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Angiogenesis inhibitors: an upcoming therapy for cancer and wet age-related macular degeneration

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Angiogenesis, the process of new blood vessel formation, plays a role in healthy physiological processes such as embryonic development, normal growth of tissues, wound healing and the female reproductive system. However, as with all physiological processes, in some situations it can become pathological. Macular degeneration and cancer, although two distinct diseases, share a common association. Wet age-related macular degeneration (AMD) and tumour growth and subsequent metastasis rely on the inappropriate growth of blood vessels.

Cancer and AMD: a global health problem

Drug development in macular degeneration and cancer has progressed rapidly over the past ten years. Today, 25–30 million people worldwide suffer from AMD, the most common cause of vision loss and blindness. AMD Alliance International, an organization dedicated to raising awareness of AMD, has predicted that the incidence of the disease will triple in the next 25 years, as a result of the rapidly growing 65-and-over demographic.

There are two types of macular degeneration: the more common 'dry' kind, involving thinning of the macula retinae (the point at the back of the eye at which light is focussed), and the more damaging 'wet' stage. In wet AMD, new blood vessels grow behind the retina – a process called choroidal neovascularization – and fluid leakage from these vessels damages the photoreceptors in the macula and distorts vision. In cancer, similar neovascularization occurs in response to tumour growth. When tumour cells furthest from the blood supply become hypoxic, the release of hypoxia-inducible factor 1a is triggered and induces the expression of angiogenic growth factors. These stimulate the mitogenesis of endothelial cells that initiate the formation of new blood vessels.

Worldwide, nine million deaths result from cancer each year, a figure the WHO anticipates will rise to 20 million by 2020, again due to increased life expectancy and lifestyle changes. For the past 50 years, cancer therapy has adopted a direct strategy in the form of cytotoxic drugs. Drawbacks to this treatment, such as drug-resistant clone selection resulting from genetic instability and the destruction of normal cells, denote a window of opportunity for antiangiogenic cancer therapeutics. In 1961, Judah Folkman postulated that tumours cannot grow larger than the head of a pin without a blood supply. Furthermore, he proposed that the prevention of new blood-vessel growth would consequently offer a novel method of treating cancer.

A shared aetiology

Pathological angiogenesis is now recognized as a major problem associated with many serious and life-threatening diseases, but therapeutic focus on this area has, until recently, been inadequate. However, a growing number of therapeutics is currently being developed to intervene and control angiogenesis. Figure 1

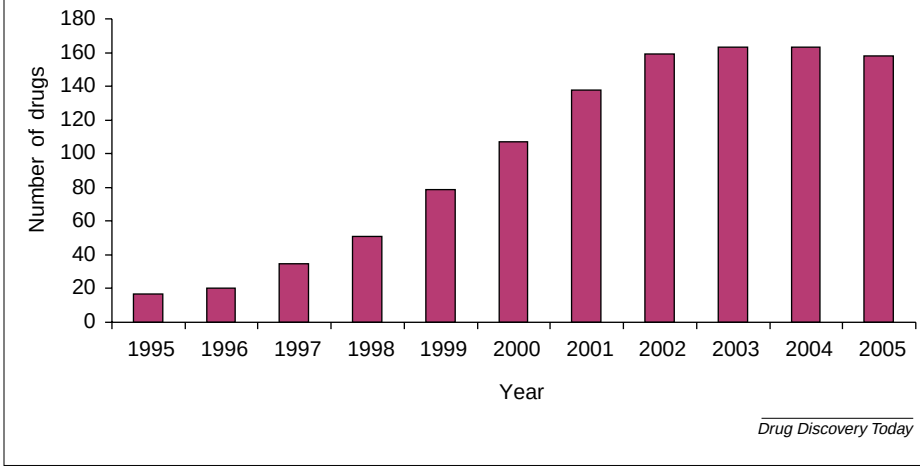

FIGURE 1

Development of angiogenesis inhibitors over the past 10 years. The number of angiogenesis inhibitors in active development has risen steadily between 1996 and 2002.

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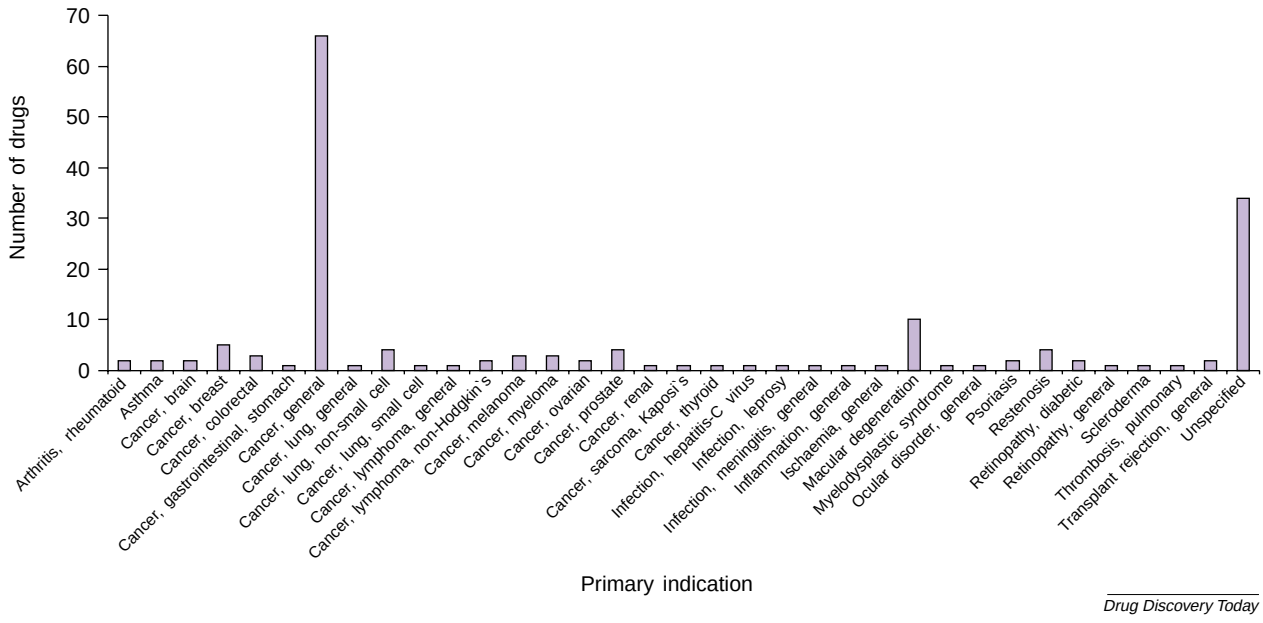

FIGURE 2

Frequency of angiogenesis inhibitors in active development for cancer and AMD. The greatest frequency of angiogenesis inhibitors are being developed for cancer and AMD, with 68 (39%) and 9 drugs (6%), respectively, being in development currently.

illustrates the steady increase in the number of drugs between 1996 and 2002 in active development with angiogenic inhibitory effect. Angiogenesis inhibitors are used to treat a broad range of diseases but by far the two most popular indications are AMD, which accounts for 6% of angiogenesis inhibitors, and cancer, with 39% (Figure 2).

The aetiology shared by wet AMD and cancer means that some other techniques are applicable to both disorders. Photodynamic therapy (PDT) is an established method of treating wet AMD (by blocking the leaking veins) and can also be used for the treatment of cancer. PDT involves use of light to activate a chemical, previously introduced into the body. The light causes formation of free radicals, which in turn cause selective damage to certain tissues.

The popularity of angiogenesis inhibitors compared with radical formation agonists for the treatment of cancer and ophthalmological conditions is apparent from Figure 3, with the number of angiogenesis inhibitors increasing by a factor of six over the past nine years, whereas the number of drugs that act as radical formation agonists – PDT drugs – has remained relatively constant.

Three decades of research

After three decades of research in the antiangiogenesis field, angiogenesis inhibitors in diverse forms are now starting to yield commercial products. Pharmaprojects includes details of 19 drugs in active development for macular degeneration and cancer. Of these, 11 are angiogenesis inhibitors and take the form of a variety of pharmaceutical agents, such as oligonucleotides, antibodies, antibiotics, small interfering RNAs, cytostatic factors and small-molecule peptides.

Recent months have seen the launch of two important angiogenesis inhibitors. Bevacizumab, a humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody developed by biotech giant Genentech, was launched in the USA in 2004 for use in combination with 5-fluorouracil for the treatment of colorectal cancer. It has achieved sales of US$555 million. In 2005, a trial undertaken by the Bascom Palmer Eye Institute in wet AMD patients demonstrated improved vision after 12 weeks of bevacizumab therapy.

In 2005, Gilead Sciences launched in the USA the first antiangiogenic drug for AMD, pegaptanib octasodium (an oligonucleotide aptamer that inhibits VEGF), for the treatment of wet AMD. It also has potential as an anticancer agent. VEGF is one of the best studied growth factors; as a consequence, it has become a popular target for antiangiogenic drug development.

Elsewhere, development continues. RNA-interference specialist Intradigm is conducting trials with its preclinical candidate, ICS-283, for both wet AMD and cancer. ICS-283 is a siRNA therapeutic agent that inhibits the VEGF pathway by blocking expression of pro-angiogenesis proteins, rather than inhibiting the functions of these proteins. OxiGENE's combretastatin A-4 prodrug is in Phase II trials for wet AMD and a variety of cancers. It is a cytostatic extract from an African tree, *Combretum caffrum*, and unlike other angiogenesis inhibitors it destroys preformed blood vessels in addition to preventing the growth of new ones. It works by influencing the microtubules of the cytoskeleton of immature endothelial cells, lining the vasculature. By disturbing the tubulin structure, the endothelial cells change shape and halt blood flow through the capillary.

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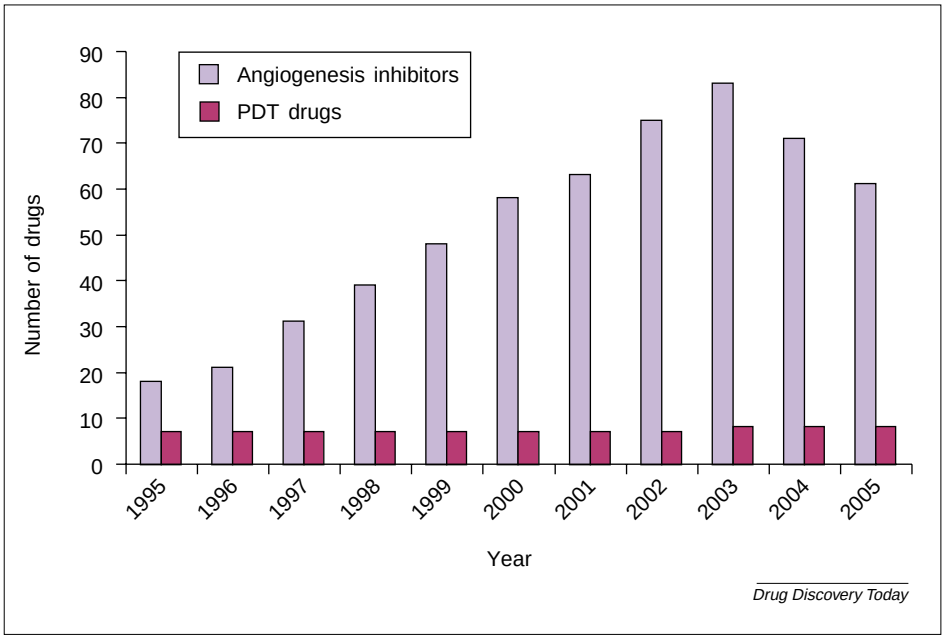

FIGURE 3

Comparison of angiogenesis inhibitors and photodynamic therapy drug development over the past 10 years. The development rate of angiogenesis inhibitors for the treatment of ophthalmological conditions and cancer has exceeded the rate in development of photodynamic drugs for the same indications sixfold between 1995 and 2003.

US-based Genaera has recognized the importance of angiogenesis inhibitors as significant future therapies and has taken the strategic decision to focus the majority of its resources on its Phase II compound, squalamine, an antibiotic discovered in dogfish shark tissue for the treatment of wet AMD and cancer.

Encouraging outlook

Pharmaprojects has revealed a significant number of drugs sharing a pharmacological activity that are under development for both cancer and wet AMD. The success of pegaptanib octasodium and bevacizumab as angiogenesis inhibitors (launched for the treatment of wet AMD and cancer, respectively, and in development for cancer and wet AMD, respectively), indicates the tremendous potential that antiangiogenic therapy will have in the future. With a significant proportion of the drugs highlighted by Pharmaprojects also focusing on blocking various stages of angiogenesis rather than solely disrupting the function of VEGF (as with pegaptanib octasodium and bevacizumab), the outlook for future treatments remains positive.

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Broad spectrum immune monitoring in immune-mediated inflammatory disorders

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The high attrition rate of new candidate drugs is a major concern for the drug development industry and an intensively discussed subject in this journal. The translation of data from preclinical research in relatively simple laboratory animal models to the complex diseases in the human population appears to be the Achilles heel of the drug development process. Multiplexed assay systems could help to better understand the crucial differences between pathogenic processes in animal models and the human disease.

Introduction

The ageing societies of Europe and North America are facing an increasing prevalence of chronic immune-mediated inflammatory disorders (IMID), such as rheumatoid arthritis (RA), multiple sclerosis (MS) and inflammatory bowel disease (IBD). During the past decades the drug development industry has invested heavily in biotechnology research aiming to identify the most relevant therapeutic targets for these conditions and to develop safe, effective therapies for them. Despite years of intensive research in industry and academia, really effective therapies are lacking for the majority of IMID. Moreover, several clinical

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