

## A NOVEL IL12-BASED IMMUNOCYTOKINE TARGETING FIBROBLAST ACTIVATION PROTEIN (FAP) FOR THE TREATMENT OF CANCER

<sup>1</sup>Lisa Nadal, <sup>1</sup>Frederik Peissert, <sup>1</sup>Abdullah Elsayed, <sup>2</sup>Tobias Weiss, <sup>2</sup>Thomas Look, <sup>2</sup>Michael Weller, <sup>3</sup>Geny Piro, <sup>3</sup>Carmine Carbone, <sup>3</sup>Giampaolo Tortora, <sup>1</sup>Mattia Matasci, <sup>1</sup>Nicholas Favalli, <sup>1</sup>Riccardo Corbellari, <sup>1</sup>Cesare Di Nitto, <sup>1</sup>Eleonora Prodi, <sup>4</sup>Chiara Libbra, <sup>4</sup>Simone Galeazzi, <sup>4</sup>Claudiopietro Carotenuto, <sup>5</sup>Cornelia Halin, <sup>1</sup>Emanuele Puca, <sup>4</sup>Dario Neri, <sup>1</sup>Roberto De Luca\*. <sup>1</sup>Philochem AG, Otelfingen, Switzerland; <sup>2</sup>University Hospital Zurich, Zurich, Switzerland; <sup>3</sup>Catholic University of the Sacred Heart, Rome, Italy; <sup>4</sup>Philogen S.p.A, Siena, Italy; <sup>5</sup>ETH Zurich, Zurich, Switzerland

**Background** Fibroblast Activation Protein (FAP) has been described as the “next billion-dollar nuclear theranostics target”<sup>1</sup>, since more than 28 different tumor types have successfully been imaged in patients with radiolabeled FAP ligands. <sup>2-3</sup> FAP can be found in the tumor microenvironment (TME) of most malignant solid tumors, while being absent in most healthy tissues. Thus, it is an attractive target for both imaging and therapeutic applications. Monoclonal antibodies targeting TME antigens have been considered for the delivery of bioactive payloads, such as proinflammatory cytokines. Antibody-cytokine fusions (also called immunocytokines) may exploit the tumor-homing properties of the antibody moiety, in order to concentrate the cytokine payload at the site of disease and enhance the therapeutic index.<sup>4</sup> Interleukin-12 (IL12) have been extensively studied in oncology. IL12 strongly promotes NK cells, CD4+ and CD8+ T cells to produce interferon-gamma (IFN-g), one of the most relevant mediators of anti-cancer immunity.<sup>5</sup>

**Methods** In this work, we describe the generation of a novel anti-FAP antibody, called 7NP2. The tumor recognition properties of the antibody were validated by immunofluorescence procedures performed on cancer biopsies from human patients. A fusion protein consisting of the 7NP2 antibody linked to interleukin-12 was generated and the anti-cancer activity of the murine surrogate product (named mL12-7NP2) was evaluated in mouse models. To prepare for future clinical trials, a fusion protein consisting of human IL12 linked to the 7NP2 antibody was further investigated in a toxicology study in *Cynomolgus* monkeys.

**Results** Biodistribution analysis in tumor bearing mice confirmed the ability of the product to selectively localize to solid tumors while sparing healthy organs. Encouraged by these results, therapy studies were conducted *in vivo*, showing a potent anti-tumor activity in immunocompetent and immunodeficient mouse models of cancer, both as single agent and in combination with immune checkpoint inhibitors. The fully human product was tolerated when administered to non-human primates.

**Conclusions** The results obtained in this work provided a rationale for future clinical translation activities using IL12-7NP2.

### REFERENCES

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**Ethics Approval** Mouse experiments were performed under a project license (license number 04/2018) granted by the Veterinärämamt des Kantons Zürich, Switzerland, in compliance with the Swiss Animal Protection Act (TSchG) and the Swiss Animal Protection Ordinance (TSchV).

Procedures on *Cynomolgus* monkeys (including housing, health monitoring, restrain, dosing, etc) and ethical revision were performed according to the current Italian legislation (Legislative Decree March 4th, 2014 n. 26) enforcing the 2010/63/EU Directive on the protection of animals used for biomedical research.

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