SIMICA

THERAPEUTIC SITE-SELECTIVE
PROTEIN-MODIFICATION CHEMISTRIES

Newsletter VI

January 2022

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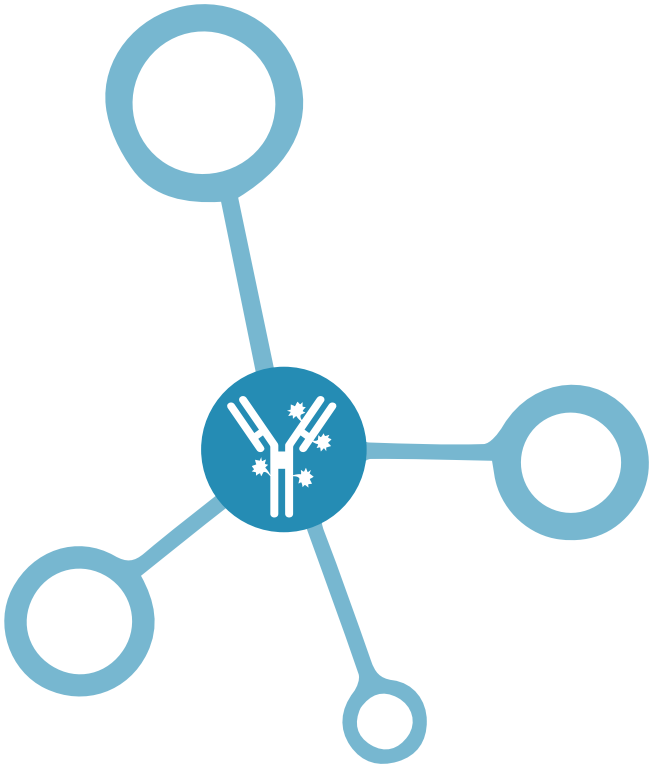

OVERVIEW OF THE PROJECT

The SIMICA Project intends to place the Instituto de Medicina Molecular João Lobo Antunes within the core of a European network of laboratories that seeks to produce cutting-edge research in the field of site-selective protein modification.

Did you know that:

An ADC typically consists of a monoclonal antibody (mAbs) attached to a small drug molecule, in most cases a cytotoxic agent. An ADC hybridizes the advantages of potent cytotoxicity with a highly specific targeting ability.

Timeline of FDA approved ADCs

The first market authorization granted by the FDA to a monoclonal antibody for human usage was for muromonab-CD3 (Orthoclone OKT®3) by Ortho Biotech (currently part of Johnson & Johnson, Inc.) in 1992 for acute allograft rejection in renal transplant patients, for example. This was followed by a wave of FDA approved antibodies for cancer therapy. In 1997 Rituximab (Rituxan®), an anti-CD20 mAb from Roche/ Genentech was approved to treat non-Hodgkin's lymphoma and chronic lymphocytic leukemia. In the year after, the same company gained approval of Trastuzumab (brand name Herceptin®), an anti-HER2 (Human Epidermal Growth factor Receptor 2) mAb to treat HER2 overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Another achievement in oncology was the approval of Bevacizumab (branded by Roche/ Genentech as Avastin®) in 2004, as an anti-VEGF mAb to treat metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma and metastatic renal cell carcinoma.

Shifting to immunology, the approval of the anti-TNFα antibody Adalimumab (Humira®, an AbbVie product) in rheumatology field, changed the paradigm in the treatment of auto-Immune disorders (e.g. rheumatoid arthritis).

Meet the SIMICA Advisory Board

Peter Senter joined Seattle Genetics in August 1998 and now serves as Vice President of Chemistry. His group carries out research in anticancer drug design, antibody-drug conjugate technologies for cancer therapy. Several of the molecules generated in Senter's lab have entered clinical trials, and two of them have been approved: Adcetris for relapsed Hodgkin lymphoma and certain non-Hodgkin lymphoma, and Etopophos for solid tumor therapy. Peter Senter has authored more than 150 scientific publications and holds more than 40 issued patents. He received an AB in Biochemistry from the University of California, Berkeley, a PhD in Chemistry from the University of Illinois, and did postdoctoral research at the Max Planck Institute of Experimental Medicine in Göttingen, Germany.

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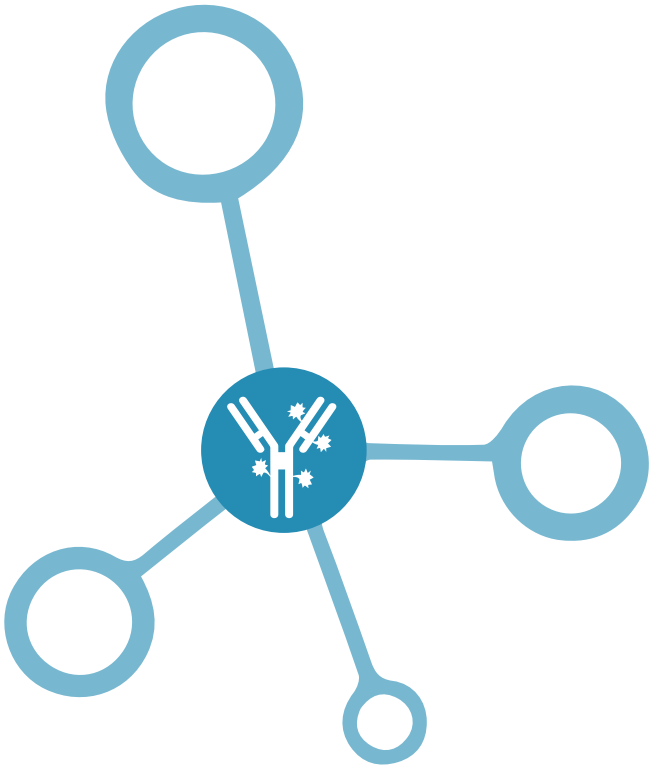

Nevertheless, most of these agents are administered in combination therapies with small molecules in the oncology field. This has led to the idea of combining the efficacy of small molecules and the selectively of mAb's. This goal was achieved using the advantages of DNA recombinant technology and standard chemistry, allowing the preparation of one single entity i.e. an antibody, a cytotoxic payload and a chemical linker (previously described on Newsletter 5). The first ADC approved by the FDA was gemtuzumab ozogamicin (Mylotarg™) as a single therapeutic agent in patients with CD33-positive Acute Myeloid Leukemia (AML) in 2000. This ADC targets CD33 positive cells using the mAb portion, while the small molecule ozogamicin targets DNA causing strand scission (calicheamicin class) (https://www.adcreview.com/gemtuzumab-ozogamicin-mylotarg/). The enthusiasm around the ADCs led so far to the approval of eighteen biological toxical agents, each of them for applications in oncology. A brief overview is provided in the table below regarding current marketed ADCs.

Drug name	INN	Approved Geo's	Company	Area	Indication
Adcetris®	brentuximab vedotin	Global	Takeda	Oncology	Anaplastic Large Cell Lymphoma (ALCL); Cutaneous T-Cell Lymphoma; Hodgkin Lymphoma (B-Cell Hodgkin Lymphoma)
Aidexi®	disitamab vedotin	China	RemeGen	Oncology	Adenocarcinoma Of The Gastroesophageal Junction; Gastric Cancer; Transitional Cell Carcinoma (Urothelial Cell Carcinoma)
Akalux®	cetuximab sarotalocan	Japan	Rakuten	Oncology	Recurrent Head And Neck Cancer Squamous Cell Carcinoma
Besponsa®	inotuzumab ozogamicin	Global	Pfizer	Oncology	B-Cell Acute Lymphocytic Leukemia (B-Cell Acute Lymphoblastic Leukaemia)
Blenrep®	belantamab mafodotin-blmf	Global	GSK	Oncology	Refractory Multiple Myeloma; Relapsed Multiple Myeloma
Elahere®	mirvetuximab soravtansine-gynx	Global	ImmunoGen Inc	Oncology	Epithelial Ovarian Cancer; Fallopian Tube Cancer; Peritoneal Cancer
Enhertu®	fam-trastuzumab deruxtecan-nxki	Global	AstraZeneca	Oncology	Adenocarcinoma Of The Gastroesophageal Junction; Gastric Cancer; HER2+ Breast Cancer; Non-Small Cell Lung Cancer
Kadcyla®	trastuzumab emtansine	Global	Roche/ Genetech	Oncology	HER2+ Breast Cancer
Licartin®	iodine I 131 metuximab	Global	Chengdu Huasun Bio	Oncology	Liver Cancer
Lumoxiti®	moxetumomab pasudotox-tdfk	Global	Innate Pharma	Oncology	Hairy Cell Leukemia
Mylotarg®	gemtuzumab ozogamicin	Global	Pfizer	Oncology	Acute Myelocytic Leukemia (AML, Acute Myeloblastic Leukemia)
Padcev®	enfortumab vedotin-ejfv	Global	Astellas Pharma	Oncology	Metastatic Transitional (Urothelial) Tract Cancer
Polivy®	polatuzumab vedotin-piiq	Global	Roche/ Genetech	Oncology	Diffuse Large B-Cell Lymphoma
Tivdak®	tisotumab vedotin-tftv	Global	Genmab	Oncology	Cervical Cancer
Trodelvy®	sacituzumab govitecan	Global	Gilead	Oncology	Triple-Negative Breast Cancer (TNBC)
Ujvira®	trastuzumab emtansine biosimilar	India	Zydus	Oncology	HER2+ Breast Cancer
Zevalin®	ibritumomab tiuxetan	Global	Acrotech	Oncology	B-Cell Non-Hodgkin Lymphoma; Follicular Lymphoma
Zynlonta®	loncastuximab tesirine-lpyl	Global	Swedish Orphan Biovitrum	Oncology	Diffuse Large B-Cell Lymphoma
SYD985	trastuzumab duocarmazine	Global Registration	Byondis	Oncology	HER2+ Breast Cancer