ADVANCED CATHETER THERAPIES

A NOVEL ENDOVASCULAR DRUG DELIVERY SYSTEM FOR PRECISION TARGETING IN MULTIPLE INDICATIONS

There remain numerous diseases for which effective treatment can only be obtained by trained medical professionals using advanced treatment delivery procedures. Here, Paul Fitzpatrick, Chief Executive Officer, Advanced Catheter Therapies, introduces the Occlusion Perfusion Catheter™, an innovative device that can target high concentrations of drug to precisely defined locations. Clinical trials of the device using long-established drugs are providing promising results, in terms of safety, tolerability and efficacy, even in very difficult to treat and even otherwise untreatable conditions.

In the world of injection devices, it is easy to focus on the novel and ever expanding field of biologics and biosimilars, and the narratives of connectivity and "at home" self-injection. However, many indications require treatments that, whilst neither novel nor unknown, are highly effective yet come with serious side effects or are highly toxic and, as such, must be administered by medical professionals. Such treatments present valuable opportunities for novel device design; there is a clear and present demand for technologies that target these indications, whilst improving upon the efficacy and mitigating the adverse effects of their treatments.

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One such area is peripheral arterial disease (PAD). In the US alone, treatment of PAD costs an annual US$21 billion (£15.2 billion) and affects over five million people.[1] PAD requires endovascular treatment, most commonly percutaneous transluminal angioplasty, also called "balloon angioplasty". Recently, the new technology in this space is drug-coated balloons (DCBs). In regular balloon angioplasty, a narrowed artery is widened by a balloon being inflated inside it on the end of a catheter, whereas DCB technology has the balloon coated in an anti-proliferative to help prevent restenosis.

DCBs are not without problems however; toxic anti-proliferative drugs can be washed downstream and fail to penetrate quickly beyond the intima, the innermost layer of the artery. DCB trials have also struggled to produce satisfactory results in below the knee (BTK) arteries. This is of particular note, as critical limb ischemia (CLI), the most severe manifestation of PAD, is strongly associated with atherosclerotic disease of BTK vessels.[1]

Thus, the hypothesis was drawn that a novel catheter could provide the solution to DCB shortcomings by offering a device

Mr Paul J Fitzpatrick
Chief Executive Officer
T: +1 423 321 8964
E: paul@acatheter.com

Advanced Catheter Therapies Inc
25 E Main Street
Chattanooga
TN 37408
United States

www.acatheter.com

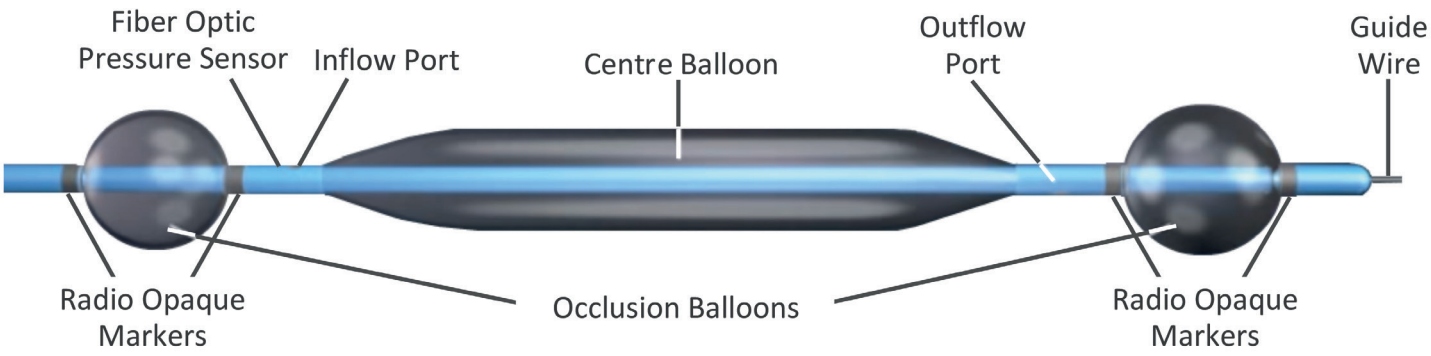

Figure 1: Schematic of the Occlusion Perfusion Catheter™.

that was able to treat multiple lesions, larger lesions and deliver drugs more effectively to the medial wall. It was upon this hypothesis that, in 2008, Advanced Catheter Therapies (ACT) was founded, and that the Occlusion Perfusion Catheter™ (OPC) was developed. Being designed as a universal device, in addition to PAD, the OPC has potential in the treatment of various therapeutic areas, including venous insufficiency, clot management, oncology, dialysis grafts and AV fistulas.

OCCLUSION PERFUSION CATHETER™

The OPC was developed to be a universal and targeted drug delivery device, able to deliver drugs locally without drug being taken up into the bloodstream and delivered systemically. As a starting point the OPC was designed to uniformly deliver, circumferentially and longitudinally within the treatment area, therapeutic agent to the medial layer. Paclitaxel was selected as the first product to be delivered via the device due to it being a well characterised anti-proliferative.

Fundamentals of the OPC

When setting out to design a universal drug delivery device, ACT settled on a set of fundamental requirements that the design had to fulfil.[1] This list guided the development of the OPC and stated that the device had to be able to:

- Deliver a drug uniformly to the medial wall, both circumferentially and longitudinally.
- Deliver a multitude of various therapeutic agents (e.g. small molecule drugs, biologics, stem cells), being a truly universal delivery device.
- Create a "Treatment Chamber" within a blood vessel, that could be filled and washed to eliminate the risk of systemic delivery.
- Monitor and control pressure and drug volume within the treatment chamber.
- Be used on multiple lesions within the same patient.
- Be used on long lesions with a single device.
- Optimise re-endothelialisation.

Operation of the OPC

The OPC is a novel catheter featuring occlusion balloons, a central balloon and inflow and outflow ports for drug delivery (Figure 1). The operative steps are:

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- **Step 1:** The catheter is inserted and moved into position so that the occlusion balloons are on either side of the lesion. The occlusion balloons are deployed, halting blood flow and creating a treatment chamber within the vessel.
- **Step 2:** Any blood remaining in the treatment chamber is washed out with saline solution, thus ensuring that blood will not interact with any drug to be delivered.
- **Step 3:** The outflow port is closed and the desired amount of drug delivered into the treatment chamber. The pressure within the chamber is controlled by inflation of the central balloon and monitored by a fibreoptic sensor. The pressure ensures the drug is delivered all the way into the medial wall (Figure 2).

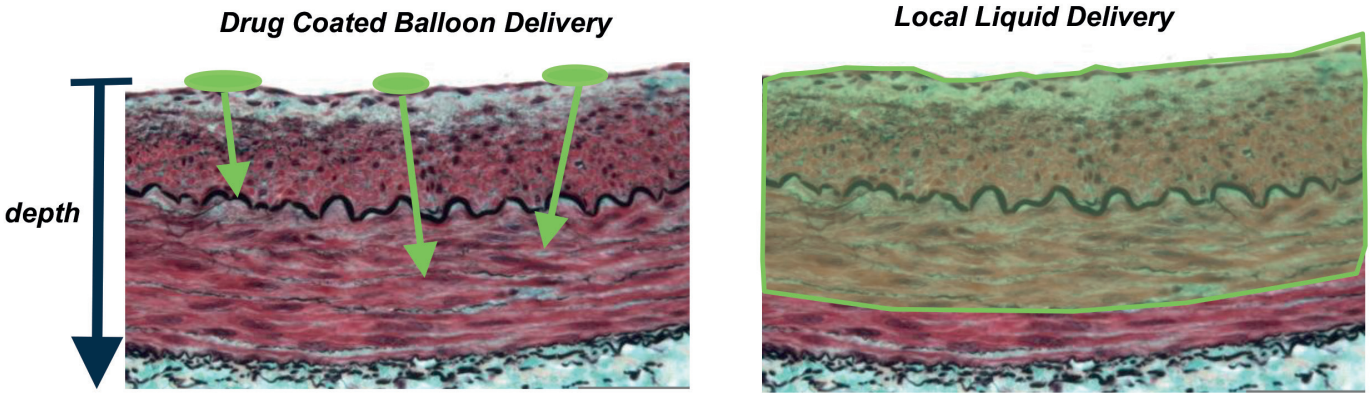

Figure 2: The OPC's local liquid delivery method results in immediate penetration of drug into the medial wall (right), compared with the time dependent diffusion from DCB technology (left).

- **Step 4:** The outflow port is reopened and saline solution is again used to wash the treatment chamber. This greatly reduces, or even eliminates, the possibility of systemic drug circulation, thus hugely reducing adverse events due to drug toxicity.
- **Step 5:** The occlusion balloons are deflated, allowing normal blood flow to resume. The OPC is then ready to be removed or redeployed to the next site within the patient.

Advantages of the OPC

There are a significant number of advantages to the OPC when compared with DCBs. The major advantage, as previously stated, is the creation of a pressure-controlled treatment chamber, which enables the drug to quickly and consistently penetrate into the medial wall, whereas for DCBs, much like stents, store drugs within the intima. DCBs are also limited by their length, requiring multiple balloons to treat long lesions, a problem solved by the OPC.

The treatment chamber also offers an unprecedented flexibility in drug delivery, opening up the potential for sequential drugs to be delivered, or even mixed *in vivo*, with a single device. This enables safer delivery as well, because the isolated nature of the treatment chamber enables the flushing with saline solution, vastly reducing systemic toxicity of drugs deployed within.

Worth mentioning also is the economic benefit of the OPC. Because a single device is used for the delivery of multiple agents to multiple locations in a single patient, the savings in time and materials are significant. With the addition of the central balloon to control pressure, the amount of drug to be delivered can also be carefully controlled, further reducing costs.

CLINICAL RESULTS

To date, two clinical studies have investigated the OPC's effectiveness, with results from one having already been reported. After promising results from *ex vivo* and preclinical studies, a study was conducted by Bunch F *et al* to assess the "feasibility, safety and initial efficacy of paclitaxel administration" using the OPC for the "prevention of restenosis in infrapopliteal *de novo* and restenotic lesions".[2]

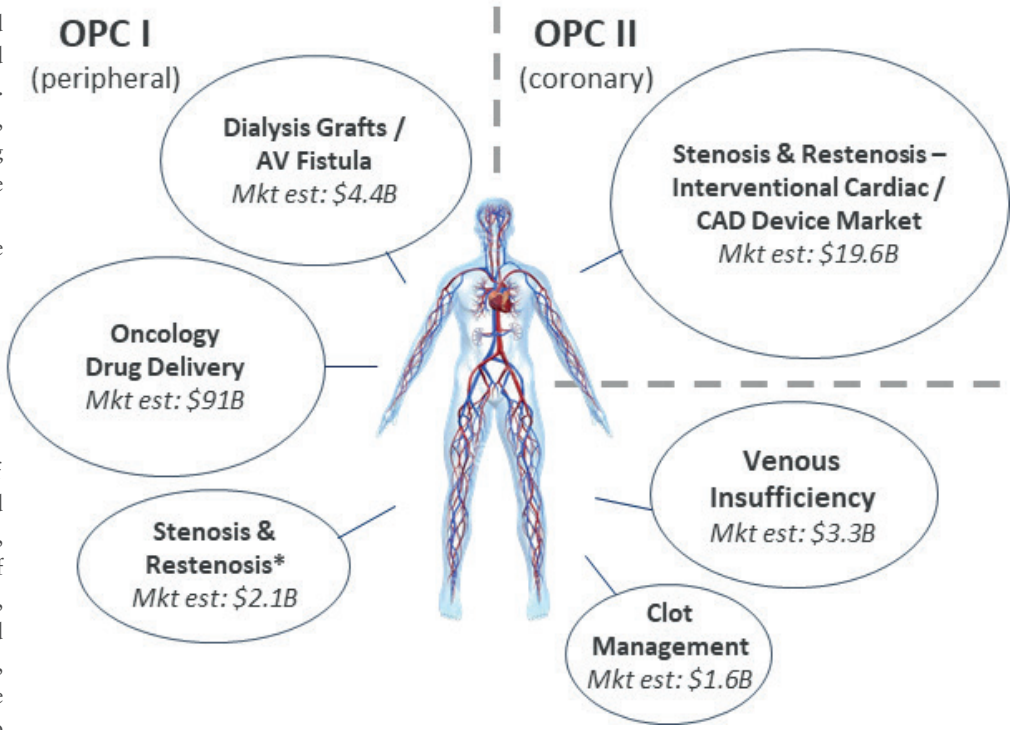

Figure 3: Potential markets for the OPC.

Buy	Build	License
Acquire ACT's OPC patent estate and licensing revenue streams	Become a co-development partner for OPC II	License the use of FDA cleared OPC I for use in new markets

Table 1: Opportunities presented by the OPC.

This first in human, multicentre study reported that, across the 10 patients tested, all tolerated the procedure well. At the six-month follow-up 70% of patients demonstrated the successful efficacy endpoint of freedom from clinically driven target lesion revascularisation (CD-TLR). 0% of patients demonstrated thrombosis, major amputation in the target limb or target limb death at either the 1-, 3- or 6-month follow-ups. The conclusion stated that the OPC showed a favourable safety and efficacy profiles and suggested that subsequent studies should be performed on a larger subject base and with direct comparison to DCBs.

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FUTURE OUTLOOK

The OPC has three separate 510k clearances, an established safety profile and US FDA approval for any drug, organ or disease. The OPC is, however, only the first in a pipeline of products in development to provide the next generation of targeted endovascular drug delivery.

There is huge market potential for this technology (Figure 3). The current OPC is designed to treat peripheral indications, such as PAD, currently focusing on stenosis and restenosis, a $2.1 billion market. Currently in development is the OPC II, looking towards being suitable for similar use for coronary indications, a $19.6 billion market. The technology has the potential to address a much wider array of markets,

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including venous insufficiency ($3.3 billion), dialysis grafts/AV fistula ($4.4 billion) and oncology drug delivery ($91 billion).

ACT currently holds eighteen patents across three devices, including the OPC and OPC II. The company envisages several opportunities for investors and partners in the future (Table 1), including licensing the FDA-approved OPC for use in new markets; partnering for the development of OPC II; and potentially even acquisition of ACT's OPC patent estate and revenue streams.

ABOUT THE COMPANY

Advanced Catheter Therapies, Inc (ACT) is a research and development medical device company with a portfolio of innovative catheter technologies targeting vascular disease including thrombosis, inflammation, occlusions and restenosis. ACT has initially focused its resources on the development of the 510(k) cleared and patented Occlusion Perfusion Catheter™ (OPC).

REFERENCES

1. *Teeslink R, Yazdani KS,"Occlusion Perfusion Catheter (OPC) – A Universal Drug-Delivery Device – Next Generation".Vascular Disease Management, 2017, Vol 14(9).*
2. *Bunch F et al, "A universal drug delivery catheter for the treatment of infrapopliteal arterial disease: results from the multi-center first-in-human study". Catheter Cardiovasc Interv, 2017, Vol(0), pp 1-6.*

ABOUT THE AUTHOR

Paul J Fitzpatrick brings 24 years of diverse, entrepreneurial business and healthcare experience to Advanced Catheter Therapies (ACT), with a proven track record of delivering results. His experience includes serving as Founder, Chief Executive Officer, President, Board Director, Chief Operating Officer and Executive Vice-President. Mr Fitzpatrick is a graduate of the Daniel Freeman Hospital Paramedic School (Los Angeles, CA, US), earning his board certification as a National Registered Paramedic, and holds a degree in paramedic technology from Northeastern University in Boston, where he served as an adjunct faculty member for 10 years.