EACR European Association for Cancer Research

LIF As We Know It

From Basic Science to Clinical Trials

28 - 29 May 2018

Barcelona, Spain

Scientific Organiser

Joan Seoane

Programme Book

Scientific Programme

Day 1 - Monday 28 May

12.30 – 13.00	REGISTRATION Foyer of VHIO
13.00 – 14.00	WELCOME LUNCH
14.00 – 14.10	CONFERENCE INTRODUCTION Cellex Auditorium
	SESSION 1: LIF IN CANCER I Session Chair: Joan Seoane
14.10 – 14.40 Q&A: 14.40 – 14.50	**Joan Seoane** VHIO, Spain "Immunomodulatory role of LIF in cancer"
14.50 – 15.20 Q&A: 15.20 – 15.30	**Cédric Gaggioli** IRCAN, France "A journey into the tumor microenvironment: a LIF(e) story"
15.30 – 16.00 Q&A: 16.00 – 16.10	**Wenwei Hu** Rutgers Cancer Institute, USA "LIF, a Friend or Foe – its role in reproduction and cancer"
16.10 – 16.45	COFFEE BREAK
	SESSION 2: EARLY PHASE CLINICAL TRIALS Session Chair: José Baselga
16.45 – 17.15 Q&A: 17.15 – 17.25	**José Baselga** MSKCC, USA "Update on clinical development of anti-LIF antibodies as cancer therapy"
17.25 – 17.55 Q&A: 17.55 – 18.05	**Lillian Siu** University of Toronto, Canada "Incorporating predictive biomarker development in first-in-class phase I trials – myth or must?"
18.05 – 18.35 Q&A: 18.35 – 18.45	**Josep Tabernero** VHIO, Spain "New development strategies in Immuno-Oncology"
18.45 – 19.00	BUS TO EVENING RECEPTION
19.00 – 20.30	EVENING RECEPTION Hotel Alimara All participants are invited to join this networking event. Drinks and hors d'oeuvres will be served in the garden of the hotel. The event will finish at 20:30, and the rest of the evening is free for you to enjoy Barcelona.

Day 2 - Tuesday 29 May

	SESSION 3: LIF IN CANCER II Session Chair: Tony Hunter
09.00 – 09.30 Q&A: 09.30 – 09.40	**Tony Hunter** Salk Institute, USA "LIF produced by stromal cells is a paracrine factor acting on tumor cells in pancreatic cancer"
09.40 – 10.10 Q&A: 10.10 – 10.20	**Benjamin Neel** NYU School of Medicine, USA "Targeting SHP2 in cancer"
10.20 – 10.50 Q&A: 10.50 – 11.00	**Peter Heinrich** Albert-Ludwig University, Germany "IL-6 type cytokines: signaling through the gp130-JAK-STAT pathway and its regulation"
11.00 – 11.30	COFFEE BREAK
11.30 – 12.00 Q&A: 12.00 – 12.10	**Andrew Lowy** UCSD, USA "Identifying novel targets for pancreatic cancer therapy"
12.10 – 12.40 Q&A: 12.40 – 12.50	**Manuel Serrano** IRB Barcelona, Spain "Critical role of the LIF-family of cytokines during the early phases of reprogramming into pluripotency"
12.50 – 13.50	LUNCH
	SESSION 4: LIF IN INFLAMMATION Session Chair: Su Metcalfe
13.50 – 14.20 Q&A: 14.20 – 14.30	**Su Metcalfe** University of Cambridge, UK "NanoBioMedicine: Nano-formulation of LIF to treat Multiple Sclerosis, an inflammatory autoimmune disease of the CNS"
14.30 – 15.00 Q&A: 15.00 – 15.10	**Niels Hellings** Hasselt University, Belgium "IL-6 class cytokines are master regulators of neuroimmunological disease"
15.10 – 15.40 Q&A: 15.40 – 15.50	**Keith Pennypacker** University of Kentucky, USA "Age-related differences in the response to Leukemia Inhibitory Factor after experimental stroke"
15.50 – 16.15	GENERAL CONCLUSIONS & AWARD PRESENTATION
16.15 – 17.00	COFFEE & FINAL NETWORKING

IL-6 type cytokines: signaling through the gp130-JAK-STAT pathway and its regulation

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Cytokines are important mediators of intercellular communication in higher organisms. They comprise growth factors, interleukins, interferons and chemokines. Interleukins are synthesized and released by numerous different cell types. They act on various target cells (pleiotropy). Their actions are often redundant, i.e. similar biological responses are achieved by several different cytokines.

They exert their actions - which can be auto- or paracrine - through specific cell surface receptors and can be classified into pro- and anti-inflammatory cytokines and in cytokines with both pro- and anti-inflammatory properties. To the latter class belongs the family of IL-6 type cytokines, which consist of interleukin-6 (IL-6), IL-11, leukemia-inhibitory factor (LIF), oncostatin-M (OSM), cardiotrophin-1 (CT-1) and ciliary neurotrophic factor (CNTF).

The 3D structure of IL-6 type cytokine family members is a compact bundle of 4 anti-parallel α-helices in an up-up-down-down configuration, although they do not have homologous primary structures. IL-6 type cytokines bind to plasma membrane receptor complexes, which contain the common long chain signal transducing β-receptor glycoprotein 130 (gp130).

IL-6 and IL-11 use a homodimer of gp130. The other members of the IL-6 family - LIF, OSM, CT-1, cardiotrophin-like cytokine (CLC) and CNTF - signal via heterodimers composed of gp130 and LIF receptor β (LIFRβ). With the exception of LIF and OSM other IL-6 type cytokine family members require an α-receptor. LIF and OSM signal directly through a heterodimer composed of gp130 and LIFR. While gp130 is ubiquitously expressed, the expression of α-receptor subunits is more limited to defined cell types allowing a more specific regulation of signaling for individual cytokines.

All members of the IL-6 type cytokine family signal from the plasma membrane to the cell nucleus via the gp130/LIFR - JAK (Janus kinase) - STAT (signal transducer and activator of transcription) pathway. As the molecular mechanism of this pathway has been elucidated in great detail for IL-6, major emphasis will be put on the

mechanisms involved in the regulation of IL-6 signaling, i.e.

(i) dephosphorylation of JAKs, gp130, STAT3 by the tyrosine phosphatase SHP-2

(ii) induction of the feed-back inhibitors SOCS1 and SOCS3 (suppressors of cytokine signaling)

(iii) complex formation of activated STAT dimers with specific protein inhibitors (PIAS)

(iv) cross-talk between JAK/STAT signaling and the pro-inflammatory cytokines IL-1 and TNF-α.

- competition of STAT3 and NF-κB for binding to an overlapping response element
- SOCS3 - mRNA stabilization by IL-1
- acceleration of gp130 internalization after serine phosphorylation induced by IL-1 activated MK-2

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Speakers

José Baselga
MSKCC, USA

Cédric Gaggioli
IRCAN, France

Peter Heinrich
Albert-Ludwig University, Germany

Niels Hellings
Hasselt University, Belgium

Wenwei Hu
Rutgers Cancer Institute, USA

Tony Hunter
Salk Institute, USA

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