Selective targeting of angiogenesis and of tumour stroma

Keywords
Neoplasm, stroma, angiogenesis, selective targeting, combination therapy, antibody, small molecules, oncofetal antigens, tumour neo-vasculature

Summary
Targeted delivery of therapeutic agents to the tumour microenvironment is a novel avenue for cancer treatment towards the development of more efficacious and better-tolerated anticancer drugs.

This project aims to identify new molecular targets which are selectively expressed in tumour stroma and in the neo-vasculature of aggressive tumours and to develop new therapeutic strategies based on high affinity binding molecules capable of selective localisation in tumour stroma and/or vascular structures. An effort to move the most promising product(s) generated within this Integrated Project into clinical trials is the ultimate scope of the project.

Potential application is the pharmacological treatment of solid neoplasms, maintaining or improving the present percentage of respondents, survival, disease-free interval, with improved safety and a better quality of life.

Problem
The majority of pharmacological approaches for the treatment of solid tumours suffers from poor selectivity, thus limiting dose escalation (i.e., the doses of drug which are required to kill tumour cells cause unacceptable toxicities to normal tissues). The situation is made more dramatic by the fact that the majority of anticancer drugs accumulate preferentially in normal tissues rather than in neoplastic sites, due to the irregular vasculature and to the high interstitial pressure of solid tumours.

One avenue towards the development of more efficacious and better tolerated anti-cancer drugs relies on the targeted delivery of therapeutic agents to the tumour environment, thus sparing normal tissues.

Aim
In the past, our consortium has developed innovative anticancer imaging and therapeutic strategies, based on recombinant antibody fragments, which have moved from the bench to the clinic. With the STROMA project, we plan to strengthen and extend the leading position of our European network in research and in the pharmaceutical development of ligand-based, targeted anticancer therapies, with a particular emphasis on the targeting of tumour neo-vasculature and tumour stroma.

This project focuses on the:
• Identification and validation of molecular targets which are selectively expressed in the stroma and in neo-vascular sites of aggressive solid tumours. Endothelial cells and stromal cells are genetically more stable than tumour cells and can produce abundant markers, which are ideally suited for tumour targeting strategies.
• Isolation of high-affinity binding molecules (small organic compounds, antibodies), which are specific for markers of angiogenesis and/or the tumour stroma, and are capable of selective localisation in the tumour environment, after intravenous administration.
• Development of therapeutic strategies, based on specific binding molecules capable of selective localisation around tumour vascular structures and/or in the tumour stroma.
• Dissemination of the research activities of the project.
Expected results

Flow chart, outlining the main expected results, leading from target identification to the development of novel anticancer therapeutics.

Potential applications

We will consider the project as fully successful if at least one molecule enters clinical development for pharmacological treatment of solid neoplasms, maintaining or improving the present percentage of respondents’ survival, disease-free interval, with improved safety and better quality of life.

Project website: www.stromaip.org

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