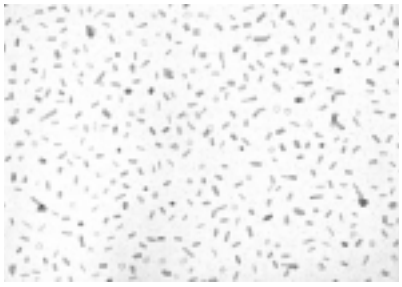

Figure 1. DNA nanoparticles of Copernicus Therapeutics. Electron micrograph of polyethylene glycol (PEG)-stabilized compacted DNA particles (amplification 3×10^4). Figure courtesy of Copernicus Therapeutics (http://www.cgsys.com).

DNA will be administered by a bronchoscope to an isolated bronchial segment. Subsequent trials will administer aerosols of compacted DNA to the whole lung.

Terry Flotte, a researcher of CF gene therapy from the University of Florida (http://www.ufl.edu/), was enthusiastic about the work: 'It is essential that these sorts of therapies continue to be tested in patients because, in the final analysis, there is no other way to move forward toward better therapies for this disease', he commented.

Davis is optimistic about the applicability of the technique to a wide variety of other diseases, including gene therapy to produce blood-clotting factors and surfactant proteins and as a timed response to afflictions such as severe asthma attacks. She also commented on the possible use of the technique as a protection from the side-effects of other therapies: 'It may be possible to protect the lung against known, expected toxicity from radiation therapy or chemotherapy drugs by delivering a protective gene at the right time. This might allow fully effective doses of radiation or chemotherapy to be administered, which might otherwise not be tolerable.'

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CDK inhibitor shows promise for inflammatory kidney disease

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An inhibitor of cyclin-dependent kinase (CDK) has been well tolerated in Phase Ia clinical trials and is due to enter Phase Ib trials for glomerulonephritis (GN), a group of inflammatory kidney diseases, in autumn 2002. Details of this were announced by Spiros Rombotis, Chief Executive of Cyclacel (http://www.cyclacel.com), at the *BioEquity Europe 2002* meeting in Zurich, Switzerland (14–15 May 2002).

Glomerulonephritis

Glomerulonephritis is a group of kidney diseases caused by inflammation and cell proliferation that result in gradual, progressive destruction of internal kidney structures (glomeruli). Although rare, GN is the third most common cause of end-stage renal disease (ESRD). This group of diseases causes 20–50% of all renal failures that necessitate kidney dialysis or transplantation. GN also develops in people with certain cancers, liver cirrhosis and some infectious diseases.

Current treatments include high-dosage steroid and cytotoxic drug therapy; however, these are often ineffective and have a high risk of toxic side effects. New therapies directed at specific cytokines and growth factors are under development, as are less toxic forms of immunotherapy [1].

In the developing world, ~700,000 people are affected by GN, and in the USA 330,000 people are on dialysis for ESRD. US$17 billion is spent annually in the USA alone on ESRD.

CYC202

The lead drug from Cyclacel, CYC202, is a small-molecule inhibitor of CDK, which regulates the proliferation of cells. CYC202 is a tri-substituted purine and is a highly specific inhibitor of CDK2/cyclinE activity, inducing selective apoptosis in cancer cells. During glomerulogenesis, visceral glomerular epithelial cells exit the cell cycle and become terminally differentiated. Cell proliferation is under the control of cell-cycle regulatory proteins, such as p21 [2].

The use of CDK inhibitors in the treatment of inflammatory disease of the kidney is to suppress abnormal proliferation of non-cancerous kidney cells that destroy renal function. Cancer treatment using CDK inhibitors emulates the activity

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of tumour suppressor genes (such as p21 and p53), which stop cancer cells at certain cell-cycle checkpoints and cause them to self-destruct.

Robert Jackson, Executive Director of R&D at Cyclacel, said: 'CYC202 is a molecule that acts on the cell cycle… As in cancer, certain kidney diseases are characterized by abnormal cell proliferation and we are now exploring the potential of CYC202 in treating these conditions.'

Clinical trials

Preclinical data

Cyclacel has completed several preclinical studies in rodent models of GN, which sugest that CYC202 causes cellular responses and improvement of kidney function. The drug can activate the cell-cycle checkpoints and delay cell-cycle progression or induce apoptosis of excessively proliferating cells. This activity could reduce or prevent the initial proliferative phase of many forms of GN and preserve renal function. Results from two different animal models of GN suggest that this could indeed be the case.

A model of IgA nephritis [3] suggested that significant reductions in mesangial cell proliferation, together with reductions in cell matrix formation, could be achieved by dosing with Roscovitine (a less potent form of CYC202). These reductions in proliferation were accompanied by improvements in markers of renal function: these studies have been extended and confirmed using CYC202. Cell proliferation and renal scarring were reduced and kidney function was improved. In a separate experiment at a different centre CYC202 was tested in a model of crescentic GN (nephrotoxic nephritis) where the proliferation of epithelial cells leads to the formation of characteristic crescents. The results were an impressive effect on crescent formation, associated with reductions in mesangial cell proliferation and reductions of protein in the urine. These data suggest that CYC202 is efficacious in two different models of renal disease at doses well tolerated in humans. Rombotis said: 'These trials showed that the drug has activity against the proliferation of two populations of kidney cells, the core mesangial cells and the nephron tubule podocytes,' (Fig. 1).

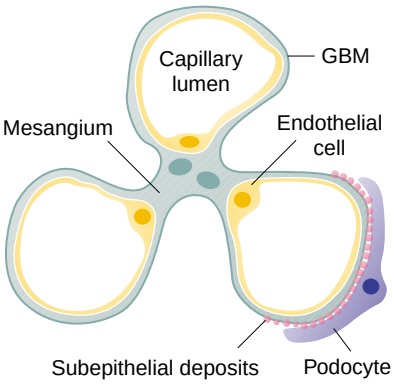

Figure 1. Glomerulonephritis membranous subepithelial deposits. The figure shows the core mesangial cells and the nephron tubule podocytes, two types of kidney cells. Abbreviation: GBM, glomerular basal membrane.

Phase I trials

In a Phase Ia study for GN, the tolerability and pharmacokinetics of single oral doses of CYC202 were investigated. No clinically relevant adverse events or changes in clinical laboratory tests or other safety parameters were observed. Phase Ib trials will include dose escalation and the evaluation of kidney function by blood and urine analysis.

Stuart J. Shankland, Associate Professor of Medicine in the Division of Nephrology (University of Washington Medical Center; http://faculty.washington.edu/uwrenal/) commented: 'GN remains a leading cause of progressive renal disease. Regardless if the underlying cause is immune or non-immune, the typical response to injury is characterized by glomerular cell proliferation, which underlies the accumulation of matrix proteins and reduced renal function. Thus, from a therapeutic standpoint, selectively inhibiting glomerular cell proliferation would be a major therapeutic breakthrough. CYC202…would significantly fill this void.'

Cancer trials

CYC202 is also in multicentre Phase Ib clinical trials for cancer; Phase Ia trials showed that the drug is well tolerated and first-in-class for oral availability. Preclinical data was conducted in different human tumour xenografts (uterine, lung and colon), which were responsive to treatment with CYC202 across all tumour types: Phase II studies are due to commence by the end of 2002.

The Phase Ib trials for cancer are ongoing in France and the UK and so far produced none of the side effects that are typically associated with cancer chemotherapy, such as reduction of blood cell counts, inflammation of mucosal linings and loss of hair.

Rombotis said that, for GN, CYC202 had the potential to provide a long-term decrease in the effects of renal disease, with minimal side effects. Jackson added: 'CYC202 has been shown to cause cell-cycle arrest in both normal and malignant cells. In addition to exploring its potential for the treatment of cancer, we intend to study its activity in other diseases of abnormal cell division, including inflammatory kidney diseases, as the preclinical data suggest that an effective cell-cycle block can be achieved at doses that are well tolerated in humans.'

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