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Novel platform to design efficacious cancer targeted immunotherapies

Introduction

Since the approval of rituximab 20 years ago, antibody-based immunotherapies have dramatically changed the natural history of several cancer types. However, due to the difficulty in identifying tumor-associated antigens, **only a few antibody-based drugs have entered into clinical use**. Furthermore, more than 50% of the available therapeutic antibodies target only a few antigens, and consequently **no targeted immunotherapeutic option exists for the majority of cancer types**. Therefore, it has become of pivotal importance to design immunotherapies against novel tumor-associated antigens efficacious in halting currently untreatable tumors.

Medical Need

Immunotherapies raised against widely expressed antigens or promiscuous epitopes are at risk of high toxicity hindering their clinical efficacy. On the other hand, **immunotherapies against highly cancer-specific antigens**, which are poorly expressed or inaccessible, **show diminished efficacy.** Nowadays, the target-first approaches involve the discovery of tumor-specific antigens from high-throughput RNA- and DNA-sequencing data, or protein-based methodologies. Such strategies allow optimal tumor-antigen specificity due to dataset analyses, however the accessibility of tumor antigens remains uncertain and cannot be easily predicted. Additionally, such approaches cannot accurately predict a variety of post-translational modifications, which can either generate novel tumor-associated epitopes or mask expected antigenicity.

Solution/Technology

Alternative to the target-first approach is the antibody-first line of action. This strategy uses unbiased, phenotypic screening to select antibodies against true tumor-associated antigens. The inventors developed and optimized an **antibody-screening strategy against tumor cells** growing in immune-competent animals, which incorporates *in vivo* and *ex vivo* library-depletion steps to counter-select antigens expressed on healthy tissues. Currently, there are no examples of immunotherapies based on antibodies obtained from *in vivo* screenings.

As a proof of concept of our approach, three independent antibodies were isolated showing tumor binding and strong anti-tumor effect against diseases with high unmet medical need, such as refractory T-ALL and metastatic melanoma, highlighting their potential for diagnostic and therapeutic uses, both alone and when fused to pro-inflammatory cytokines.

Applications

Such workflow **can be tailored and applied to virtually any tumor model** and allows for the identification of novel immunotherapies through the *in vivo* selection of specificity and evaluation of tumoricidal efficacy. As such, the platform described herein provides a rational, high-throughput, rapid workflow to discover and pre-clinically validate treatment options for the benefit of patients.

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Advantages

New antibodies can be selected against cancer cells without prior knowledge of target antigen, using high complexity antibody phage libraries. This approach provides the advantage of **immediately generating a viable antibody that can be directly tested *in vivo* in relevant species for specific diseases.**

Opportunity

Istituto Europeo di Oncologia is seeking for partners interested in further developing the antibodies derived from our proprietary screening platform towards the clinical practice.

Inventors

Pier Giuseppe Pelicci, MD PhD, is the Director of Research at IEO and Chairman of the Department of Experimental of Oncology. He is a worldwide leading expert in the leukemia field.

Luisa Lanfrancone, PhD, is the Director of Target identification and validation Unit at IEO, with main research focus on aggressive cancers with highly unmet medical need.

Paul E. Massa, PhD, is a scientist expert in the generation, isolation and pre-clinical validation of novel antibody- and cell-based immunotherapies.

Massimiliano Mazza, PhD, is now enrolled as principal investigator at IRST IRCCS S.r.l. based in Meldola (FC), Italy. Main interest is the identification and development of novel immunotherapies by screening tissue samples from patients.

References

Patent Application: PCT/EP2019/066217.

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