

### Preclinical and clinical development of a DC-based melanoma therapeutic vaccine

M. Salcedo<sup>1</sup>, N. Bercovici<sup>1</sup>, A. Nardin<sup>1</sup>, M.-T. Duffour<sup>1</sup>, E. Ferrière<sup>1</sup>, K. Labroquère<sup>1</sup>, S. Martin<sup>1</sup>, S. Massicard<sup>1</sup>, F. Vernel-Pauillac<sup>1‡</sup>, F. Audhuy<sup>1</sup>, J.-P. Abastado<sup>1\*</sup>, E. Tartour<sup>2</sup>, R. Taylor, D. Landais<sup>3</sup>, C. Robert<sup>4</sup>, B. Escudier<sup>4</sup>, G.A. McArthur<sup>5</sup>, M. Prince<sup>5</sup>, M.-A. Richard<sup>6</sup>, J.-J. Grob<sup>6</sup>, M.-T. Leccia<sup>7</sup>, I. Templier<sup>7</sup>, T. Lesimple<sup>8</sup>, V. Quillien<sup>8</sup>, C. Chabannon<sup>9</sup>, F. Viret<sup>9</sup>, M. Viguier<sup>10</sup>, H. Bachelez<sup>10</sup>, E. Vasseur<sup>11</sup>, P. Saiag<sup>11</sup>, M. Buffet<sup>12</sup>, I. Gorin<sup>12</sup>

1 IDM, Paris, France; 2 Hôpital Européen Georges Pompidou, Paris, France; 3 IDM, Irvine, CA, USA; 4 Institut Gustave Roussy, Villejuif, France; 5 Peter Mc Callum Cancer Institute, Melbourne, Australia; 6 Hôpital Ste Marguerite, Marseille, France; 7 CHU A. Michallon, Grenoble, France; 8 Centre Eugène Marquis, Rennes, France; 9 Institut Paoli-Calmette, Marseille, France; 10 Hôpital St Louis, Paris, France; 11 Hôpital A. Paré, Boulogne-Billancourt, France; 12 Hôpital Cochin-Tarnier, Paris, France.

Uvidem® is a melanoma vaccine co-developed with Sanofi-Aventis

The investigational drug Uvidem® is a cryopreserved autologous dendritic cell vaccine for the treatment of patients with advanced/high risk malignant melanoma. We have standardized a clinically compatible process to generate large quantities of monocyte-derived dendritic cells (DCs), in serum-free medium containing GM-CSF and IL-13. The vaccine includes DC loaded with lysates produced from 3 allogeneic melanoma tumor cell lines: M44, COLO 829 and SK-MEL-28.

Here we describe preclinical studies on Uvidem as well as the results from a Phase I/II clinical trial in advanced melanoma patients. In preclinical studies, DCs derived from healthy donors loaded with melanoma lysates were studied for their ability to cross-prime CD8 T cells specific for tumor associated antigens (TAA) *in vitro*. The TAA expressed by melanoma cell lines and their lysate counterparts was characterized. For the clinical trial, DC were loaded with melanoma lysates or tetanus toxoid then frozen in cryobags. For one of two randomized groups of patients, DC were treated with maturation agents before cryopreservation. After thawing, Uvidem was administered by intradermal and subcutaneous injections. A total of 49 patients were treated. Safety, clinical and immune responses were evaluated. The characteristics of DC derived from patients included in the clinical study were compared to DC derived from healthy donors.

We showed that the melanoma lysates used in Uvidem vaccine contain several melanoma and tumor shared antigens. In addition, DC loaded with these lysates were shown to prime specific T cells capable of recognizing naturally processed epitopes on melanoma cells. We demonstrated that autologous DC produced in large scale from stage IV melanoma patients prepared according to IDM proprietary procedure have properties comparable to healthy donor DC in terms of *in vitro* maturation and migration. Thus, they have a potential for *in vivo* T cell stimulation. In the clinical trial, 15 out of 49 treated patients completed 6 doses. The analysis of immune responses suggests that Uvidem vaccine is able to trigger specific T cells *in vivo*. Ten out of 13 patients who received 6 vaccinations (77%) and who could be analyzed for immune responses showed appearance or increased levels of vaccine-specific T cells after treatment. Four other patients who received less than 6 vaccinations were also immune responders. Appearance of immune responses was not associated to vaccination with either matured or non-matured DC. Disease stabilizations occurred late, after initial progression on the study and were observed in 10 patients (20% of all treated patients). Interestingly 8 out of the 14 immune responders (57%) had stabilization of their disease and 100% of the patients who stabilized their disease had received 6 doses of vaccine.

Current address:

\* Institut Cochin, Paris, France

‡ Institut Pasteur de Nouvelle-Calédonie