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## Immunotherapy

# A new pathway for modulating anti-tumoral immune response

Researchers from Inserm, CNRS, Paris-Sud University, Gustave Roussy, and Institut Curie have identified a new agent in regulating *PD-L1* gene expression: the *eIF4F* complex, which plays a role in controlling protein synthesis.

This complex could become a predictive marker for response to immunotherapy. Furthermore, the researchers demonstrate, for the first time, that inhibition of the *eIF4F* complex gives rise to an anti-tumoral effect related to decreased *PD-L1* expression, which therefore elicits immune system intervention.

The researchers hope that *eIF4F* inhibitors will be able to be used as anti-cancer agents in the future, alone or, more than likely, in combination with other treatments.

Just a few years ago, the immune system, our defense against disease, seemed unequipped to fight cancer. Advances in immunotherapy are making it possible to correct these shortcomings: the immune system can now learn to recognize and destroy cancer cells. Lymphocytes are thus rediscovering their initial ability to fight rather than protect tumors.

The *PD-1* (programmed cell death) molecule, expressed on the surface of T cells, binds to another molecule present on the surface of certain tumor or immune cells, *PD-L1*. This interaction in a way renders the tumor cell invisible to the immune system, by deactivating (or disarming) T cells.

In recent years, immunotherapy targeting the *PD-L1/PD-1* interaction has revolutionized the treatment of melanoma and other types of cancer.

However, many patients do not respond to treatment. These agents are highly effective for several months or years, but only in 10 to 20% of patients, for all types of cancer combined.

*“The development of biomarkers is therefore a key issue in identifying patients liable to respond to treatment,”* explains **Professor Caroline Robert, Head of the Dermatology Department at Gustave Roussy.**

*“A high *PD-L1* level in tumors is a major indicator since this is often associated with a good response to anti-*PD1* agents. However, the mechanisms for regulating *PD-L1* expression have not been fully elucidated,”* points out **Stephan Vagner, Inserm Research Director and Head of the RNA Biology Team at Institut Curie.**

In this latest publication, the researchers demonstrate, for the first time, that a complex known as *eIF4F*, involved in initiating the translation of messenger RNA into proteins, regulates *PD-L1* expression and that, by targeting *eIF4F* in tumor cells, anti-tumoral immunity can be stimulated, thus mimicking the effect of immunotherapy.

In this study, the researchers mainly used melanoma as a model, but also conducted tests with lung cancer, breast cancer, and colon cancer cells.

They will now go on to evaluate the findings of the study on the formation of the eIF4F complex, as a predictive marker for response to immunotherapy.

They are, moreover, developing other melanoma treatment models, based on the use of eIF4F complex inhibitors, in combination with other treatments, to increase therapeutic efficacy and fight resistance.

## **References**

### **'Translational control of tumor immune escape via the eIF4F-STAT1-PD-L1 axis in melanoma'**

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Michaël Cerezo <sup>1,2,12</sup>, Ramdane Guemiri <sup>1,2,3,4,5,12</sup>, Sabine Druilennec <sup>5,6,7</sup>, Isabelle Girault <sup>1,2</sup>, Hélène Malka-Mahieu <sup>3,4,5</sup>, Shensi Shen <sup>1,2</sup>, Delphine Allard <sup>1,2</sup>, Sylvain Martineau <sup>3,4,5</sup>, Caroline Welsch <sup>1,2,3,4,5</sup>, Sandrine Agoussi <sup>1,2</sup>, Charlène Estrada <sup>5,6,7</sup>, Julien Adam <sup>1,8</sup>, Cristina Libenciu <sup>9</sup>, Emilie Routier <sup>9</sup>, Séverine Roy <sup>9</sup>, Laurent Désaubry <sup>10</sup>, Alexander M. Eggermont <sup>2,9</sup>, Nahum Sonenberg <sup>11</sup>, Jean Yves Scoazec <sup>8</sup>, Alain Eychène <sup>5,6,7</sup>, Stéphan Vagner <sup>3,4,5,9,13\*</sup> and Caroline Robert <sup>1,2,9,13\*</sup>

<sup>1</sup>INSERM U981, Gustave Roussy, Villejuif, France

<sup>2</sup>Université Paris-Sud, Université Paris-Saclay, Kremlin-Bicêtre, France

<sup>3</sup>Institut Curie, PSL Research University, CNRS UMR 3348, Orsay, France

<sup>4</sup>Université Paris-Sud, Université Paris-Saclay, CNRS UMR 3348, Orsay, France

<sup>5</sup>Equipe Labellisée Ligue Contre le Cancer, Paris, France

<sup>6</sup>Institut Curie, PSL Research University, CNRS UMR 3347, INSERM U1021, Orsay, France

<sup>7</sup>Université Paris-Sud, Université Paris-Saclay, CNRS UMR 3347, INSERM U1021, Orsay, France

<sup>8</sup>Department of Pathology and Laboratory Medicine (BIOpath), Gustave Roussy, Université Paris-Saclay, Villejuif, France

<sup>9</sup>Oncology Department, Gustave Roussy, Université Paris-Saclay, Villejuif, France

<sup>10</sup>CNRS-Strasbourg University, UMR7200, Illkirch, France

<sup>11</sup>Department of Biochemistry, McGill University, Montréal, Québec, Canada

<sup>12</sup>These authors contributed equally: Michaël Cerezo, Ramdane Guemiri.

<sup>13</sup>These authors jointly supervised this work: Stéphan Vagner, Caroline Robert

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## **Press contacts**

**Gustave Roussy:** Claire Parisel +33 (0)1 42 11 50 59 [claire.parisel@gustaveroussy.fr](mailto:claire.parisel@gustaveroussy.fr)

**Institut Curie:** Catherine Goupillon +33 (0)1 56 24 55 23 [service.presse@curie.fr](mailto:service.presse@curie.fr)

## **Research contacts**

Caroline Robert +33 (0)1 42 11 42 10 [caroline.robert@gustaveroussy.fr](mailto:caroline.robert@gustaveroussy.fr)

Stephan Vagner +33 (0)1 69 86 31 03 [stephan.vagner@curie.fr](mailto:stephan.vagner@curie.fr)

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