

The ‘Holy Grail’ in Immuno-Oncology: AC BioScience SA is Aiming to Potentiate Anti-PD-1 Therapy Efficacy through Tumor Cell Conditioning Strategy

Andreas Schläpfer^{*a}, Christian Auclair^a, Bassam Janji^b, Manale Karam^a, and Muhammad Zaeem Noman^b

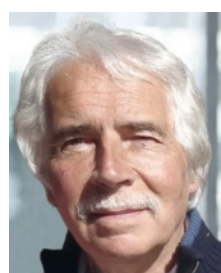
Abstract: AC BioScience is a Swiss biotech company based at the EPFL Innovation Park and Biopôle, dedicated to developing groundbreaking therapies to fight a range of cancers and infectious diseases. We are about to start clinical trials with two of four leading-edge cancer drugs mainly focusing on immune-oncology and tumor vascular normalization with multi-billion \$ sales potential. Here, we present our strategy and one of our pioneering drug candidates that has already shown exceptional results with tumor cell conditioning to improve the efficacy of immune checkpoint inhibitors.

Keywords: AC Bioscience SA · ACB1801 · Cancer therapies · Immune checkpoint inhibitors · Swiss biotech



Nutrition business.

Chief Executive Officer and co-founder is **Andreas Schläpfer**, who has extensive experience in business strategy and global management. He holds a Master’s Degree in Economics from St. Gallen University. He spent more than three decades as a senior executive at the Nestlé Group (CEO in France, Russia, Thailand/Indochina) and as Global Business Head/Senior Vice President in charge of Nestlé’s Infant



Bioengineering at the Ecole Normale Supérieure de Cachan. He co-founded the Graduate School of Oncology at the Institut Gustave Roussy and founded the Master’s programme in Cancer Research.

The Chief Scientific Officer and co-founder is **Professor Christian Auclair**, an eminent expert in pharmacology, molecular oncology and innate immunity. He is an Emeritus University Professor (exceptional class) and Doctor in Science (PharmD, PhD). Professor Auclair is a former Deputy Director at CNRS in the Department of Life Sciences and was subsequently Head of the Department of Biochemistry

1. Business Case, Context, Motivation

During his life-long research activities and senior role in the leading cancer research organizations in France, Professor Christian Auclair gained a unique insight and translational knowledge of oncology-related activities carried out over the years. He also noted that a number of discoveries in basic research had not been pursued further because of shifting research priorities and altered budget allocations. Some of the molecules at the center of

this research held exceptional promise for the lives and survival rates of innumerable cancer patients.

When Professor Auclair met Andreas Schläpfer, a former senior executive at the Nestlé Group, the two came to the decision that the most promising of these molecules should be taken through (pre)clinical research, with a vision to aid cancer patients in need. As a result, AC BioScience SA was created at the EPFL Innovation Park near Lausanne in March 2017.

2. Solution, Scientific Approach

The huge progress in cancer research in the past two decades has led to a renewed interest in combining conventional treatments based on new rationales. The realization that cancer progression is not exclusively due to cancer deregulated cell proliferation, but also involves the nature of tumor microenvironment and the global immune response has opened new ways for the design of new combination treatments.

AC BioScience is pioneering the development of several ground breaking cancer therapies, two of which will start with clinical trials in 2021: One of its innovative approaches aims to improve the treatment of metastatic pancreatic adenocarcinoma using a proangiogenic S1P lyase inhibitor acting as a tumor vascular normalizer that will help drugs to better access solid tumors and oxygenation. A successful proof of concept would provide a premise for a similar strategy to be implemented for all poorly vascularized solid tumors, thus, providing a transformative new standard for cancer treatment.

AC BioScience’s second drug candidate for clinical trial is a beta-carboline derivative in a combination treatment. It deals with tumor cell conditioning to render cancer therapy more responsive to cancer treatment resulting from either genetic or pharmacologic manipulation of the malignant phenotype. Here AC BioScience presents an example of tumor cell conditioning to improve the efficacy of immune checkpoint inhibitors.

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2.1 Breakthrough in Cancer Treatment: Immune Checkpoint Inhibitors

During the past few years, immune checkpoints that maintain physiologic self-tolerance have been shown to be involved in the downregulation of anti-tumor immunity. As typical example, cytotoxic T-lymphocyte antigen 4 (CTLA-4) plays an important role in the regulation of immune activation and tolerance; CTLA-4 signaling inhibits T-cell activation, particularly during strong T-cell responses. In the same line, the binding of Programmed Cell Death Protein 1 (PD-1), a receptor expressed on activated T cells, to its ligands, PD-L1 and PD-L2, negatively regulates immune responses. The PD-1 ligands are found on most cancers, and PD-1/PD-L1/2 interaction inhibits T cell activity and allows cancer cells to escape immune surveillance.

The strategies to restore anti-tumor immunity have focused at first on monoclonal antibody-based targeting of CTLA-4 and afterward PD-1 on T lymphocytes and its main ligand (PD-L1) on tumor cells. Food and Drug Administration (FDA) has approved various anti-PD-1/PD-L1 monoclonal antibodies (mAbs) for the treatment of metastatic melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), bladder cancer, recurrent or metastatic head and neck cancer, refractory classical Hodgkin lymphoma, colorectal cancer (CRC), and metastatic Merkel cell carcinoma. Despite these successes, many patients experience intrinsic resistance, and even responding patients can develop acquired resistance to anti-PD-1 therapy.^[1] In patients suffering from metastatic melanoma, the objective response rates remain limited and are around 20% to 25% for the patients treated with anti-CTLA-4^[2] and roughly 30–35% for PD-L1 positive patients treated with anti-PD-1/PD-L1.^[3]

Numerous studies are currently going on to elucidate the mechanisms responsible for mAbs resistance and exploring effective combinatorial approaches to recover efficacy or increase sensitivity in PD-1 blockade-resistant patients is attracting research attention.

2.2 Tumor Antigen Presentation as Key of Immune Response

The cancer-immunity mechanism indicates that CD8 T cell recognition of neoantigens (arising from altered tumor proteins formed as a result of tumor mutations) displayed by the major histocompatibility complex class I (MHC-I) on tumor cells is a critical step to eliminate these tumorigenic cells *via* immune checkpoint inhibitors therapy.^[4] In this context, it has been observed that the tumor mutation burden (TMB), was a predictive marker of checkpoint blockade therapy efficacy.^[5] However, the CD8 T cell cytotoxic response depends on the efficacy of the MHC-I mediated antigen presentation machinery which is a multistep complex process often impaired in tumor cells.

Tumor antigens are first processed to peptides by the immunoproteasome. Then, these antigenic peptides are translocated from the cytosol into the endoplasmic reticulum (ER) by the transporter associated with antigen processing (TAP) which also acts as a scaffold for the final stage of MHC class I assembly.^[6] In the ER, MHC-I molecules are formed by the folding of the heavy chain α -subunit and its assembly with the β 2m subunit with the assistance of ER resident chaperons. Then, the peptide-loading complex (PLC) is formed by association of MHC-I molecule, calreticulin and ERP57 chaperons, tapasin and TAP.^[7] Tapasin acts as a bridging molecule between the MHC class I/chaperone complex and TAP facilitating the binding of high affinity peptides to the MHC-I molecules. After peptide loading, MHC-I molecules dissociate from PLC to export sites on the ER membrane where they are selectively recruited into cargo vesicles for transport to the Golgi apparatus.^[8] MHC-I/peptide complex then traffics through the Golgi apparatus to the plasma membrane (Fig. 1).

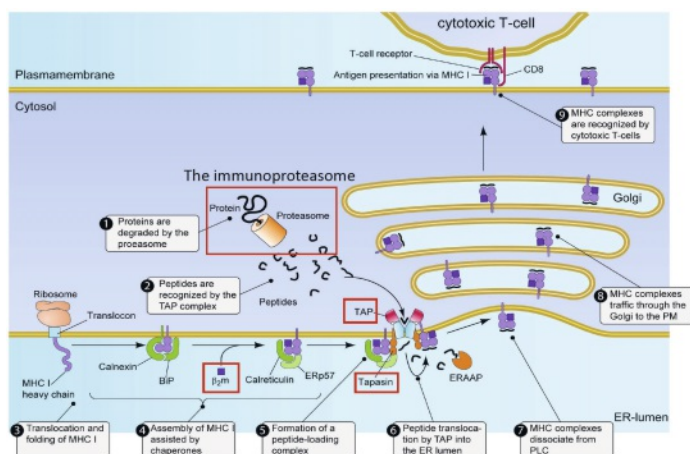


Fig. 1. Schematic representation of MHC-I-mediated antigen processing and presenting machinery. BiP, immunoglobulin binding protein; β 2m, β 2-microglobulin; ER, endoplasmic reticulum; ERAP, ER-resident aminopeptidase (trims peptides to 8–10 mers); MHC I, major histocompatibility complex class I; PLC, peptide-loading complex; TAP, transporter associated with antigen processing (adapted from ref. [9]: Abele and Tampe, 2004).

2.3 Impairment of MHC-I-mediated Antigen Presentation in Tumor Cells

As mentioned above, the MHC-I antigen presentation machinery is often impaired in tumor cells and it is well established that tumor immune escape is associated with MHC-I downregulation, as seen in different human and experimental tumors and reviewed in many reports.^[10] MHC-I expression depends on the tumor phenotype and two extreme phenotypes can be identified: a good phenotype (rejected tumor phenotype) and a bad phenotype (escape tumor phenotype) (Fig. 2). Tumors with the later profile can be derived from tumors that got established and progressed after they had escaped T-cell mediated immunosurveillance.^[10a] A tumor derived from an HLA-I positive epithelium can lose totally or partially the expression of class I molecules.^[10a] The total percentage of various types of HLA-I loss, including total loss, haplotype loss, or allelic loss, ranges from 65 to 90%, depending on the type of cancer.^[11]

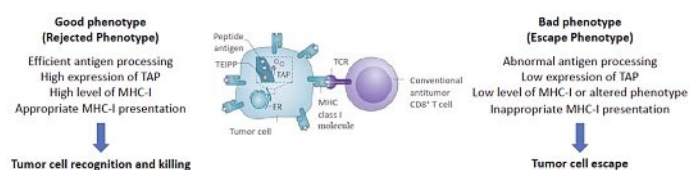


Fig. 2. Tumor phenotype heterogeneity conditions the tumor escape from immune surveillance. ER, endoplasmic reticulum; MHC-I, major histocompatibility complex class I; TAP, transporter associated with antigen processing; TCR, T-cell receptor; TEIPP, T cell epitopes associated with impaired peptide processing.

The relevance of the phenotypic classification is provided as a typical example by colorectal cancer (CRC) patients in which 35% of them have an abnormal MHC-I expression. It has been observed in CRC that TAP1 down-regulation elicits immune escape and poor prognosis.^[12] This observation can be extended to most tumor types as assessed by a recent elegant work done by Wang *et al.*^[13] In this study, the authors proposed a method to measure tumor immunogenicity score (TIGS), which combines tumor mutational burden (TMB) and an expression signature of the antigen processing and presenting machinery (APM). A clear correlation exists between pan-cancer immune checkpoint inhibitors objective response rates (ORR) and immune tumor status for

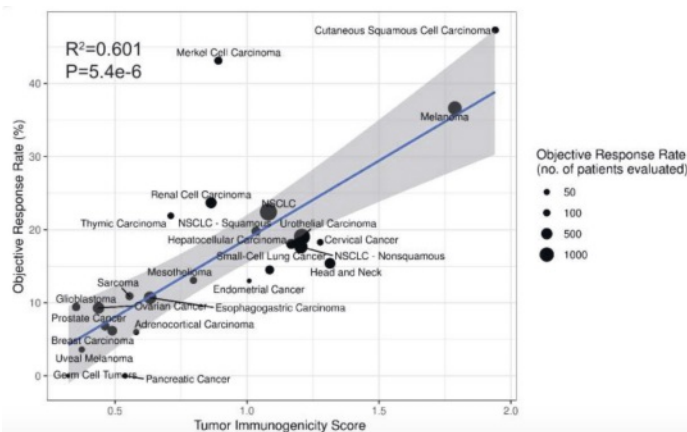


Fig. 3. Tumor immunogenicity score and predicted pan-cancer response rates to PD-1 inhibition. Correlation between Tumor immunogenicity score (TIGS) and objective response rate (ORR) with anti-PD-1 as described in published studies for which data regarding the ORR is available. The number of patients who were evaluated for the ORR is shown for each tumor type (size of the circle) (from ref. [13], Wang *et al.*, 2019).

individual patients (Fig. 3). Data in Fig. 3 clearly shows that TIGS is an effective tumor-inherent biomarker for response prediction.

It is obvious that we have a limited possibility to increase the intrinsic tumor mutational burden and the TIGS increase should be obtained by improving the antigen presentation machinery efficacy. Along this line, the challenge facing the researchers is how to turn tumor cells escape phenotype into antigen presenting cell phenotype (rejected phenotype) (Fig. 2).

2.4 The Tumor Phenotype Reversion: The Strategy to Improve Tumor Antigen Presentation

Among the suspected mechanisms of resistance to immune checkpoint targeting, AC BioScience has focused investigations on the expression of MHC-I by tumor cells and on the relationship existing between the malignant phenotype and the MHC-I functional integrity.

As with many parasites, to survive and proliferate, tumor cells should escape from the immune surveillance of the host. The host immune response can be considered as a selection pressure and according to the evolution theory, the genetic program behind the malignant phenotype provides an adaptive response allowing the escape from the immune system. The impairment of antigen presentation is one of the consequences of this adaptive response.

In this context, it is expected that the ‘manipulation’ of the malignant phenotype; *i.e.* the loss of all or part of the malignant characters (referred to as tumor reversion), would result in the unmasking of tumor cells mainly through the rescue of tumor antigen presentation.

Along this line, several years ago a scientific program started at Gustave Roussy Institute (Villejuif France) aiming to identify the specific molecular basis of malignant phenotype maintenance and key processes of which pharmacological manipulation would result in tumor phenotypic reversion. In agreement with previous observations, it was hypothesized that changes in the cytoskeletal architecture which is one of the main molecular mechanisms underlying tumor progression could be a pertinent target process for the induction of tumor phenotype reversion. Consistently, genetic-induction of actin network rearrangement in transformed cells resulted in phenotypic reversion thanks to the rescue of cell adhesion and motility controls.^[14] Based on these findings, a two-step screening strategy involving a molecular primary screening (actin dynamics modulation) followed by a cellular functional secondary screening (cell adhesion and motility) have been performed. Several compounds in the series of pyridoindole and pyridocarbazole were found

to promote actin cytoskeleton remodelling and act as tumor-reverting agent at non-cytotoxic concentration.^[15] One of these compounds (ACB1801) has been selected by AC BioScience to start, in close collaboration with the Luxembourg Institute of Health (LIH), a series of proof of concept studies using murine melanoma B16-F10, a tumor experimental model extremely resistant to anti PD-1 antibody.

3. Product/Service and Outlook: ACB1801 Elicits the MHC-I Machinery and Potentiates Anti-PD-1 in Melanoma B16-F10 Model

The murine B16-F10 melanoma model is the most used metastatic melanoma model for preclinical studies. The syngeneic B16-F10 model allows the evaluation of responses to immuno-oncology agents in immunocompetent C57BL/6 mice. In this model, checkpoint inhibitors anti-mouse PD-1 or anti-mouse PD-L1 did not produce any response in subcutaneous B16-F10 tumors. Similarly, initiation of treatment with anti-mouse CTLA-4 or anti-mouse LAG-3 as early as four days post implant did not produce any response as well. Thus, melanoma B16-F10 is an experimental tumor model resistant to checkpoint inhibitors and therefore appropriate to investigate a strategy dealing to the transformation of a resistant phenotype to responder phenotype.

In close collaboration with the LIH team headed by Dr. Bassam Janji, we have extensively investigated the effect of ACB1801 on the different components of the antigen presentation machinery, the MHC-I antigen presentation and the consequences in terms of anti-PD-1 antitumor efficacy. Some of the key results are presented and discussed below.

3.1 ACB1801 Strongly Increases MHC-I-mediated Antigen Presentation in Melanoma B16-F10 Cells

Melanoma B16-F10 treatment with ACB1801 results in a dose-dependent increase in H-2Kb bound OVA (SIINFEKL) peptide presentation as promoted by MHC-I complex at the cell membrane. Starting from 25 μ M ACB1801, the increasing effect is close to the one induced by interferon gamma (Fig. 4). It should be noted that up to 50 μ M, ACB1801 has no effect on the melanoma cell viability and cell cycle.

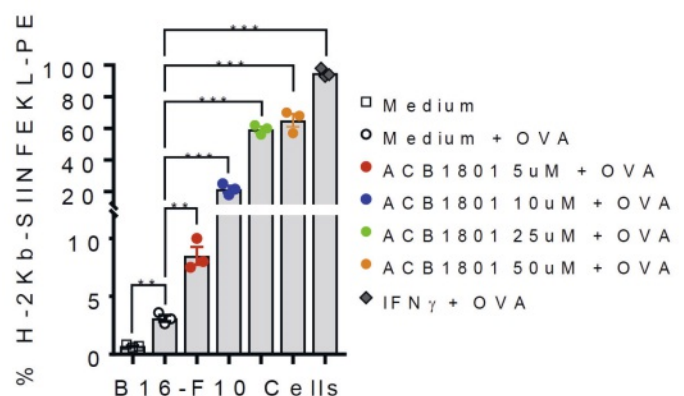


Fig. 4. Effect of ACB1801 on OVA257-264 peptide presentation by MHC-I (H-2Kb) on the surface of B16-F10 melanoma cells. B16-F10 cells un-pulsed (medium) or pulsed (medium + OVA) with OVA257-264 peptide SIINFEKL for 48 h were treated simultaneously with ACB-1801 (ACB1801 + OVA) at 5, 10, 25 or 50 μ M. Cells pulsed with OVA and treated with IFN-gamma (IFN- γ + OVA) were used as a positive control. Cells were then stained with PE anti-mouse H-2Kb bound to SIINFEKL antibody or mouse IgG1, κ PE isotype control. Data are reported as the average of 3 independent experiments and shown as mean \pm SEM (error bars). Statistically significant differences (indicated by asterisks) calculated compared to control condition (medium) using an unpaired two-tailed Student's t-test are shown (**= $p < 0.005$ and ***= $p < 0.0005$).

3.2 ACB1801 Displays an Immune-dependent Antitumor Activity

In immune-deficient mice, ACB1801 does not display any antitumor effect at an oral dose of 50 mg/kg. In contrast, a significant antitumor effect is observed in the immunocompetent model (Fig. 5). This is consistent with the fact that the improvement of antigen presentation will trigger the activation of cytotoxic CD8 lymphocytes and subsequent antitumor immune response. This mechanism is evidenced by the modification of the tumor immune landscape with an increase of CD8/T reg ratio upon ACB1801 treatment.

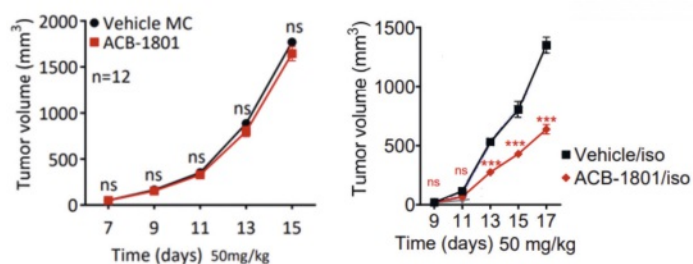


Fig. 5. The antitumor efficacy of ACB1801 in B16-F10 melanoma tumor-bearing mice. Left panel: Volume (reported in mm³) of B16-F10 melanoma tumors subcutaneously transplanted in immune-deficient NOD Scid Gamma (NSG) mice treated with vehicle (Vehicle MC) or 50 mg/kg ACB1801 (ACB1801) every day per os administration. Right panel: Volume (reported in mm³) of B16-F10 melanoma tumors subcutaneously transplanted in immuno-competent C57BL/6 mice treated with vehicle (Vehicle/iso) or 50 mg/kg ACB1801 (ACB-1801/iso) per os administration every day. Treatments were started when tumors became palpable, typically at day 7 or 9. Left curve represents 3 independent experiments of 4 mice per group. Right curve represents 3 independent experiments of 5 mice per group. All results are shown as mean \pm SEM (error bars). Statistically significant differences (indicated by asterisks) are calculated compared to control conditions using an unpaired two-tailed Student's t-test. Not significant (ns) = $p > 0.05$; and *** = $p < 0.0005$.

3.3 Combination of ACB1801 Strongly Potentiates the Anti-PD-1 Efficacy

When tested alone, anti-PD-1 has no effect on the survival of mice bearing melanoma B16-F10, as expected (Fig. 6). However, in agreement with the results shown in Fig. 4, AB1801 by itself induces a significant but limited increase in mice survival. On the other hand, a striking result is obtained using the combination of ACB1801 and the anti-PD-1 with a strong potentiation of the individual effect.

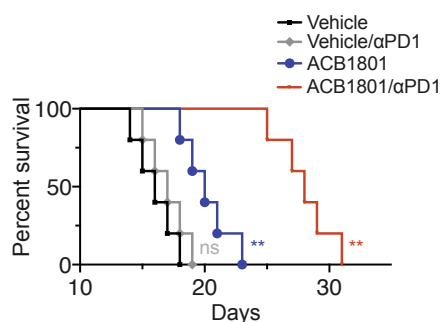


Fig. 6. Combining ACB1801 with anti-PD-1 improves B16-F10 tumor bearing mice survival. Survival of mice treated with vehicle alone (Vehicle), vehicle combined with anti-PD-1 (vehicle/ α PD1), 50 mg/kg ACB1801 (ACB1801) or anti-PD-1 combined with 50 mg/kg ACB-1801 (ACB1801/ α PD1) was analyzed. Mice survival curves were generated from 5 mice per group. Lack of survival was defined as death or tumor size > 1000 mm³. Mice survival percentage was defined using Graph Pad Prism and P values were calculated using the Log-rank (Mantel-Cox) test (ns = not significant and ** = $p \leq 0.01$).

4. Conclusion

In agreement with the clinical observations, we have demonstrated that in an experimental tumor model resistant to checkpoint inhibitors, the improvement of MHC-I-mediated antigen presentation turns a non-responder to a responder phenotype. Considering that in any tumors about 50% of individual patients display an abnormal antigen presentation, a combination involving a checkpoint inhibitor with a drug as ACB1801 appears to be highly relevant to increase the number of responder patients. ACB1801 works at non-cytotoxic concentration, is active by oral route and extremely well tolerated in animal models and consequently appears to be an attractive drug candidate for a proof of concept clinical trial.

AC BioScience



AC BioScience is a startup biotech company with an innovative vision and business model. We are dedicated to developing groundbreaking new therapies to fight a range of cancers and infectious diseases. We have obtained patent protection for one innovative cancer therapy and have filed patents for three others. Two of our four lead molecules in oncology will enter clinical stage in early 2021. The company has a subsidiary company – AC BioTech SAS – whose offices are located in the Villejuif BioPark near Paris, in proximity to the main French cancer research institutions. AC BioTech serves as a liaison point and vehicle for clinical validation activities in France.

Key Figures

Founding Year	2017
Location(s)	Headquarter: Ecublens, Switzerland Subsidiary: Villejuif, France
Legal Form	Private limited stock company (Ltd)
Founders	Andreas Schlöpfer Prof. Christian Auclair
Scientific Advisors	Prof. Martin Schlumberger Prof. Patrick Couvreur Prof. Jean-Pierre Kinet Prof. Olivier Hermine Prof. Marco Ciufolini
No of employees	5
Market capitalization	CHF 2.5 million

Key Inventions

Beta-carboline derivatives	March 2019: Patent application filed for a Beta-carboline derivative (ACB1801) for the non-toxic and immunological treatment of cancer.
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S1P lyase inhibitors	August 2017: Patent application filed for the enhancement of chemotherapy efficiency by Sphingosine-1-phosphate (S1P). August 2019: Patent application filed for various metabolites of S1P lyase inhibitors for the treatment of infectious diseases and cancer. March 2020: Patent application filed for a combination of flavonoids and S1P lyase inhibitors for the treatment of lung inflammation.
CAP6	August 2017: Acquisition of a patent for a Peptide having the sequence SEQ.1 for use as a medicament, in particular for the treatment of cancer.
RGD-peptide	March 2020: Patent application filed for RGD-peptide and use thereof for inhibiting RGD-binding integrins and for cancer treatment.
Next Milestones	
June 2021	Start clinical trials with S1P lyase inhibitors for radiotherapy and/or chemotherapy
October 2021	Start clinical trials with ACB1801 in a combination treatment with anti PD-1 drug
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