



We seek to improve
standards of care
in cancer treatment

...because we focus our scientific and research efforts
on areas of unmet medical need

WE ARE DAIICHI SANKYO



Passion for Innovation.
Compassion for Patients.™

Our purpose

To contribute to the enrichment of quality of life around the world.

Our mission

To create innovative pharmaceuticals addressing diverse medical needs.

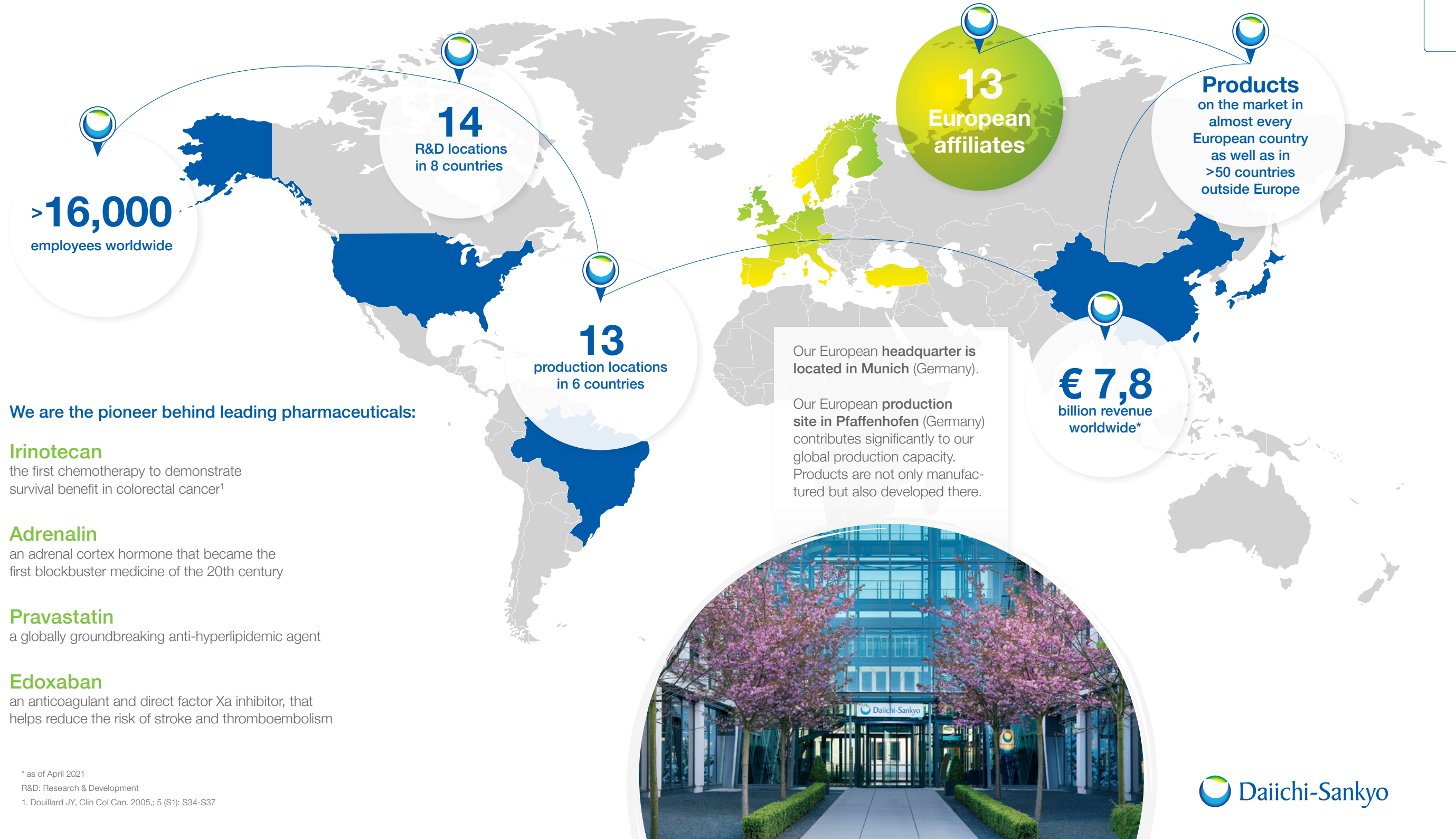
Our vision

To become an innovative global healthcare company contributing to the sustainable development of society.

WE ARE DAIICHI SANKYO



We are a global pharmaceutical company
with over 120 years of scientific expertise



* as of April 2021

R&D: Research & Development

1. Douillard JY, Clin Col Can. 2005.; 5 (S1): S34-S37

Our portfolio covers the two main causes of death in Europe:

Our cardiovascular commitment

We care for every heartbeat. Cardiovascular disease (CVD) remains Europe’s leading cause of death, responsible for more than 10,000 deaths every day.¹ We have made a long-term commitment to invest and work tirelessly to help and protect patients from CVD so that they can enjoy every precious moment that life offers. We focus on supporting the clinical community and healthcare ecosystems across Europe, today. And beyond providing medicines, we investigate new opportunities to improve care through patient-centric approaches, new technologies and partnerships. Since 2002 more than 40 million² patients across Europe have been treated with our products.

Our oncology commitment

Together for patients, together for those who stand beside them: the cancer burden is estimated to have risen to 1.3 million deaths in 2020.³ Every cancer journey is a unique and personal experience that is very complex and sometimes challenging to fully understand. We know that people living with cancer may also be a mother or father who want to see their children smile. A partner, a friend, a daughter, a son who long to kiss and hug their loved ones. It is with this knowledge that we conduct all our science and research. With passion for true innovation, we seek to transform standards of care and address areas of unmet medical need. We want to create moments that matter – for another warm embrace, another smile or touch.

Enhanced capabilities through collaboration

Some of our strategic & research partnerships



COMMITMENT

We are committed to striving for success, to show resilience and discipline, and to focus on people.

COURAGE

We have the courage to improve ourselves, to challenge, to think and act differently, and to take the customer’s perspective.

COLLABORATION

We collaborate and therefore proactively share, put our team first, and trust each other.

INTEGRITY

We adhere to our values and follow ethical standards to build our reputation.

RESEARCH & TECHNOLOGY	TRANSLATIONAL & DEVELOPMENT
<div>DARWIN HEALTH <small>PRECISION THERAPEUTICS for CANCER MEDICINE</small></div> <div> 国立がん研究センター <small>National Cancer Center Japan</small></div> <div> Max-Planck-Innovation</div> <div> LDC <small>Life Discovery Center</small></div> <div> Roche</div> <div> sysmex</div> <div> teckro</div> <div> ThermoFisher SCIENTIFIC</div> <div> Vernalis</div> <div> zymeworks <small>BIOMEDICAL RESEARCH</small></div>	<div> AgonOx</div> <div> AstraZeneca</div> <div> Bristol Myers Squibb</div> <div> Dana-Farber Cancer Institute</div> <div> GUSTAVE ROUSSY <small>CANCER CAMPUS SAINT-GERMAIN</small></div> <div> Kite <small>A GILEAD Company</small></div> <div> THE UNIVERSITY OF TEXAS MD Anderson Cancer Center <small>Making Cancer History</small></div> <div> Memorial Sloan Kettering Cancer Center</div> <div> MERCK <small>INVENTING FOR LIFE</small></div> <div> Merck KGaA <small>Darmstadt, Germany</small></div> <div> Pfizer</div> <div> Purix Biotechnology</div> <div> SARAH CANNON Research Institute</div> <div> Syneos Health</div>
<div> SBP <small>SANFORD BURNHAM PRESENTS</small></div> <div> Medical Discovery Institute</div> <div> sosei</div> <div> ultragenyx pharmaceutical</div>	<div> AMGEN</div> <div> CELIXIR <small>REGENERATIVE MEDICINE FOR LIFE</small></div> <div> UCSF <small>University of California San Francisco</small></div>

ONCOLOGY

OTHER

1 ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2020; 41(1): 111-188.
2 Daiichi Sankyo. Company presentation. Data on file.
3 <https://ec.europa.eu/jrc/en/news/2020-cancer-incidence-and-mortality-eu-27-countries>

We have more than 40 years of experience in bringing cancer therapies to patients

Launched Krestin (polysaccharide-K) in Japan to treat gastrointestinal, lung and breast cancer

Launched the first natural-type interferon beta preparations for brain tumour and skin cancer in Japan

Received approval for irinotecan, the first chemotherapy to demonstrate survival benefits in colorectal cancer¹



In January 2021, ENHERTU® (trastuzumab deruxtecan) received EMA approval for HER2-positive metastatic breast cancer in Europe*

>20 compounds in development directed at a range of diseases with unmet medical needs, with a focus on ADC technology

Launched RANMARK® (denosumab) in Japan for treatment of bone complications of multiple myeloma and bone metastases of solid tumours

* Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens SmPC at www.ema.europa.eu

ADC: Antibody Drug Conjugate
EMA: European Medicines Agency
HER2: Human Epidermal growth factor Receptor 2
1. Douillard JY, Clin Col Can. 2005; 5 (S1): S34-S37

We have a passion for true innovation

Our oncology portfolio and research focus on innovation in areas of unmet medical need



R&D investment
>€ 11 billion
2021 - 2026*

R&D expenses
of yearly revenue**
>20 %
€ 1.84 billion

We put the patient at the heart of everything we do

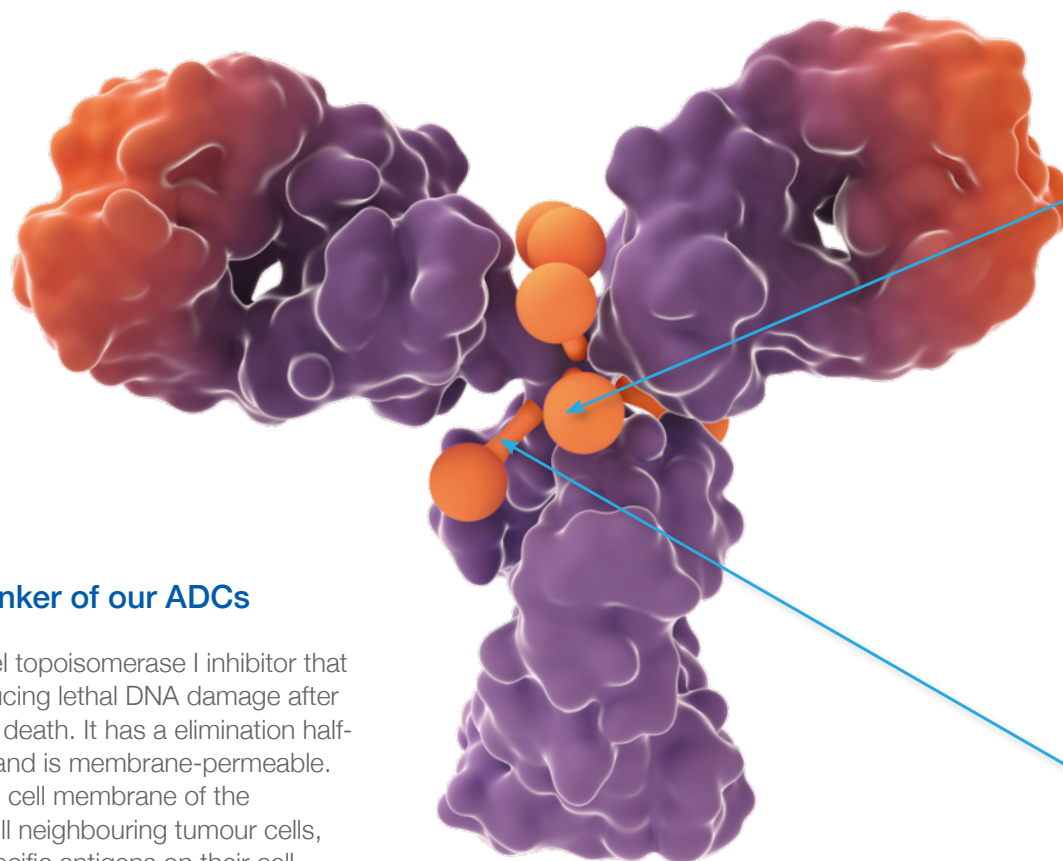
Research &
Development

* https://www.daiichisankyo.com/files/investors/library/materials/2021/20210405_5th_MTP_E.pdf ** as of April 2021
R&D: Research & Development

Our strength: science & technology

DXd ADCs are composed of 3 components^{1,6}:

- A monoclonal antibody attached to:
- A topoisomerase I inhibitor payload (an exatecan derivative) via
- A tetrapeptide-based cleavable linker



Deruxtecan, the payload-linker of our ADCs

The payload in our ADCs is a novel topoisomerase I inhibitor that exhibits potent cytotoxicity by inducing lethal DNA damage after intracellular release, leading to cell death. It has a elimination half-life (t1/2) of approximately 7 days and is membrane-permeable. Therefore, it can travel through the cell membrane of the target tumour cell and enter and kill neighbouring tumour cells, regardless of the expression of specific antigens on their cell surface. This dual action on both target and surrounding cancer cells, which is known as the bystander antitumour effect, is of great importance in molecularly heterogenous tumours.

Our DXd ADCs are designed with 7 key attributes

Our scientists have specifically engineered our ADCs to address limitations of two critical components of an ADC: the payload and the linker. Therefore, our ADCs will most effectively deliver their cytotoxic payload inside cancer cells while limiting exposure of healthy tissues to the payload.

Characteristics of Payload

Mode of action payload

DXd, an investigational topoisomerase I inhibitor ^{2,3}

High potency of payload

~10x more potent topoisomerase I inhibition than SN-38, based on a cell-free assay evaluating HIC ^{3,6}

Bystander antitumour effect

Elimination of both target tumour cells and surrounding tumour cells enabled by the high cell-membrane permeability of the payload. ^{4,6}

Low systemic exposure

Short systemic half-life of payload ⁵

Characteristics of Linker

Stable linker

In vitro plasma stability, designed to limit exposure of non-cancerous normal tissue to the payload ⁵

Linker release

Cleaved (divided) by lysosomal enzymes ³

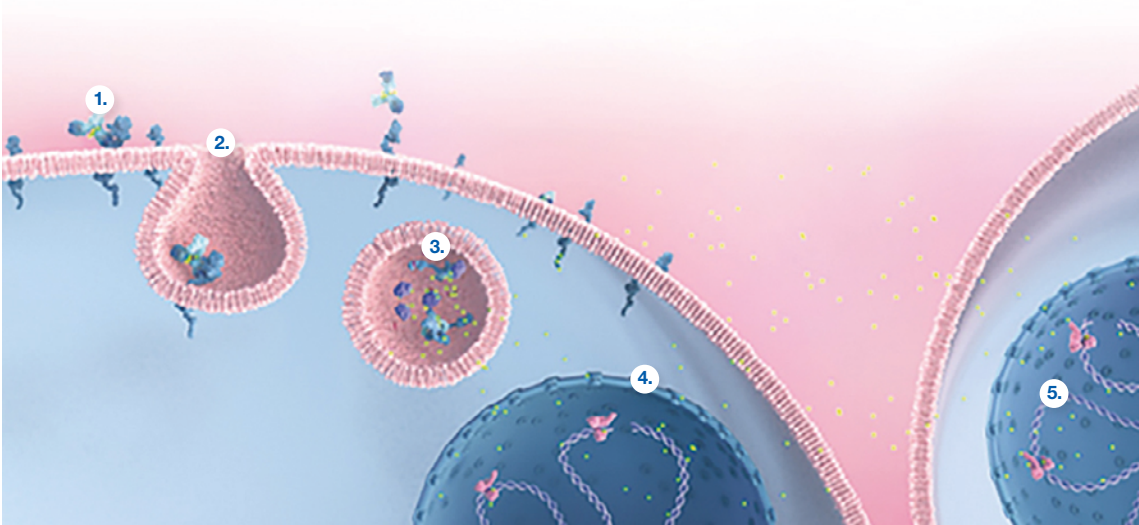
High drug-to-antibody ratio (DAR)

High number of payload entities per antibody molecule with flexibility to vary DAR during drug design. Can achieve a DAR of up to 8. ^{3,5}

Mode of action of ADCs

Our ADCs have a cytotoxic effect on cancer cells that express a specific cell surface antigen and on adjacent cancer cells without that cell surface antigen

The proposed mode of action of our ADCs is depicted in detail below



After the ADC has been administered, the stability of the ADC complex in the circulation helps to minimise systemic release of the drug payload and promotes delivery of the intact ADC to the target cancer cells.

1. Once the ADC arrives at the target cancer cell, the monoclonal antibody moiety attaches with high specificity to its target antigen (receptor) on the cell surface.
2. The ADC-receptor complex is subsequently internalised by the cancer cell by means of endocytosis.
3. After internalisation, the linker is cleaved by lysosomal enzymes, breaking down the ADC complex and releasing free payload inside the cancer cell.
4. Free payload then travels to the cell nucleus, causing irreparable DNA damage leading to cell death.
5. Owing to its high membrane permeability, free payload can diffuse into adjacent cancer cells and kill these cells as well, even if they do not have the target antigen. This effect is known as the bystander antitumour effect of the payload.

ADC: Antibody Drug Conjugate
DNA: Desoxyribonucleic acid

Interview with Prof. Fabrice André

Gustave Roussy Cancer Campus
Villejuif, France

Why are antibodies drug conjugates (ADCs) emerging so strongly in oncology?

The evolution of ADCs in recent years is quite incredible. It is offering our patients better chances. When we compare the different generations of ADCs, we realize that the new generations of ADCs provide new clinical options to patients who were resistant to the first generation of conjugated antibodies. And this is only the beginning!

What are the strengths of ADCs?

The strength of ADCs is based on three principles: less toxicity, better efficacy and the perspective of new therapeutic combinations. I believe that reducing the systemic toxicity of chemotherapy is a major step forward in patient management. Bioengineering has made it possible to create ADCs with an important DAR (Drug Antibody Ratio) and therefore higher efficacy. These antibodies carry and deliver many more chemotherapeutic molecules directly into the tumour cell, without damaging healthy tissues. The targeted action of these cytotoxic agents spares the patient's immune system, and this opens up wonderful prospects for new therapeutic combinations. Indeed, until today it was often difficult, if not impossible, to combine certain treatments because of the risk of causing too much toxicity. With ADCs, it will potentially be easier to use the synergy of certain therapies to treat patients whose treatment failed.

How does the payload influence the ADCs final mechanism of action?

The final mechanism of action depends on the chemotherapeutic payload conjugated with the monoclonal antibody. After administration of the ADC, the payload will be carried in a conjugated form to the target tumour cell. There, the ADC will bind to the target membrane receptor, followed by internalization in endosomes and, after that, transfer to lysosomes. Through the combined effect of pH and certain enzymes, such as proteases, the payload will be released and will regain its activity either by acting on microtubules or by blocking topoisomerase. The cytotoxic agent alone determines the mode of action at the cellular level. With ADCs, we find the same variety of mechanisms as with the so-called conventional chemotherapy.

What is the issue with the drug-antibody ratio (DAR)?

As you know, the payload-antibody ratio represents the amount of chemotherapy the monoclonal antibody can provide to the cell. Theoretically, the higher the DAR, the more effective the ADC will be, provided that the chemotherapeutic agent will be released well.



The issue, therefore, is to put a large number of chemotherapeutic molecules on a single antibody molecule. But one should be aware that there are factors that limit the release of chemotherapeutics. It is not known how this phenomenon occurs. For a high DAR to be a real asset, we will have to discover the precise mechanisms that promote the release of cytotoxic agents in the tumor cell and those that prevent their release. We hope that the fundamental research underway will soon provide these answers.

Is the bystander effect an asset?

The bystander effect is the effect that cells that have not absorbed an ADC will still be destroyed by a collateral effect. So that's an asset. But this raises a major question: what is the mechanism of action that is responsible for the bystander effect? The mechanism of action is assumed to be that the cell which internalized the ADC, releases its chemotherapeutic payload to neighboring cells even if the latter do not have the surface receptors corresponding to the ADC.

What is interesting about the bystander effect is that it could remove bias from the minimal number of receptors needed to internalize an ADC or facilitate the action of the ADC in the case of heterogeneous tumours.

What do you think the future of ADCs will be?

I think the ADCs will completely replace conventional chemotherapy. This will result in less systemic toxicity, less toxicity to the healthy tissues, and better efficacy. And it will be possible to make therapeutic combinations that are still impossible at this moment.

However, one key element remains to be defined: the minimum number of membrane receptors needed to internalize an ADC. When this data will be known, it will certainly open up new therapeutic perspectives.

Antibody Drug Conjugates



At Daiichi Sankyo we know that for people living with cancer every moment matters.
That's why we focus our efforts on addressing areas of unmet medical need.
We do this with passion for true innovation and by putting the patient at the heart of everything we do.
Our purpose is to contribute to the enrichment of quality of life and to improve standards of care across the world.

TOGETHER FOR OUR PATIENTS. TOGETHER FOR THOSE WHO STAND BESIDE THEM.

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