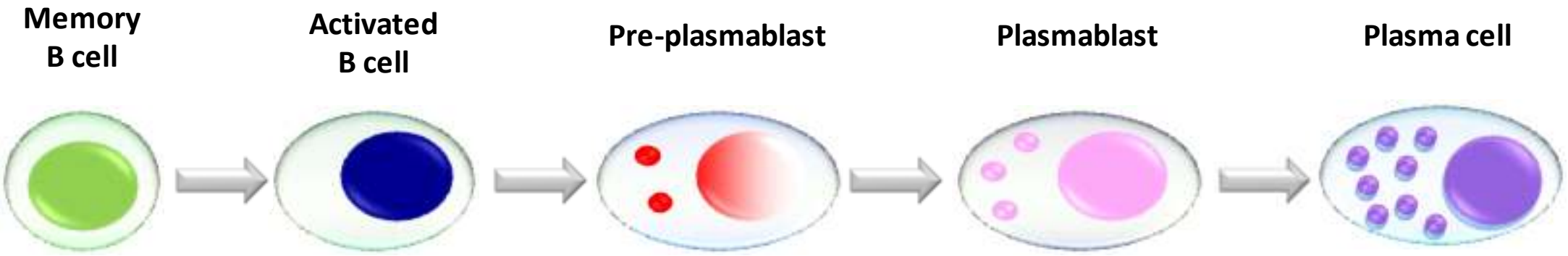
# IGF-1 is the main myeloma cell growth factor, the other growth factors being mostly dependent on an autocrine IGF-1/IGF-1R loop




Sprynski, Blood, 2009
Monoret, J Immunol, 2008

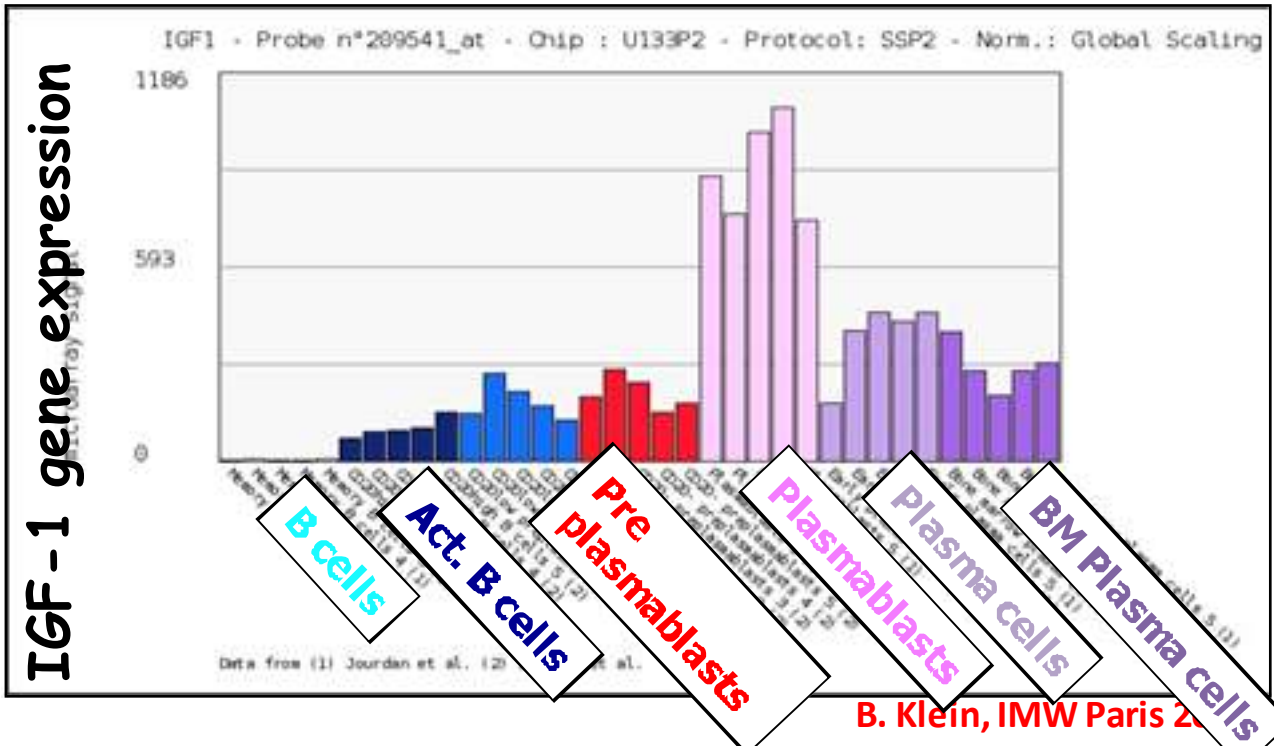
Amiot, J Immunol, 2006

# IGF-1R is not expressed by normal plasma cells



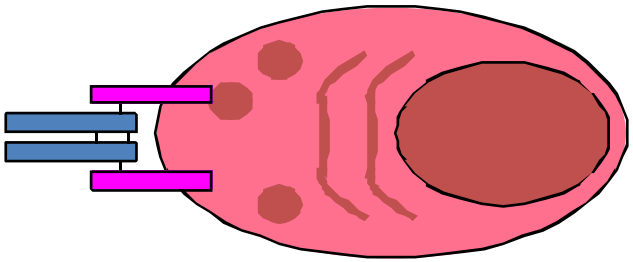

Jourdan, Blood, 2009

## IGF-1 is expressed by plasmablasts and plasma cells

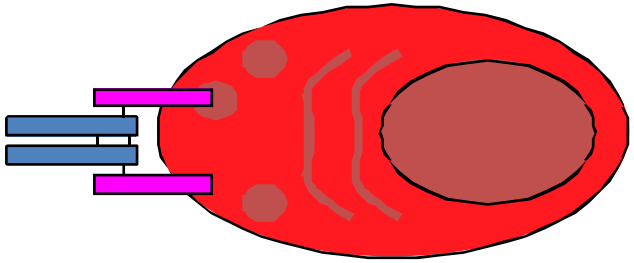



B. Klein, IMW Paris 2

# IGF-1R is aberrantly expressed in malignant plasma cells



Primary myeloma cells of
50% of the patients with newly diagnosed myeloma



Myeloma cell lines,
90% of cell lines

P53 loss or mutations

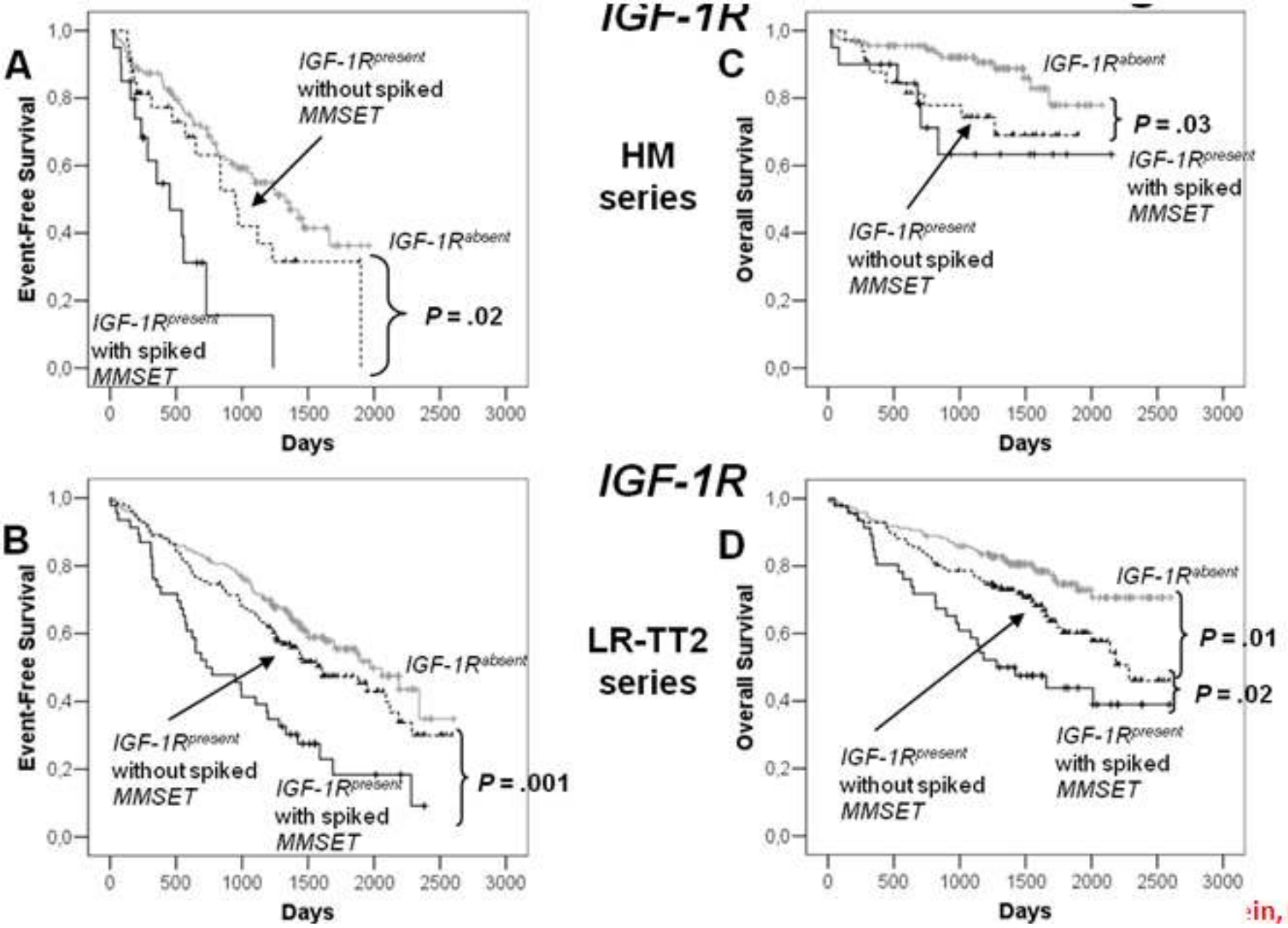
Downregulation of p53-inducible microRNAs 192, 194, and 215 (Pichiorri, 2010)

↗ IGF-1R

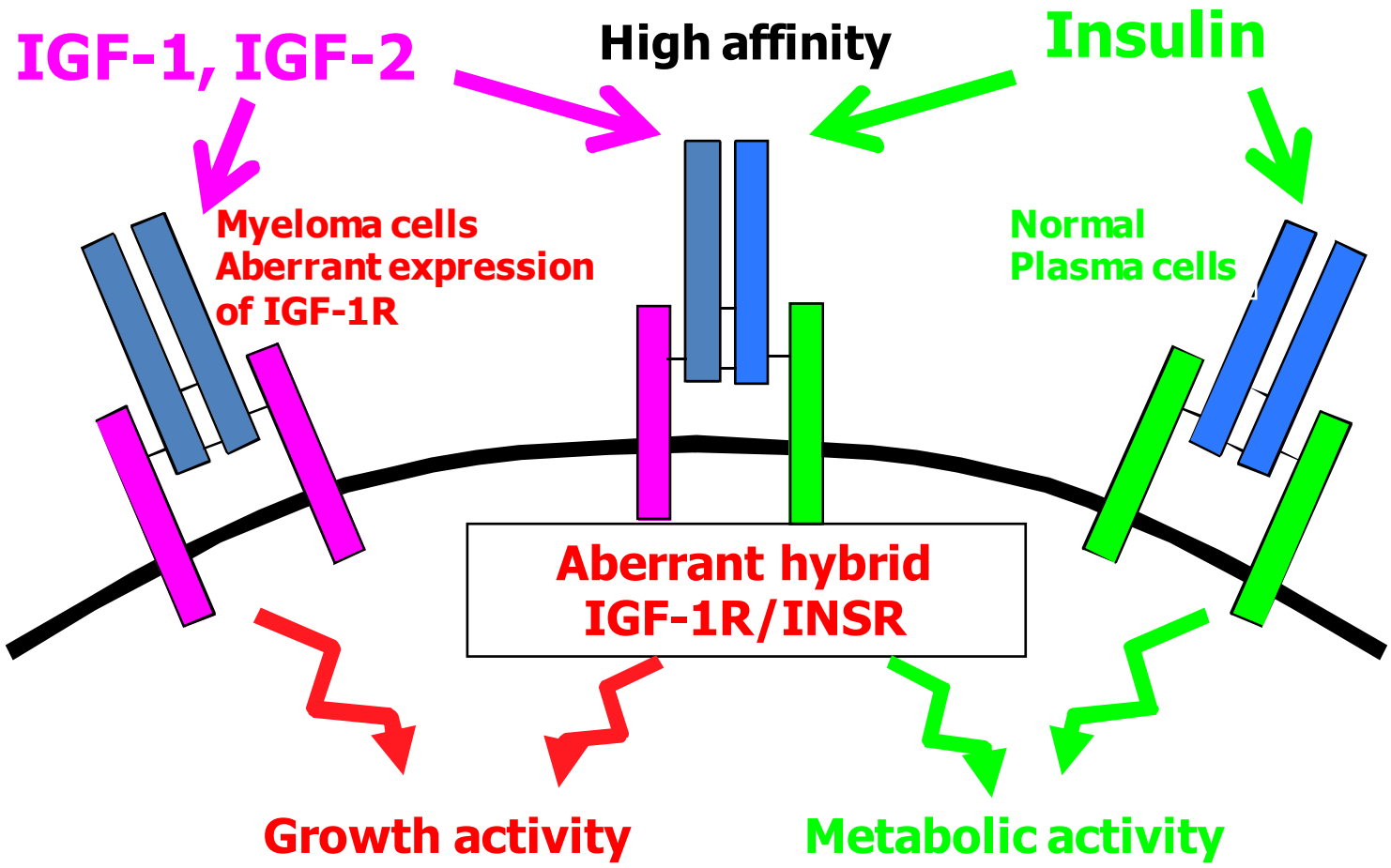
# Increased frequency of patients with IGF-1R$^{+}$ Myeloma cells in case of del17 or t(4;14)

| Patients with | Del17 (n=24) | No Del17 (n=97) |
|---|---|---|
| IGF-1R+ Myeloma cells | 58% | 27% |
| IGF-1R- Myeloma cells | 42% | 73% |
| | | |
| **Patients with** | **t(4;14)(n=20)** | **No t(4;14) (n=74)** |
| IGF-1R+ Myeloma cells | 70% | 26% |
| IGF-1R- Myeloma cells | 30% | 74% |
| | | |

# *IGF-1R* gene expression has prognostic value independently of t(4;14)



# The aberrant IGF-1R expression on malignant plasma cell confers on insulin a potent myeloma cell growth activity at physiological concentrations




Sprynski, Leukemia, 2010

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ORIGINAL REPORT

# Phase I, Pharmacokinetic and Pharmacodynamic Study of the Anti–Insulinlike Growth Factor Type 1 Receptor Monoclonal Antibody CP-751,871 in Patients With Multiple Myeloma

*Martha Q. Lacy, Melissa Alsina, Rafael Fonseca, M. Luisa Paccagnella, Carrie L. Melvin, Donghua Yin, Amarnath Sharma, M. Enriquez Sarano, Michael Pollak, Sundar Jagannath, Paul Richardson, and Antonio Gualberto*

9 responses in 27 patients in combination with dexamethasone

CP-751,871 recognizes the IGF-1R/INSR hybrid receptor

Leukemia (2011), 1-3

www.nature.com/leu

LETTER TO THE EDITOR

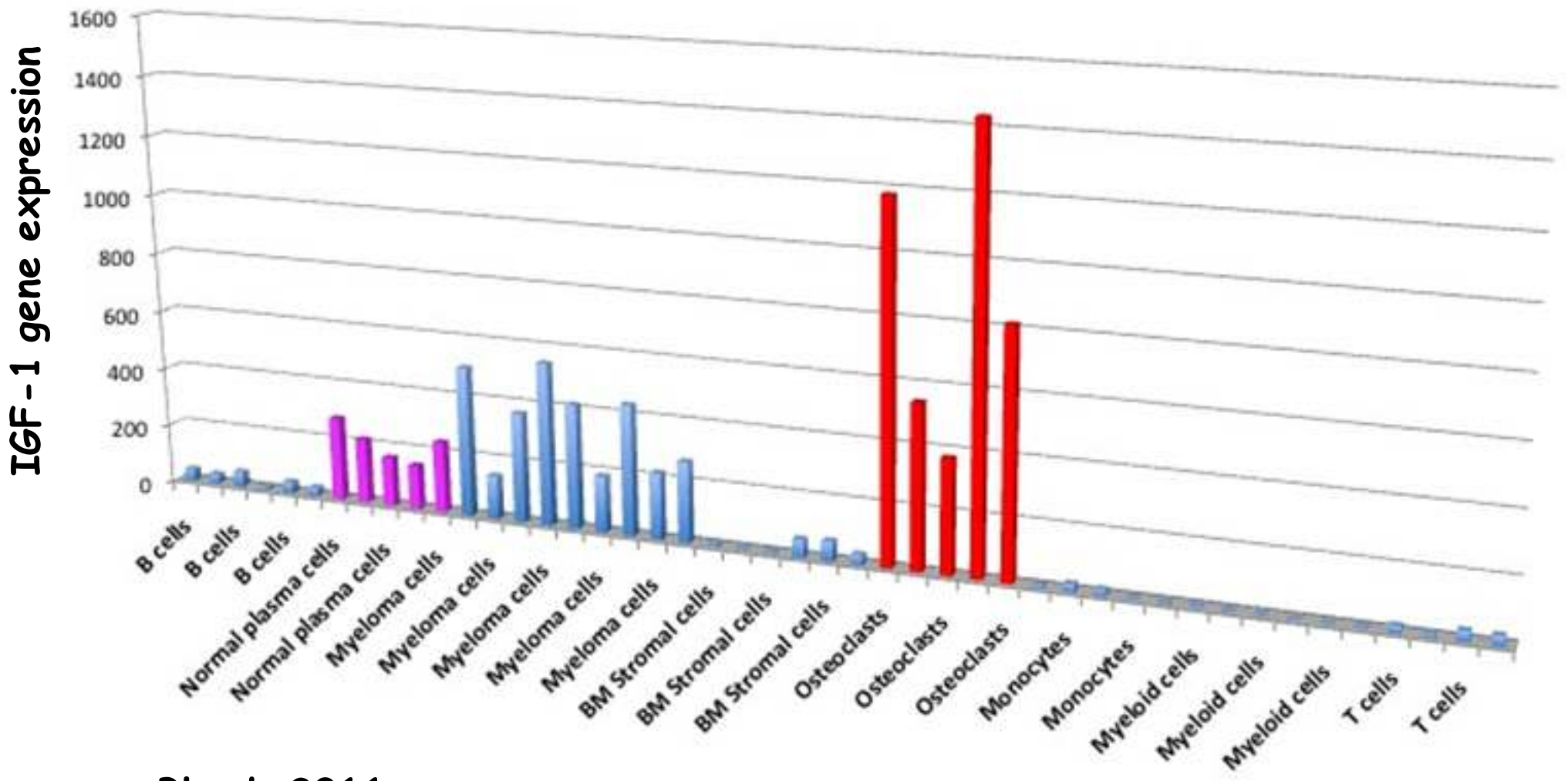
# Phase I study of the anti insulin-like growth factor 1 receptor (IGF-1R) monoclonal antibody, AVE1642, as single agent and in combination with bortezomib in patients with relapsed multiple myeloma

AVE1642 alone or in combination with Bortezomib.

No activity when the antibody was used alone.

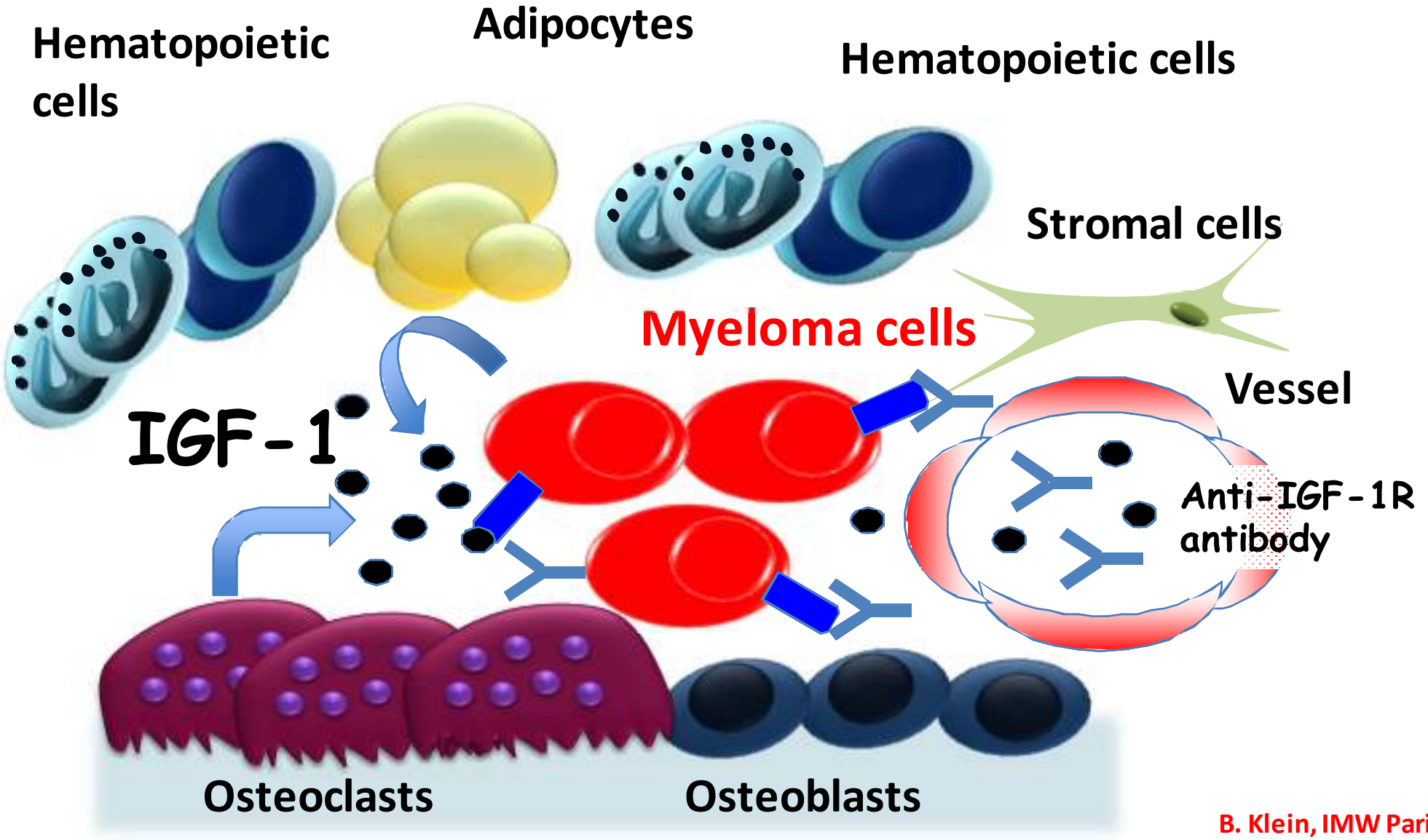
1 CR and 1 PR in 11 patients in combination with Bortezomib

# IGF-1 is mainly produced by osteoclasts and Myeloma cells in the bone marrow of patients. IGF-1 is a survival factor for osteoclasts




Moreaux, Blood, 2011

The anti-IGF-1R antibody has to diffuse in the bone marrow and block the binding of IGF-1 that is largely produced by myeloma cells and osteoclasts. Large levels of IGF-1 and of insulin also circulate in the plasma.




B. Klein, IMW Paris 2011

# Anti-cytokine therapy in association with high dose chemotherapy

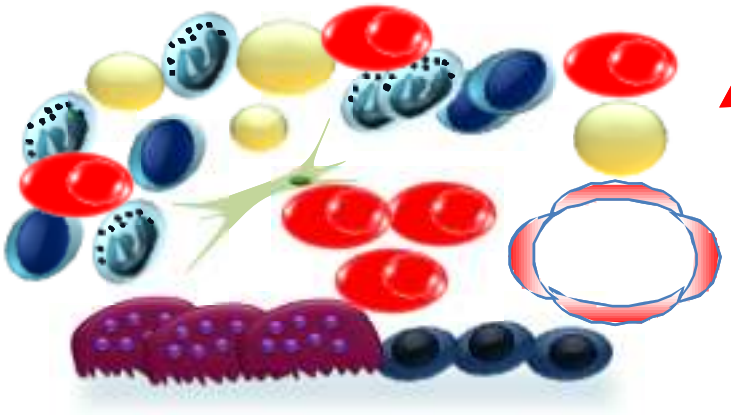
**After 4 courses of VEL-DEX**

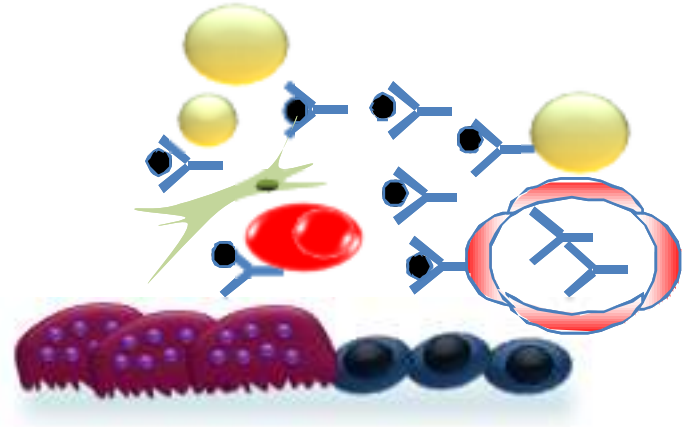
8000 cells/µl (16/22 patients)
90 myeloma cells/µl
5 normal plasma cells/µl

**High dose melphalan**

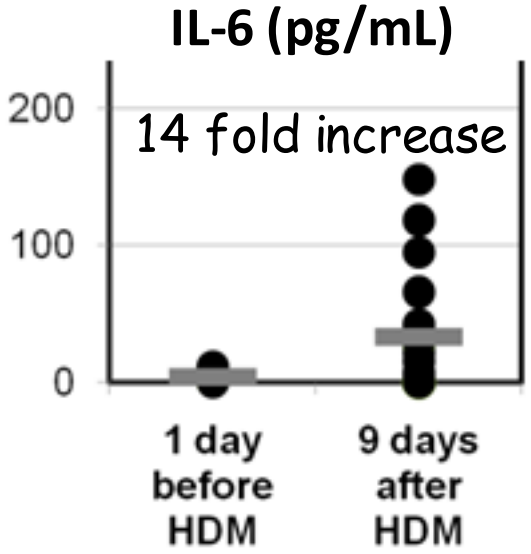
**9 days after melphalan**

400 cells/µl
6 myeloma cells/µl
3 normal plasma cells/µl





Same for other myeloma cell growth factors




**The residual myeloma cells are bathed in high levels of IL-6 and other myeloma cell growth factors in an almost empty bone marrow**

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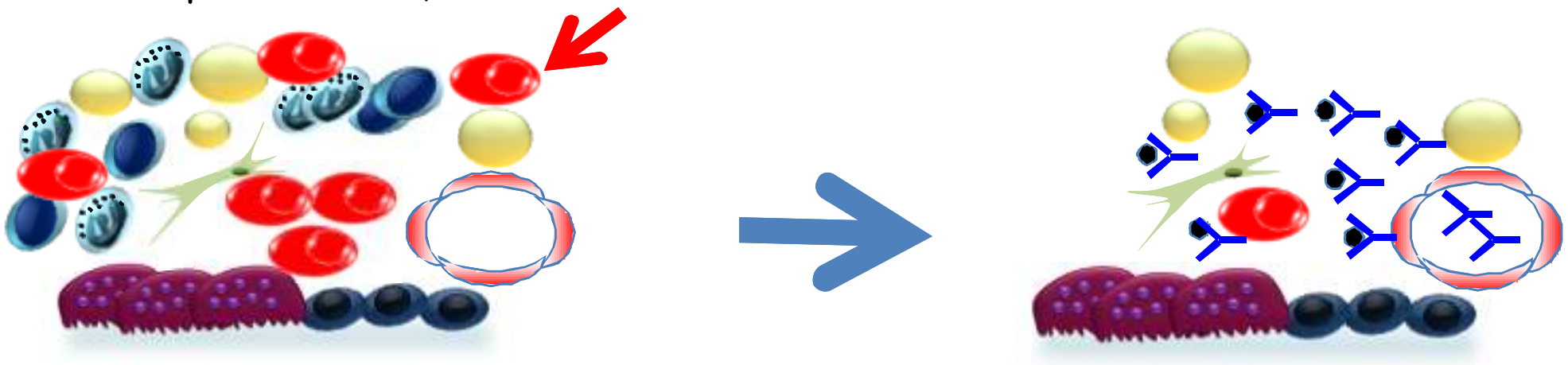
Day -5 Anti-IL-6 antibody Day 10

8000 cells/µl
90 myeloma cells/µl
5 normal plasma cells/µl

High dose melphalan

24 patients



**Optimizing the use of anti-interleukin-6 monoclonal antibody with dexamethasone and 140 mg/m$^2$ of melphalan in multiple myeloma: results of a pilot study including biological aspects**

J-F Rossi[1], N Fegueux[1], ZY Lu[2], E Legouffe[1], C Exbrayat[1], M-C Bozonnat[3], R Navarro[1], E Lopez[1], P Quittet[1], J-P Daures[3], V Rouillé[1], T Kanouni[1], J Widjenes[4] and B Klein[2]

Bone Marrow Transplantation (2005) 36, 771–779

No hematological toxicity
Less mucositis
54% in VGPR
Link between a complete inhibition of CRP and VGPR

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# Cytokine pathways: which one to target?

IGF-1 and IL-6 are the two main myeloma cell growth factors.

IL-6 is a mandatory factor to generate normal plasma cells.
A phase 3 clinical trial with anti-IL-6 antibodies in association with Bortezomib is ongoing.

IGF-1R is not expressed by normal plasma cells but IGF-1 is a plasma cell marker.

IGF-1R is aberrantly expressed by Myeloma Cells, in association with a poor prognosis. There is a link with del17 and t(4;14).

Insulin is a powerful myeloma cell growth factor at physiological concentrations, targeting hybrid receptors (IGF-1R/INSR).

Phase I studies with anti-IGF-1R antibodies show lack of toxicity but a poor efficacy.

Identify therapeutic windows to make easier the diffusion of antibodies. Use of small inhibitors. Combination of therapies using cytokine inhibitors with other molecules.

B. Klein, IMW Paris 2011

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