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Yannick Comoglio, Alvaro Javier, Feliz Morel, Rita Hanna, Magalie Leloire, Marina Pagnuzzi, Jerome Durivault, Vincent Picco, Audrey Claren, Jérôme Doyen, et al.

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Unexpected Effects of Photontherapy on VEGFC Production and Tumor Aggressiveness in Two Medulloblastoma Subgroups

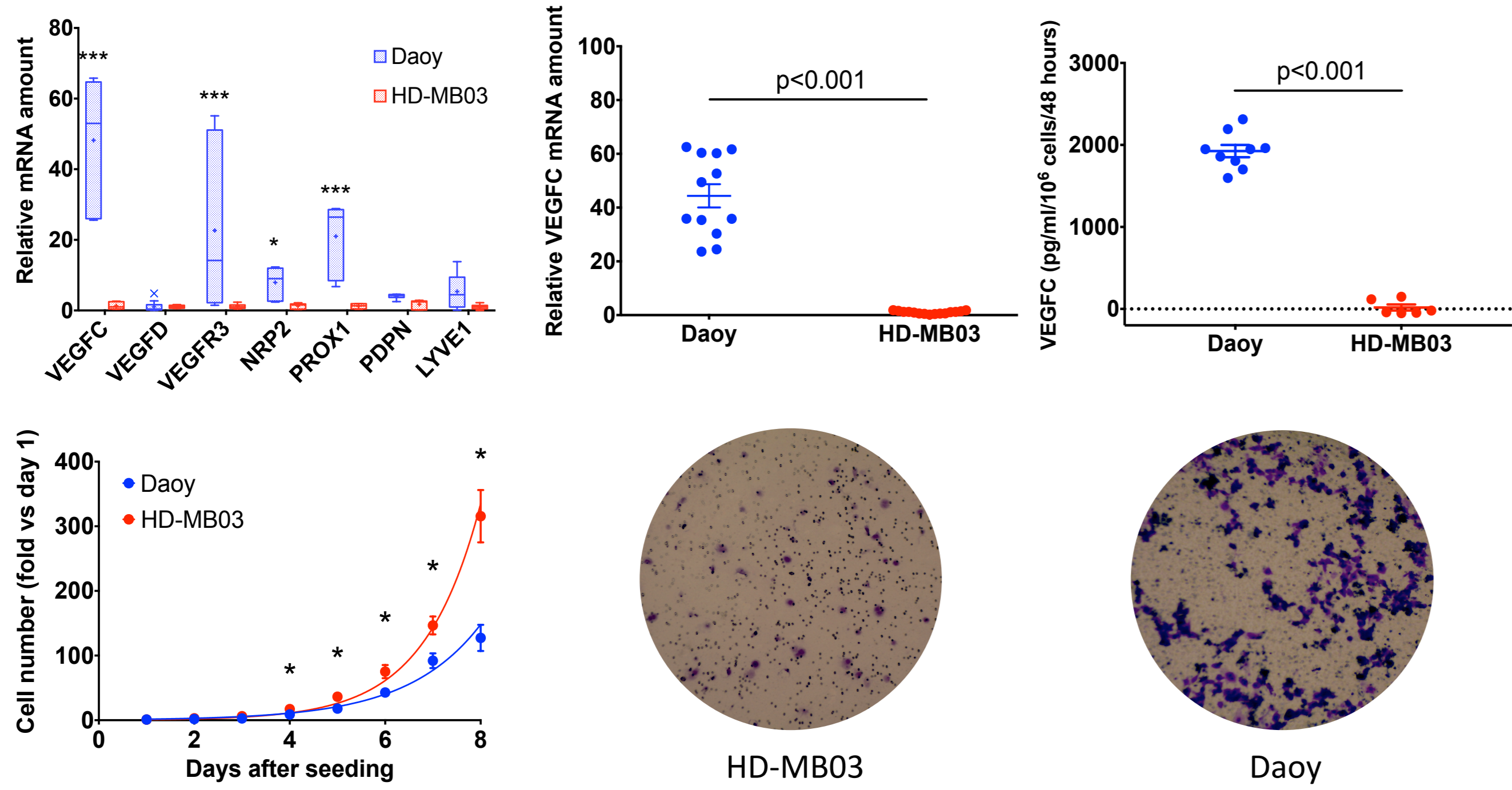
Yannick COMOGLIO^a, Manon PENCO-CAMPILLO^a, Rita HANNA^a, Vincent PICCO^b,
Alvaro Javier FELIZ MOREL^a, Magalie LELOIRE^a, Amandine MOROT^a, Marina PAGNUZZI^b,
Jérôme DURIVault^b, Gilles PAGÈS^{ab}, Sonia MARTIAL^a

a : Institute for Research on Cancer and Ageing of Nice (IRCAN), NICE, FRANCE
b : Scientific Center of Monaco (CSM), MONACO

Contact : sonia.martial@univ-cotedazur.fr

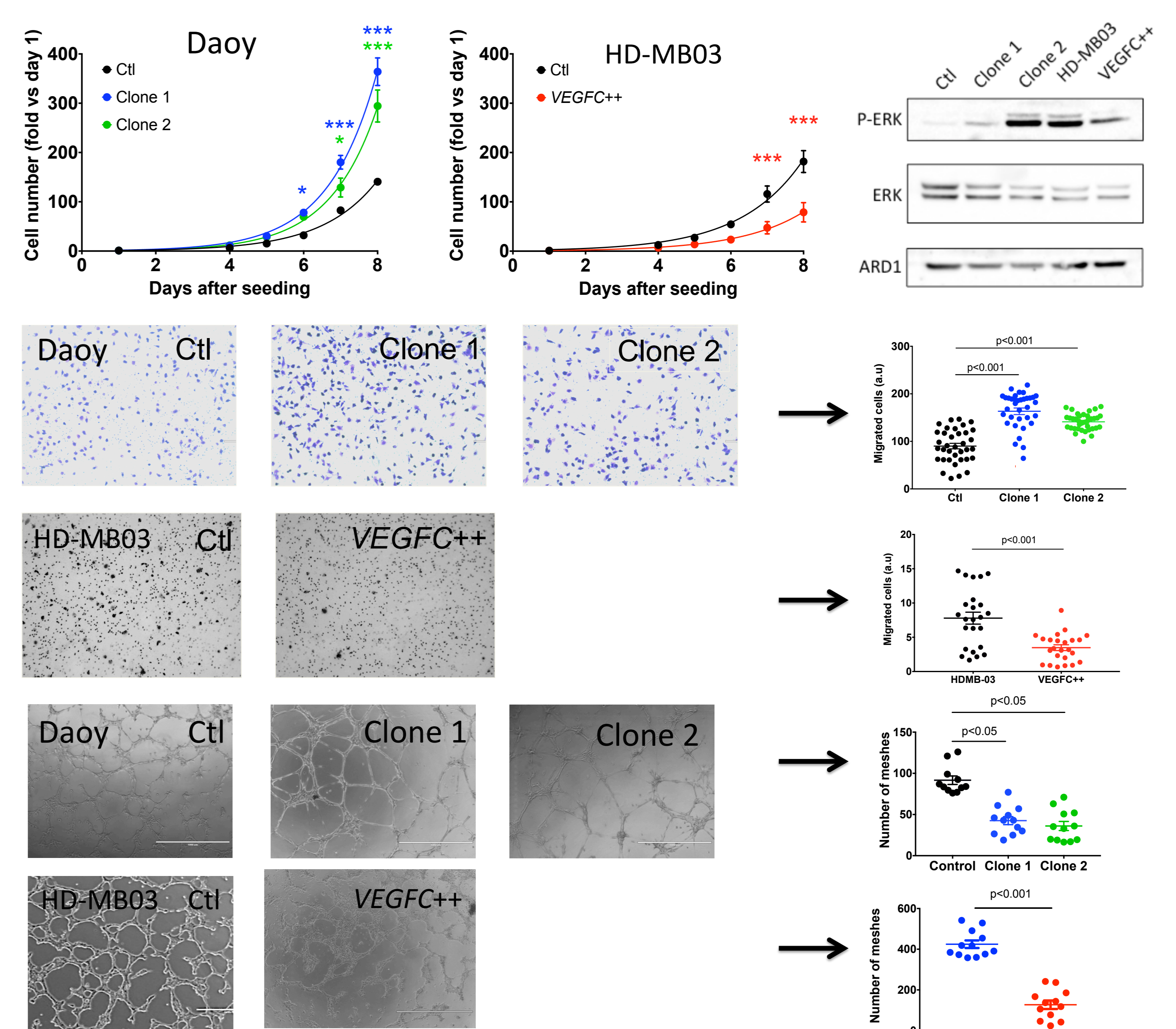
Medulloblastoma (MB) is the most common malignant cerebellar pediatric tumor. MB is a heterogeneous pathology composed of four molecular subgroups. MB treatment includes surgical resection of the tumor, craniospinal X-ray irradiation and adjuvant chemotherapy. 30% of the patients relapse. Their progression is marked by the fatal appearance of metastases within 5 years. The major actors of metastatic dissemination are the lymphatic vessel growth factor, VEGFC, and its receptor, VEGFR3. According to the current dogma, the lymphatic network is one of the main ways of tumor cell spreading. In this work, we meant to i) correlate VEGFC expression and MB aggressiveness; ii) determine the relevance of developing therapeutic strategies targeting the VEGFC / VEGFR3 axis. We showed that VEGFC mRNA expression is inversely correlated to cell aggressiveness. VEGFC decreased proliferation and migration of MB cell lines and promoted *in vitro* pseudo-vessel formation by MB cells. We generated irradiation-resistant cells and demonstrated that aggressive irradiation resistant-cells presented enhanced levels of VEGFC. Moreover, they acquired the ability to form vessel-like structures. Cells ectopically overexpressing VEGFC and irradiation-resistant cells formed smaller experimental tumors in nude mice. Opposite to the common dogma, our results give strong arguments to the role of VEGFC as a negative regulator of MB growth. However, VEGFC effect as for tumor dissemination might be MB subgroup dependent. Therefore, the use of VEGFC/VEGFR3 axis inhibitors to fight these tumors has to be considered with caution.

Intrinsic characteristics of MB cell lines



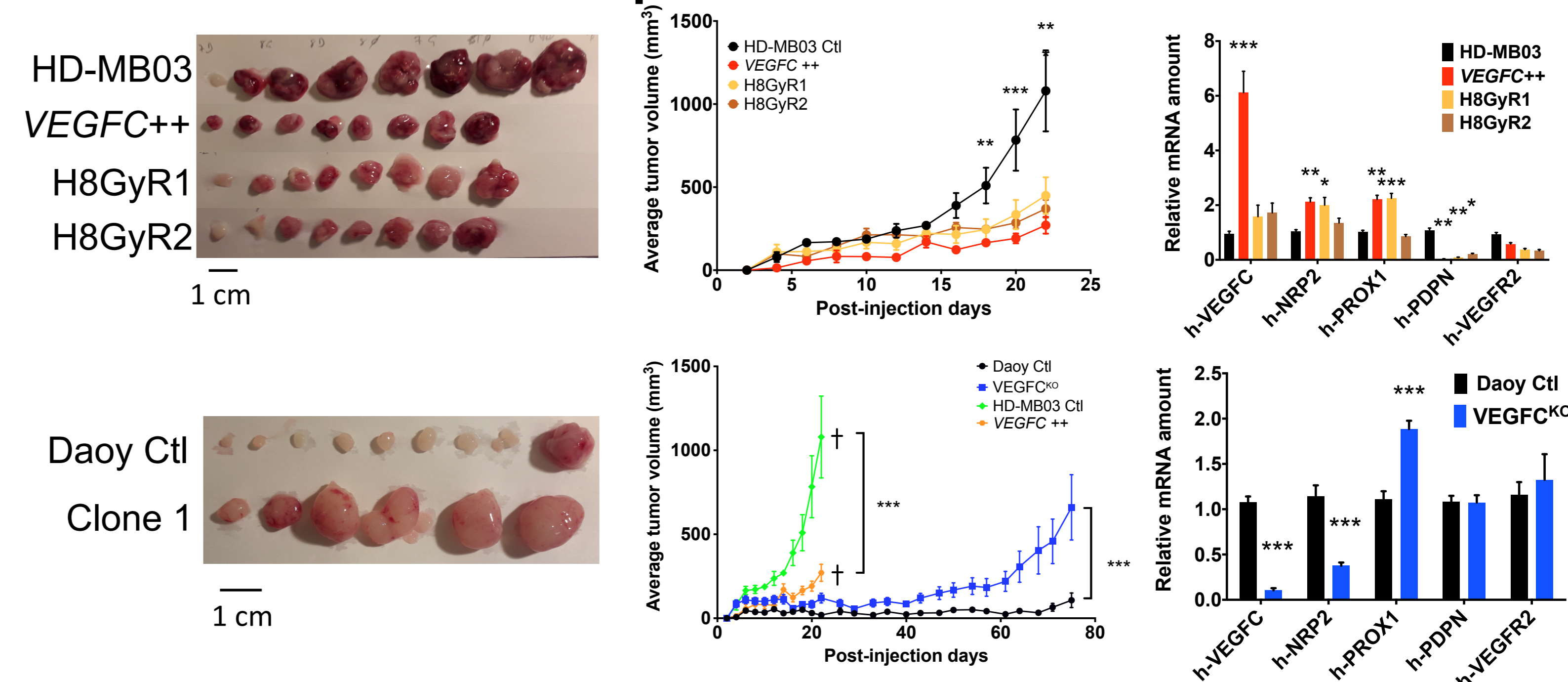
- ◆ Daoy cells (SHH): high expression of VEGFC/VEGFR3/NRP2
→ Low proliferation, high rate of migration, lymphomimicry
 - ◆ HD-MB03 cells (Grp 3): low expression of VEGFC/VEGFR3/NRP2
→ High rate of proliferation, no migration, no lymphomimicry
- VEGFC IS INVERSELY CORRELATED TO MB CELL AGGRESSIVENESS**

Effect of VEGFC expression on MB cell aggressiveness



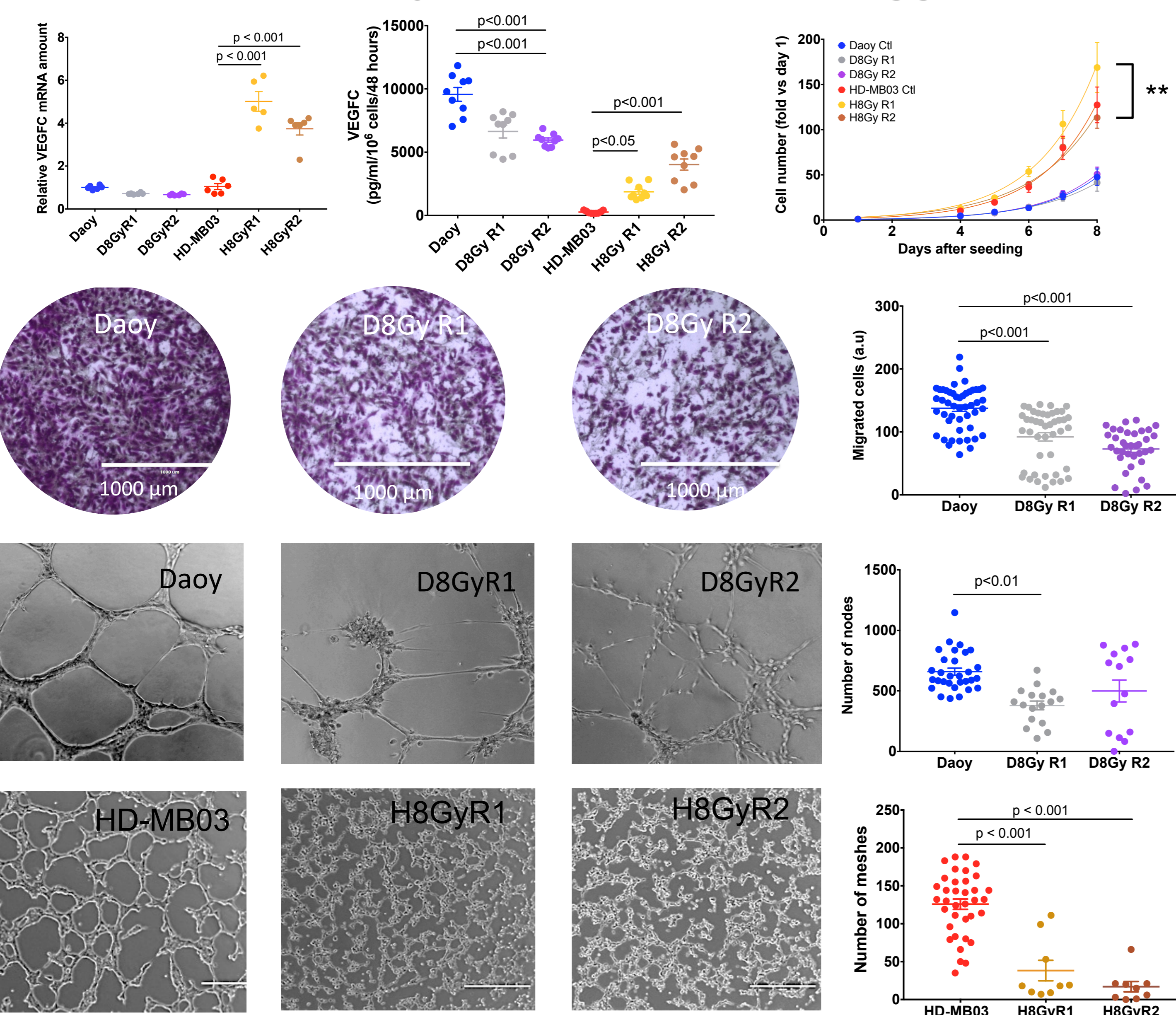
- ◆ Daoy cells (SHH): CRISPR-Cas9 knock-out of VEGFC gene
→ 2 clones with increased proliferation, higher migration, lower lymphomimicry
 - ◆ HD-MB03 cells (Grp 3): Transduction of VEGFC gene
→ 1 population with reduced proliferation, no migration, higher lymphomimicry
- VEGFC SLOWS DOWN MEDULLOBLASTOMA INTRINSIC CELL AGGRESSIVENESS**

Effect of VEGFC expression on *in vivo* MB behavior



- ◆ VEGFC-rich MB cell lines generate slower-growing tumors *in vivo*.
 - ◆ VEGFC-rich tumor cells also present high expression of NRP2 and CD146
→ VEGFC/NRP2 and/or VEGFC/CD146 signaling in MB cells and tumors,
 - ◆ VEGFC-rich tumors also present induced PROX-1 expression
- VEGFC/NRP2 SLOWS DOWN MEDULLOBLASTOMA IN VIVO AGGRESSIVENESS**

Role of VEGFC in X-ray irradiation induced aggressiveness



- ◆ VEGFC induction by irradiation is group-dependent.
 - ◆ When induced (HD-MB03; grp 3), cells proliferate slower, but show tube structuration.
 - ◆ When reduced, cells migrate less and organize less well.
- VEGFC SLOWS DOWN MEDULLOBLASTOMA ACQUIRED AGGRESSIVENESS**

Conclusion:

VEGFC is a negative regulator of medulloblastoma aggressiveness, independently of tumor group, probably via a CD146/NRP2-mediated signaling.