# Tailoring treatment for Erdheim-Chester disease:

# focus on ECD microenvironment

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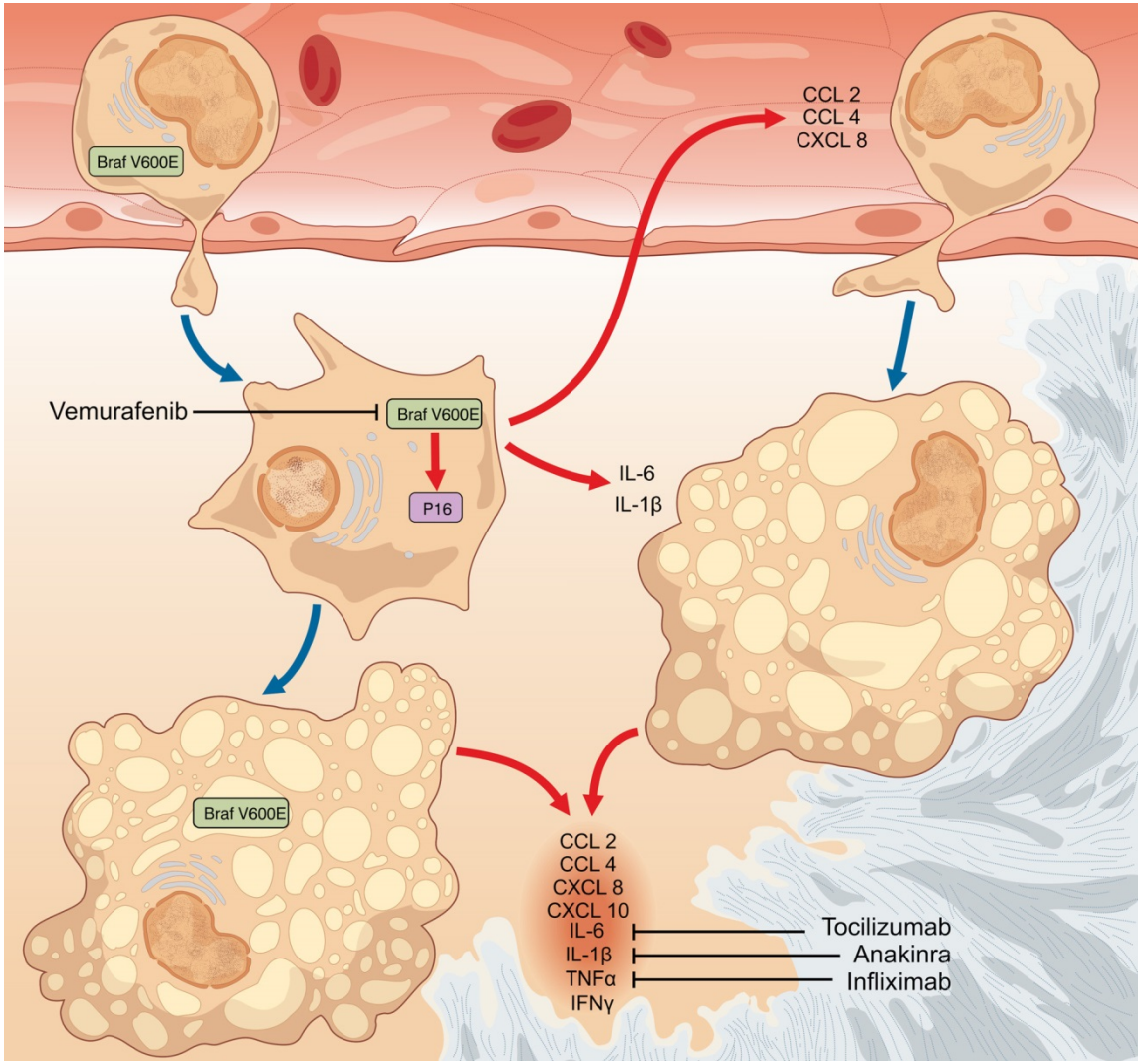
Laboratory of Lymphoid Malignancies
Division of Experimental Oncology

ECD Global Alliance Medical Symposium
Paris, Hôpital Pitié-Salpêtrière
September 15, 2016

OSPEDALE SAN RAFFAELE

Università Vita-Salute San Raffaele

# A unifying disease model for ECD




Cavalli *et al*, 2014

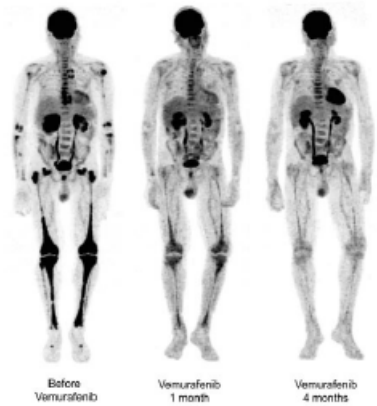
# vemurafenib treatment in Erdheim-Chester disease



**Plenary Paper**

## Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the *BRAF* V600E mutation

*Julien Haroche,[1,2] *Fleur Cohen-Aubart,[1,2] *Jean-François Emile,[3] *Laurent Arnaud,[1,2] Philippe Maksud,[4] Frédéric Charlotte,[5] Philippe Cluzel,[6] Aurélie Drier,[7] Baptiste Hervier,[1,2] Neïla Benameur,[8] Sophie Besnard,[9] Jean Donadieu,[10] and Zahir Amoura[1,2]

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Reproducible and Sustained Efficacy of Targeted Therapy With Vemurafenib in Patients With *BRAF*$^{V600E}$-Mutated Erdheim-Chester Disease

*Julien Haroche, Fleur Cohen-Aubart, Jean-François Emile, Philippe Maksud, Aurélie Drier, Dan Tolédano, Stéphane Barete, Frédéric Charlotte, Philippe Cluzel, Jean Donadieu, Neïla Benameur, Philippe A. Grenier, Sophie Besnard, Jean-Paul Ory, François Lifermann, Ahmed Idbaih, Brigitte Granel, Bruno Graffin, Baptiste Hervier, Laurent Arnaud, and Zahir Amoura*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.

# vemurafenib in Erdheim-Chester disease: unsolved issues

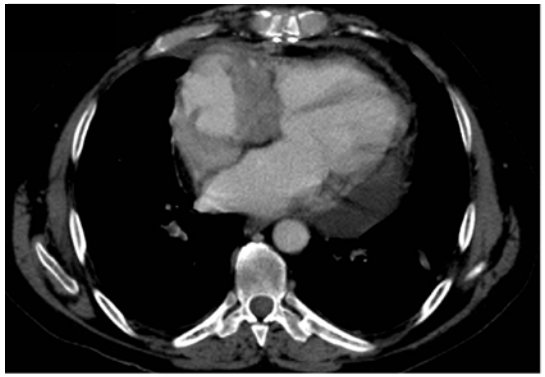
- Not all ECD patients bear the $BRAF^{V600E}$ mutation or known targetable mutations
- Vemurafenib treatment mostly results in partial clinical responses in ECD patients
- Vemurafenib treatment may be associated with severe side effects and resistance or relapse
- The molecular mechanisms exerted by vemurafenib on ECD tissues are unknown

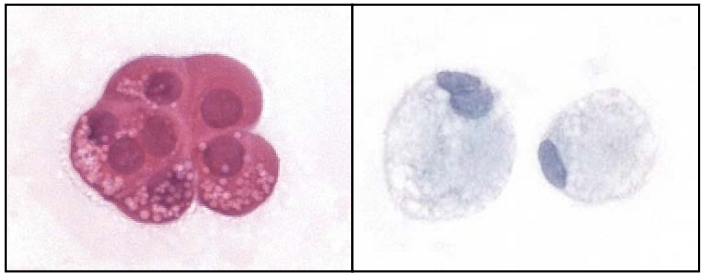
# Aims

- to investigate the pathogenic effects of ECD microenvironment to identify new target molecules and pathways

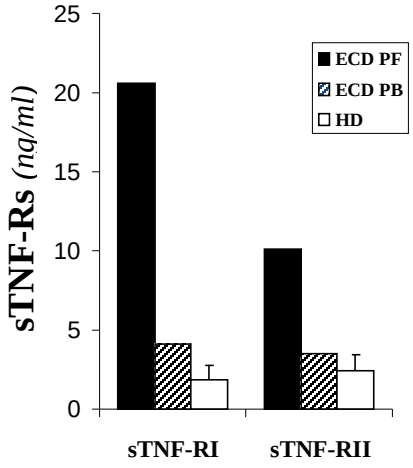
- to exploit the bioreactor technology for culturing ECD tissues to assess the impact of drugs on both ECD histiocytes and their surrounding microenvironment

# ECD exudates as a surrogate microenvironment



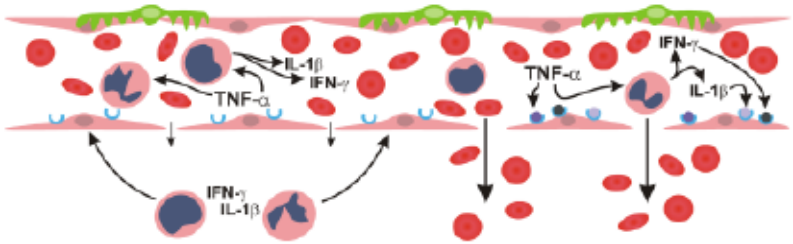


| | TNF-α | IL-1β | IL-6 | CXCL8 | CCL2 | CCL4 |
|---|---|---|---|---|---|---|
| **PF1** | 3 | 0 | 4392 | 23 | 239 | 37 |
| **PF2** | 69 | 8.4 | 8335 | 2129 | 6589 | 78 |
| **PF3** | 30 | 0 | 30680 | 70 | 99 | 81 |
| **PF4** | 13.7 | 57.2 | 4056 | 47 | 4742 | 72 |
| **PB** *(n=4)* | 1.48 ±1.25 | 0.33 ±0.24 | 16.4 ±6.8 | 36.4 ±14.3 | 68.4 ±15 | 97.6 ±15.2 |
| **HD** *(n=8)* | 0.43 ±0.26 | 0.61 ± 0.17 | 2.54 ±1.4 | 9.9 ±2.84 | 55.6 ±11.6 | 91.6 ±19.6 |

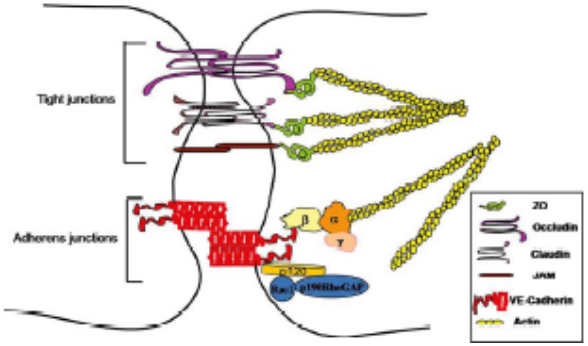


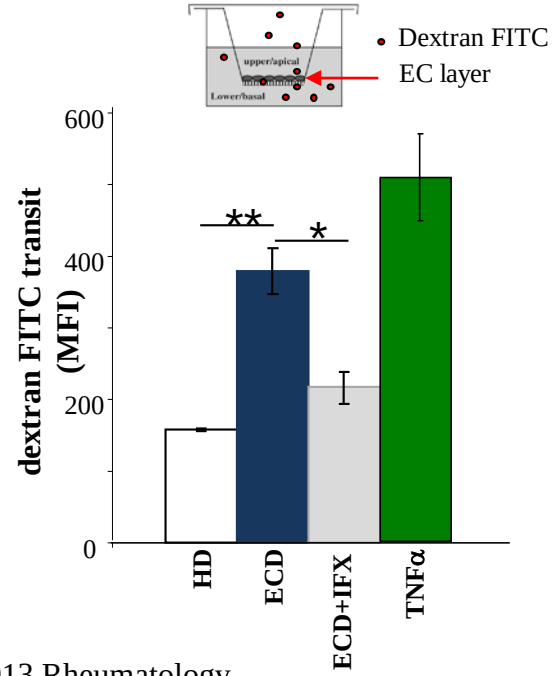

Ferrero *et al.* 2013 Rheumatology

# TNF-α in ECD pericardial fluid affects endothelial functions

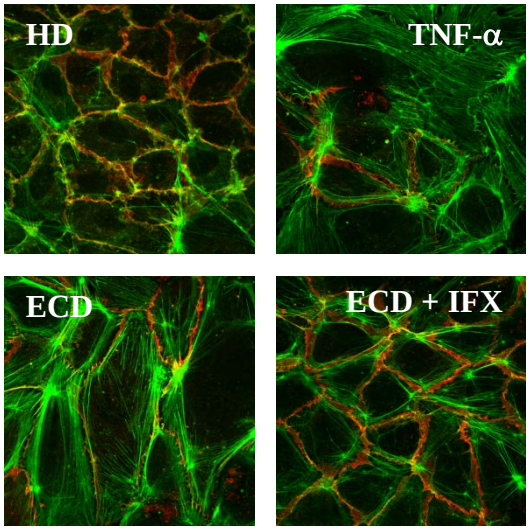



Ten Hagen *et al.* 2008



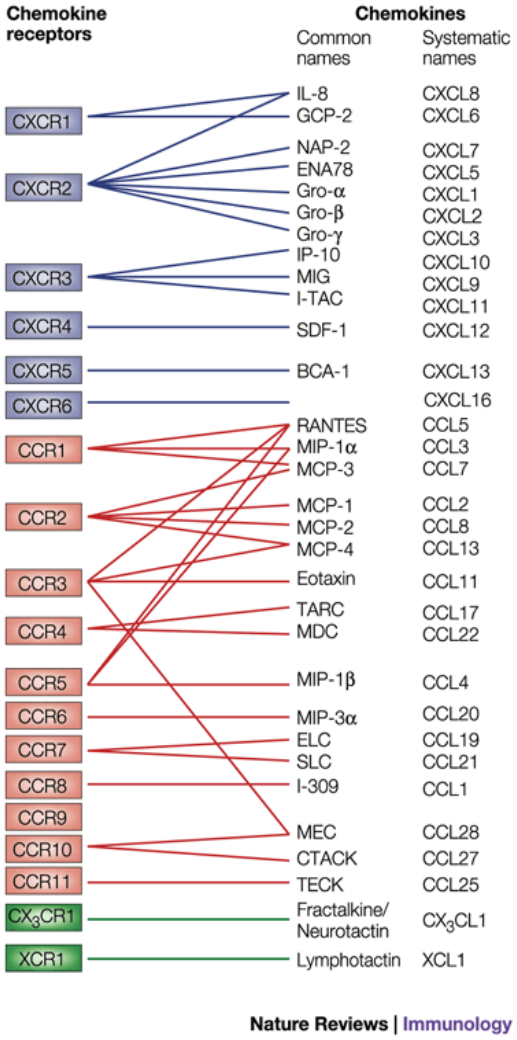



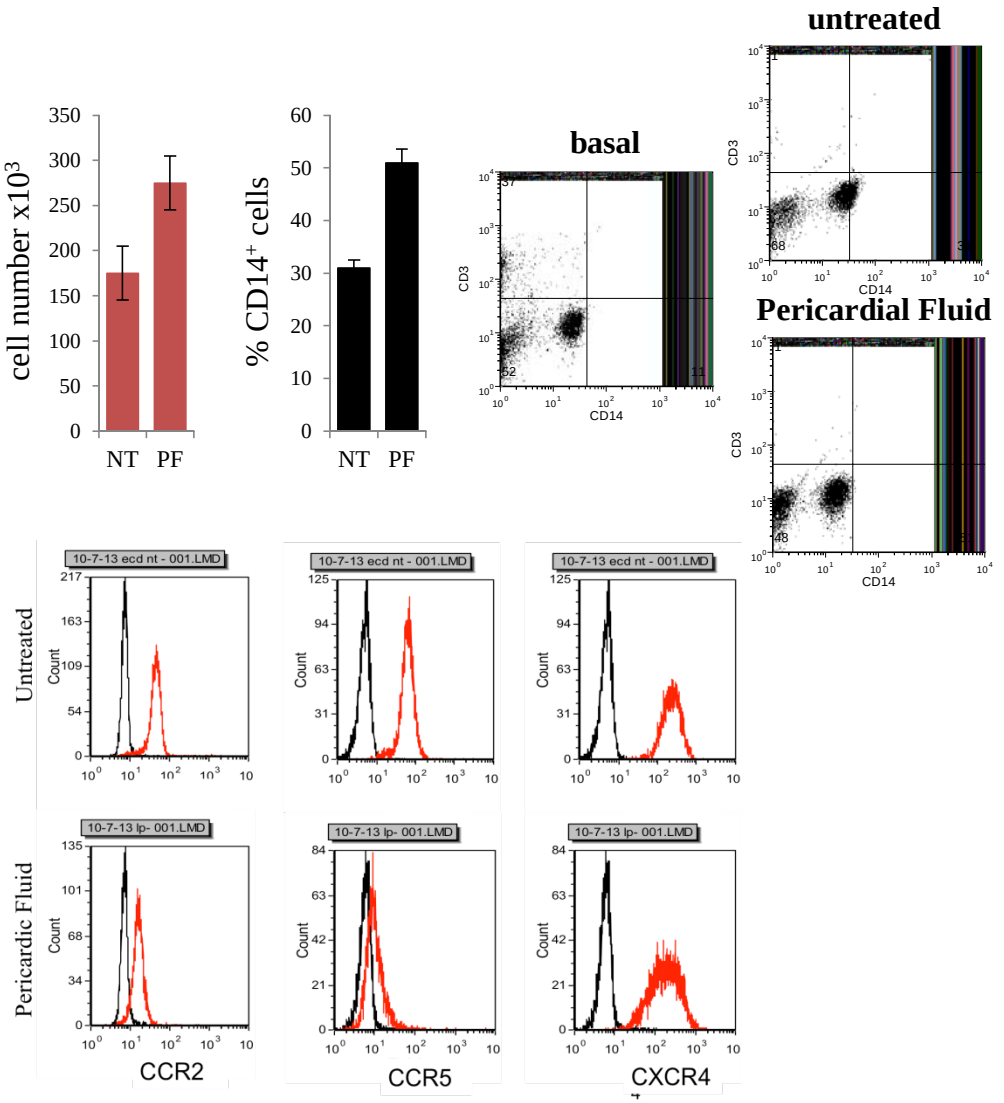

Ferrero *et al.* 2013 Rheumatology




CD31/Phalloidin

# ECD pericardial fluid promotes monocyte chemotaxis

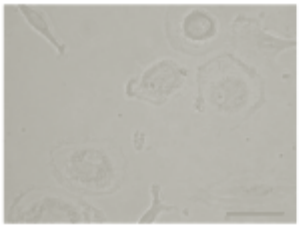


# ECD pericardial fluid affects macrophage phenotype

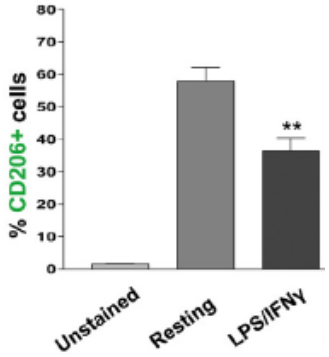
Phenotypic activation and pharmacological outcomes of spontaneously differentiated human monocyte-derived macrophages

Serena Tedesco[a], Chiara Bolego[a,*], Alice Toniolo[a], Alberto Nassi[a,1], Gian Paolo Fadini[b,c], Massimo Locati[d,e], Andrea Cignarella[a,2]



Resting

LPS/IFNγ

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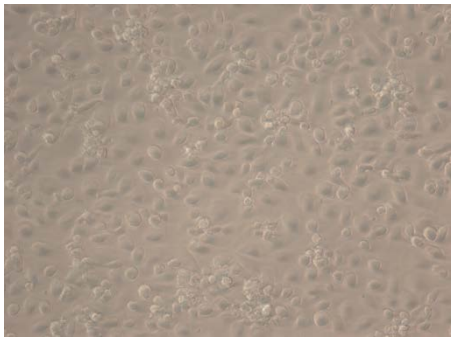
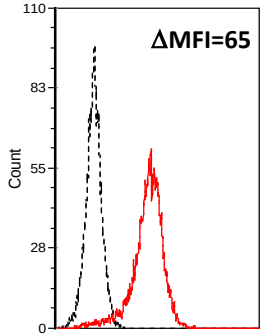
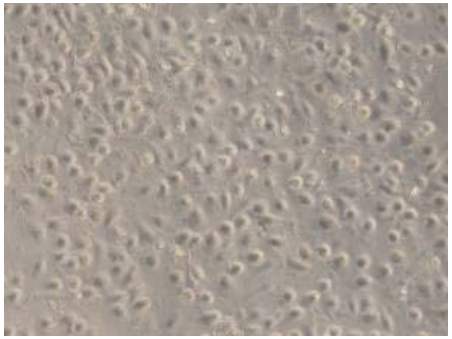
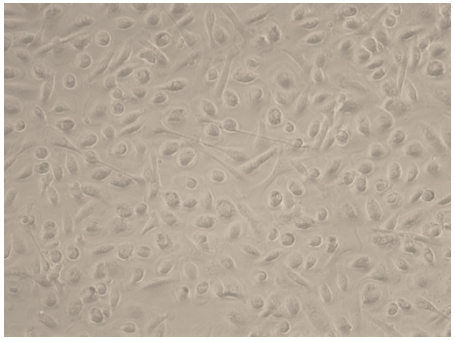
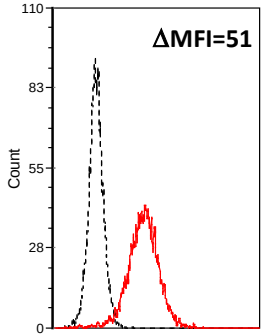


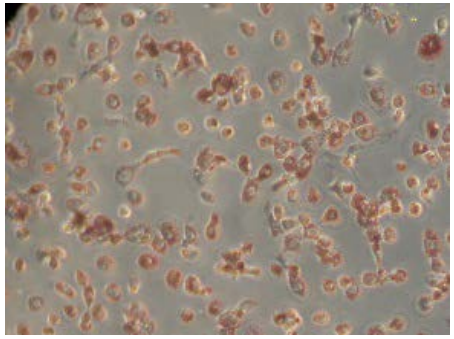


PF





**CD206** **Red Oil**

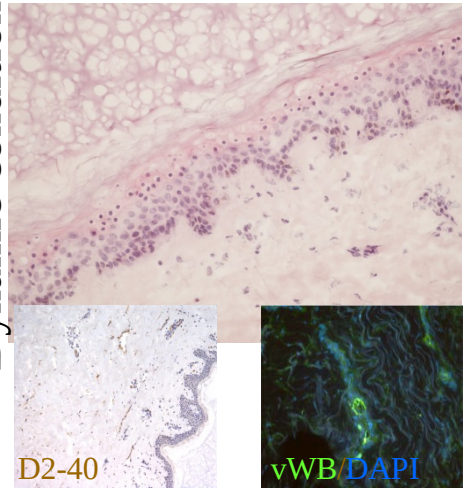
# RCCS™ bioreactor preserves architecture of normal and cancer tissues

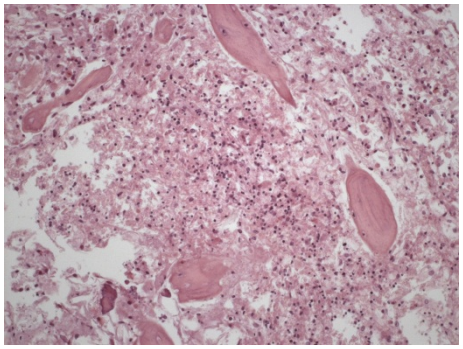
Skin

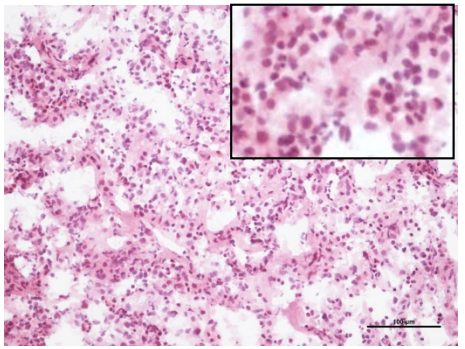
Bone Marrow

RCC

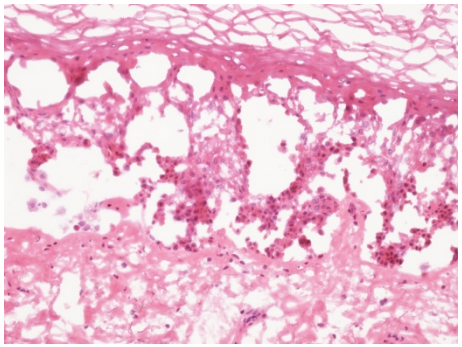
Dynamic condition

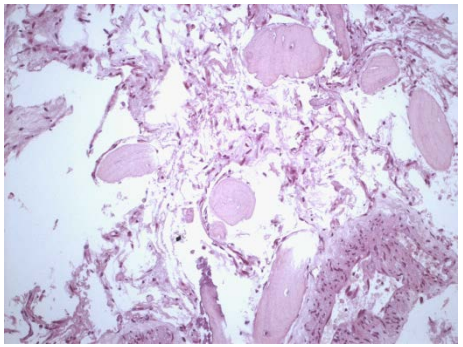


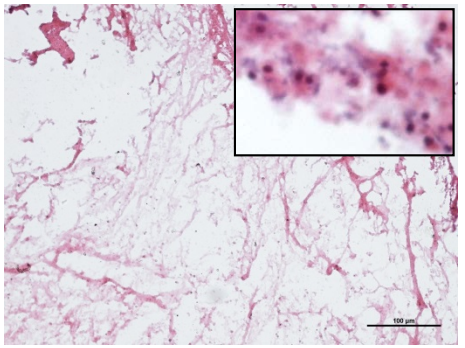





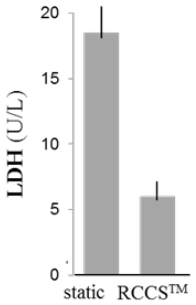
Static condition

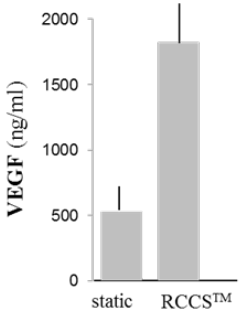






2 weeks

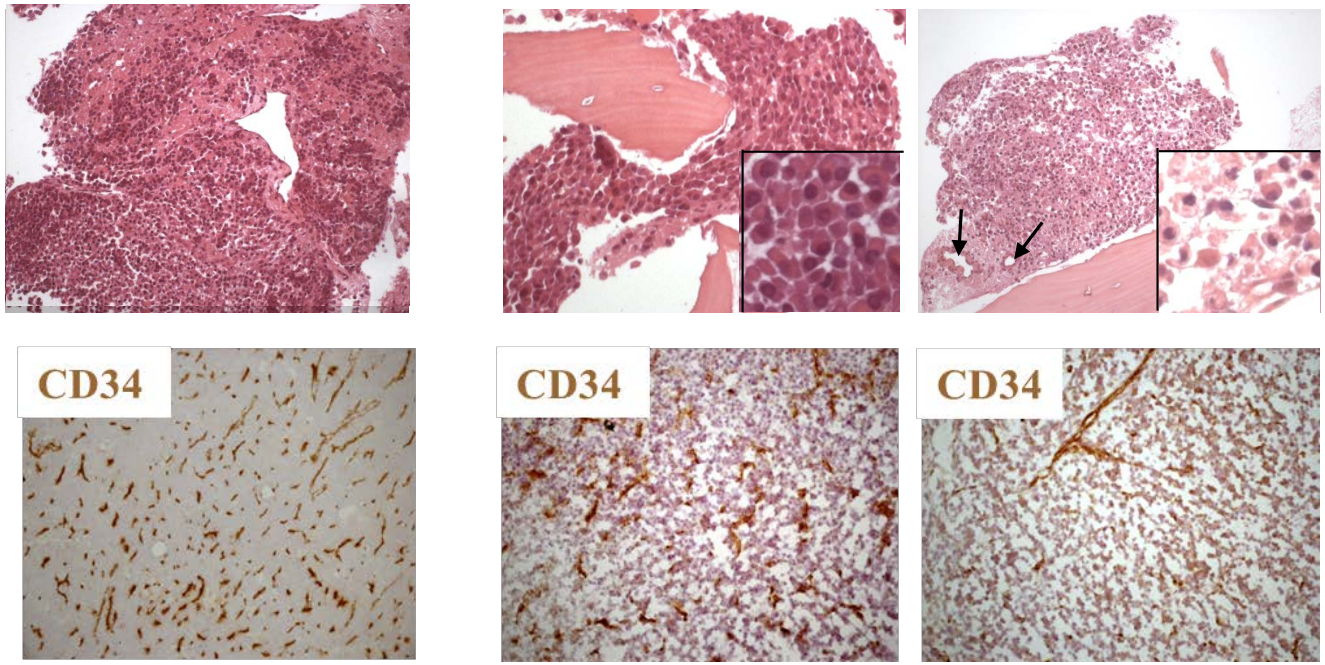


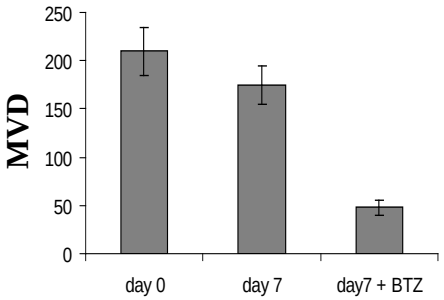



# Culture in RCCS™ Bioreactor allows drug testing in Multiple Myeloma tissues

bortezomib

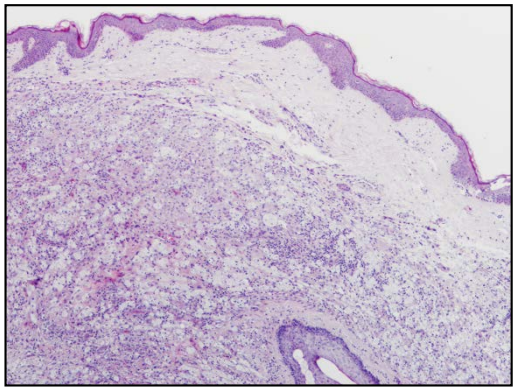
| day 0 | day 7 - | day 7 + |
|---|---|---|



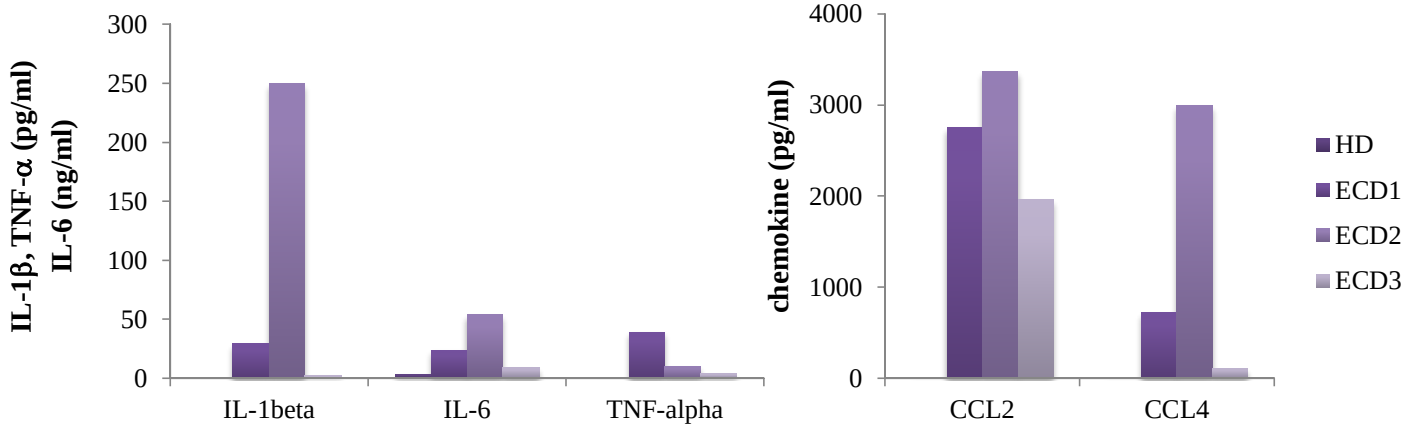




Ferrarini *et al*, 2013 PlosOne

# ECD tissues secrete cytokines and chemokines in culture in bioreactor

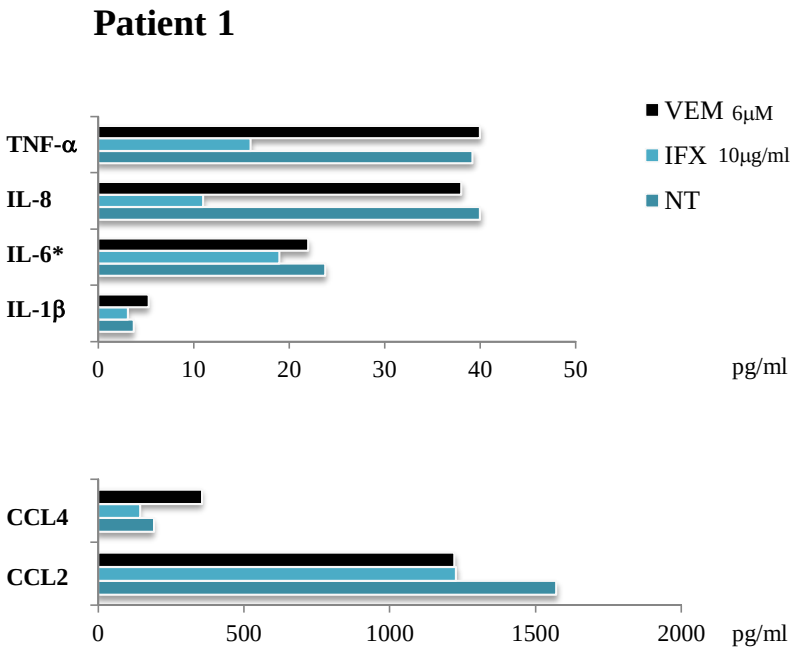


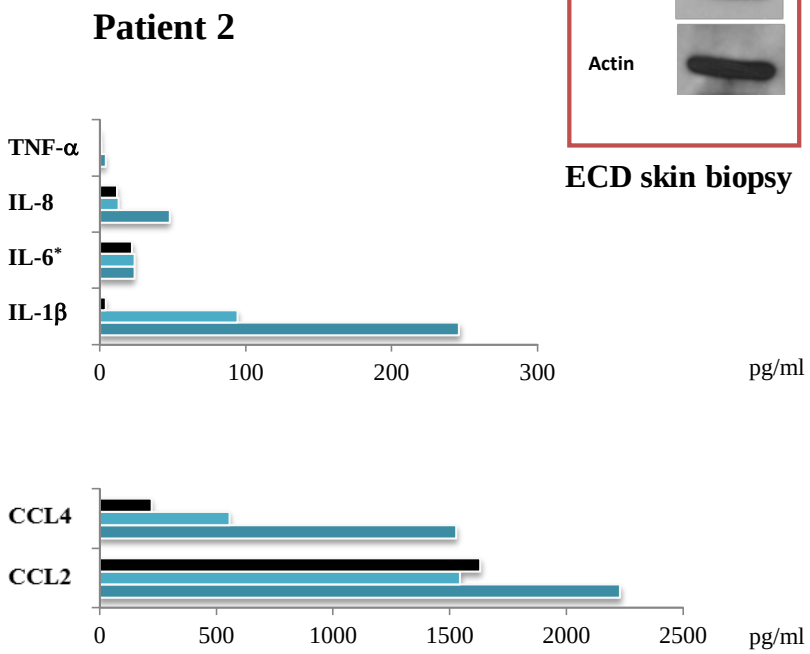
**day 4**



# Cytokine- and BRAF-inhibitors modulate cytokine/chemokine release in supernatants from ECD tissues

**day 4**



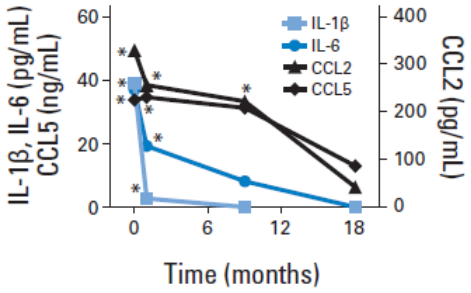







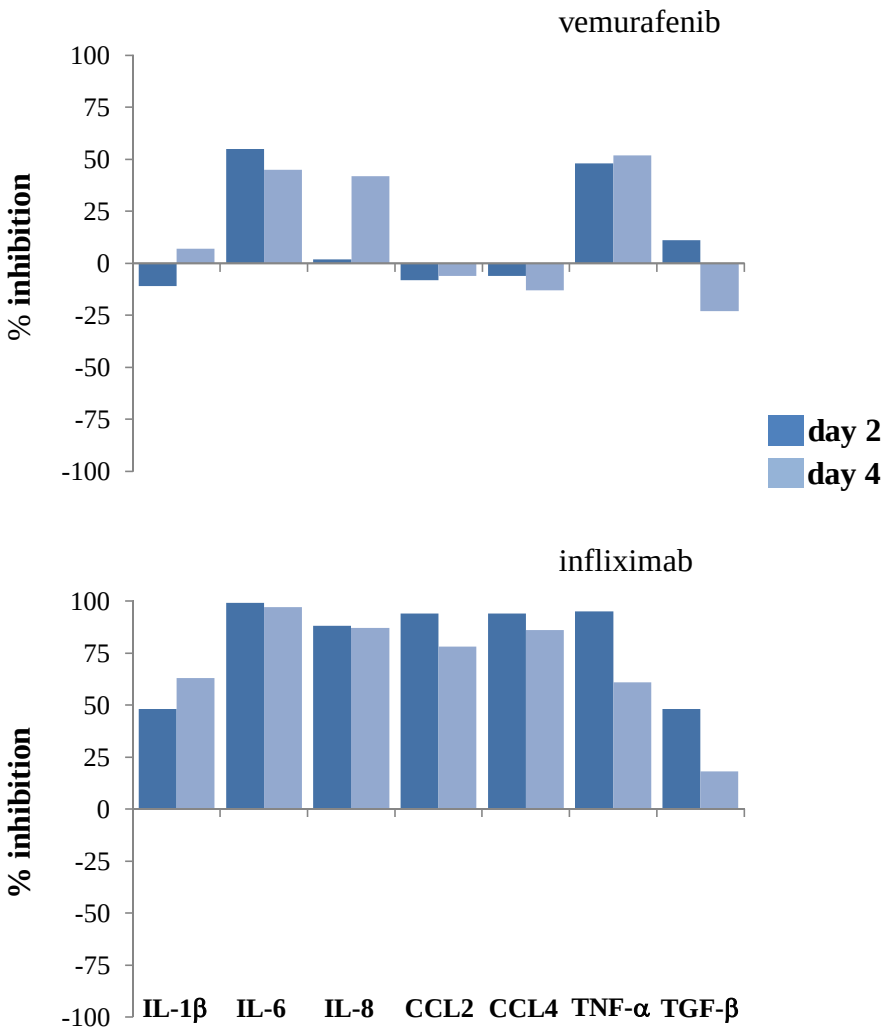
**ECD skin biopsy**

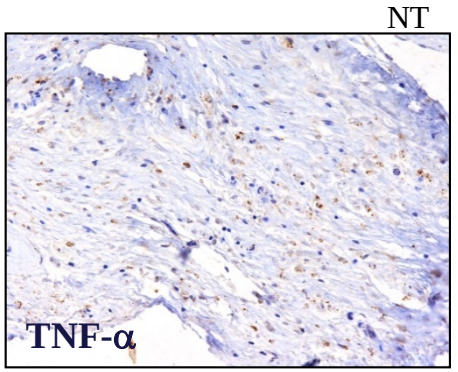
**IL-6*** concentration in ng/ml

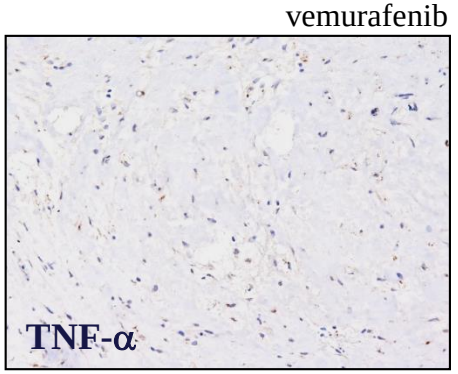



Dagna *et al*, 2012 *JCO*

# vemurafenib treatment modulates cyto-chemokine production by BRAF-mutated ECD tissues



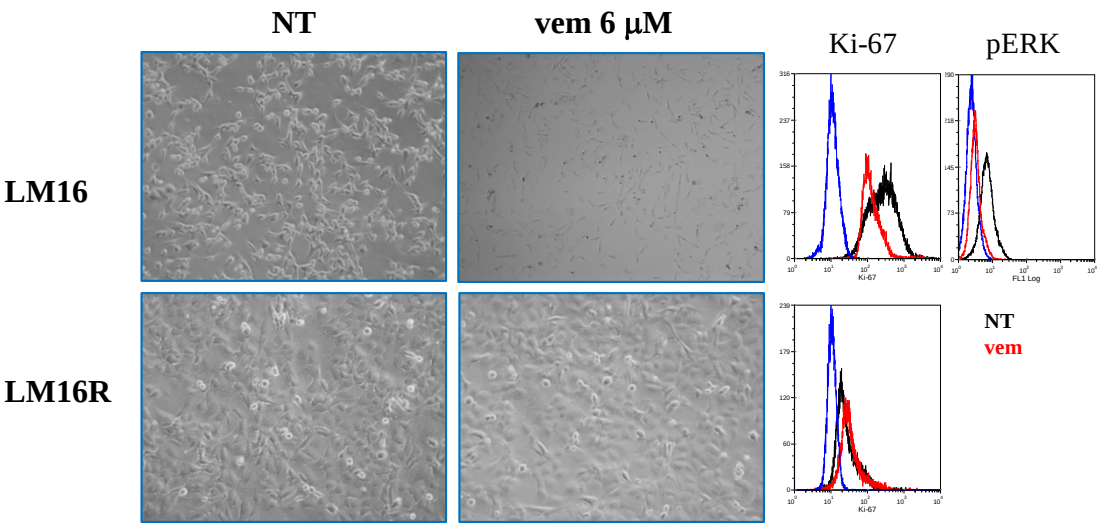



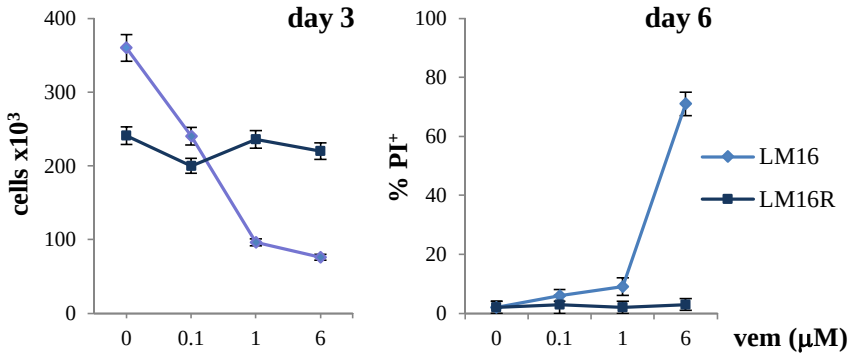
# vemurafenib affects viability, proliferation and cytokine release in human BRAF-mutated melanomas

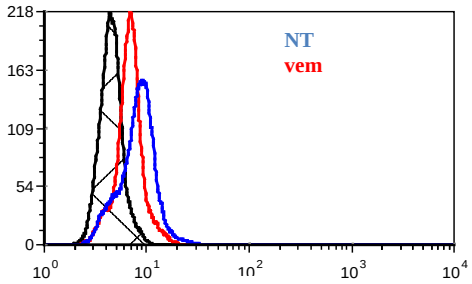
www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2015

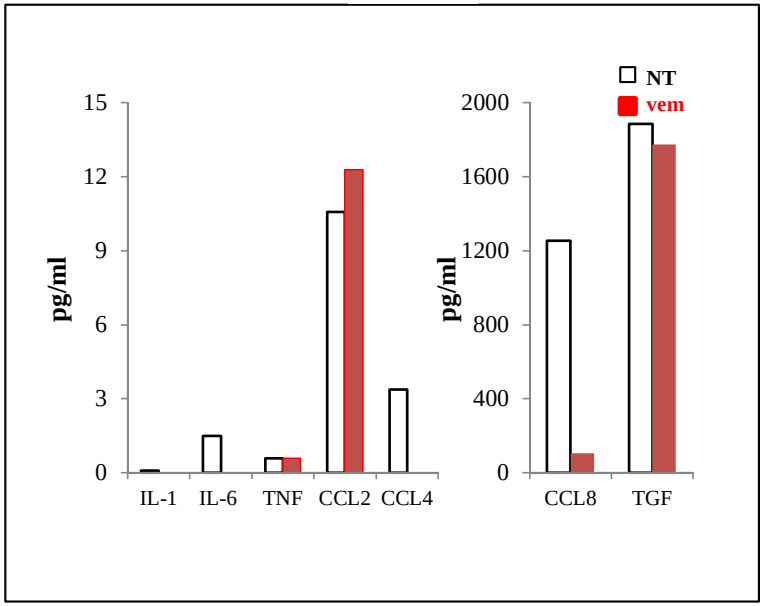
## Overcoming melanoma resistance to vemurafenib by targeting CCL2-induced miR-34a, miR-100 and miR-125b

Elisabetta Vergani[1,*], Lorenza Di Guardo[2,*], Matteo Dugo[3,*], Sara Rigoletto[1], Gabrina Tragni[4], Roberta Ruggeri[5], Federica Perrone[4], Elena Tamborini[4], Annunziata Gloghini[4], Flavio Arienti[6], Barbara Vergani[7], Paola Deho[1], Loris De Cecco[3], Viviana Vallacchi[1], Paola Frati[1], Eriomina Shahaj[1], Antonello Villa[7], Mario Santinami[5], Filippo De Braud[2], Licia Rivoltini[1], Monica Rodolfo[1]



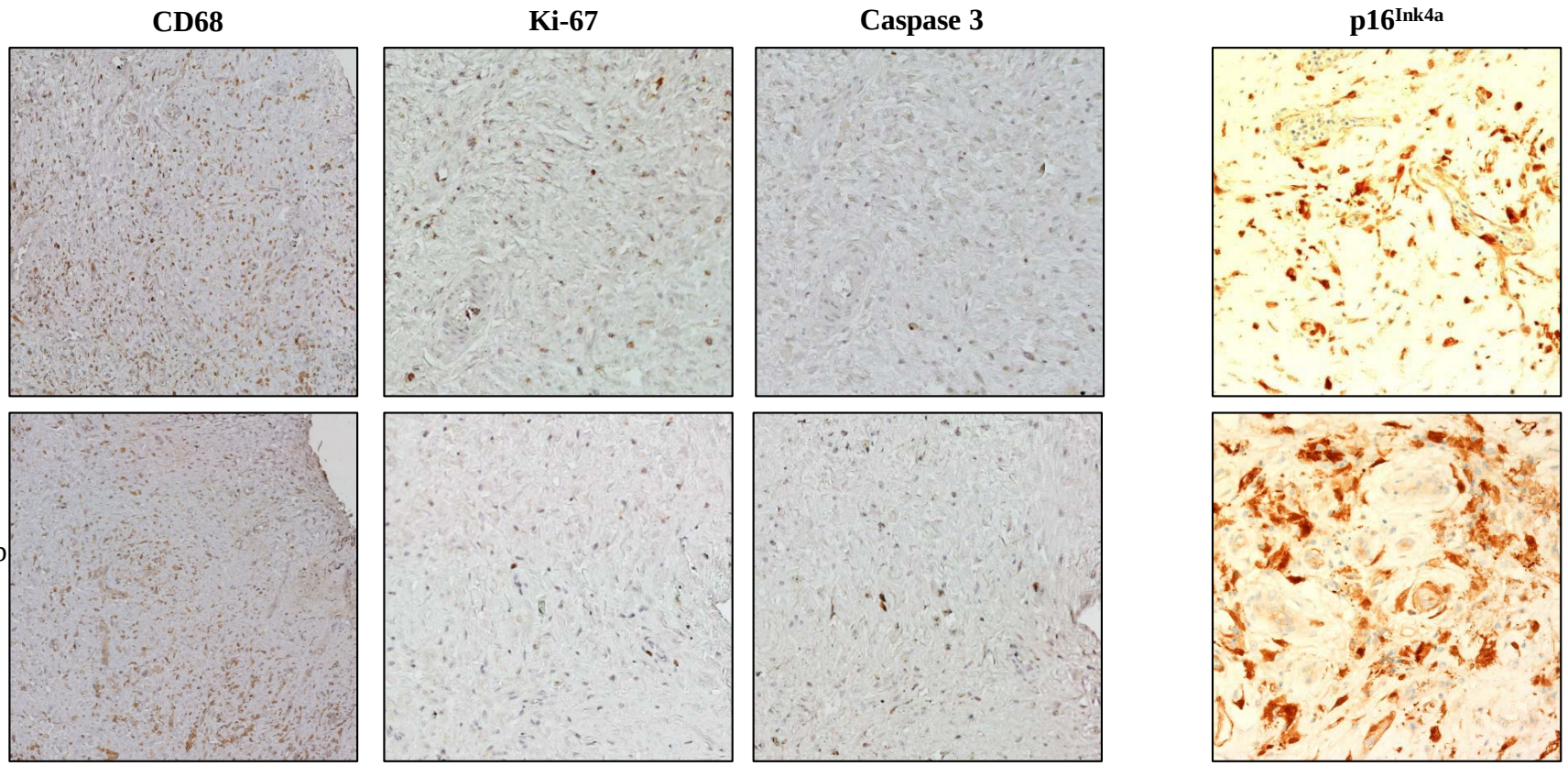



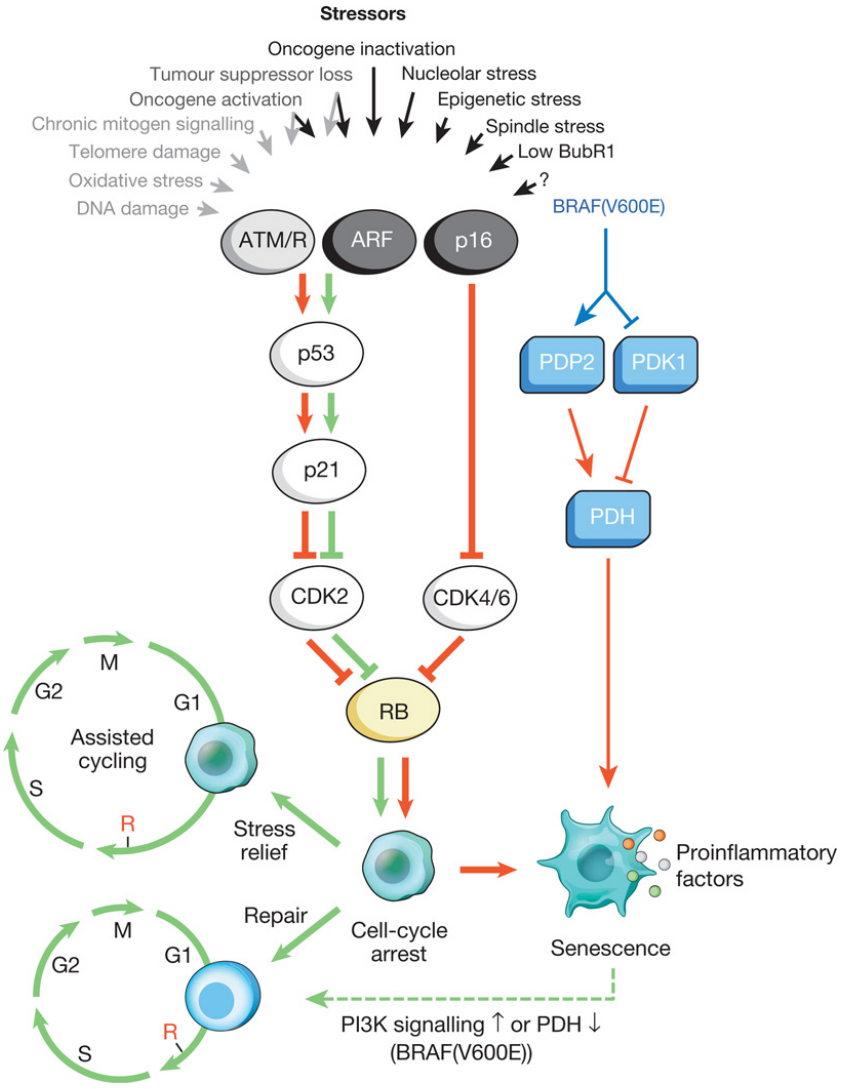




LM16

# vemurafenib treatment does not affect proliferation or survival of ECD histiocytes in short-term culture

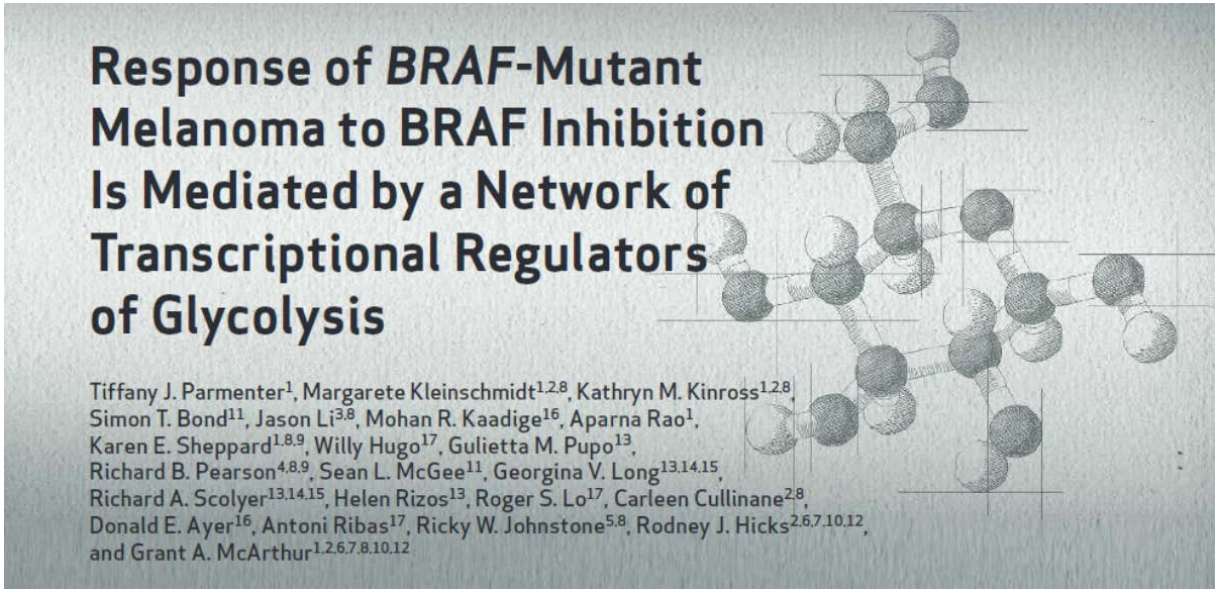


# Senescence-inducing stimuli and main effector pathways




van Deursen, 2014 Nature

# Perspectives



## Response of *BRAF*-Mutant Melanoma to BRAF Inhibition Is Mediated by a Network of Transcriptional Regulators of Glycolysis

Tiffany J. Parmenter[1], Margarete Kleinschmidt[1,2,8], Kathryn M. Kinross[1,2,8], Simon T. Bond[11], Jason Li[3,8], Mohan R. Kaadige[16], Aparna Rao[1], Karen E. Sheppard[1,8,9], Willy Hugo[17], Gulietta M. Pupo[13], Richard B. Pearson[4,8,9], Sean L. McGee[11], Georgina V. Long[13,14,15], Richard A. Scolyer[13,14,15], Helen Rizos[13], Roger S. Lo[17], Carleen Cullinane[2,8], Donald E. Ayer[16], Antoni Ribas[17], Ricky W. Johnstone[5,8], Rodney J. Hicks[2,6,7,10,12], and Grant A. McArthur[1,2,6,7,8,10,12]



See related commentary on pg 2923

ORIGINAL ARTICLE

## BRAF Inhibition Generates a Host–Tumor Niche that Mediates Therapeutic Escape

Inna V. Fedorenko[1], Jennifer A. Wargo[2], Keith T. Flaherty[3], Jane L. Messina[4] and Keiran S.M. Smalley[1,4]

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# Conclusions/Perspectives

- The cytokine milieu in ECD lesions is endowed with pathogenic activities, whose understanding may disclose new therapeutic targets

- The RCCS$^{TM}$ bioreactor allows culture of ECD tissues and the assessment of the impact of drugs, including cytokine- and BRAF-inhibitors

- The technology can be further exploited as a novel tool to identify mechanisms of action/resistance of BRAF/MEK inhibitors on ECD histiocytes and their microenvironment for future combination therapies

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