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Therapeutic focus – Oncolytic viruses enter pivotal year

Billed as a pivotal year for the novel field of oncolytic viruses, 2011 has started in the best possible manner with Amgen's $425m acquisition of BioVex, one of the sector's leading players (*Amgen provides BioVex investors a welcome early exit, January 25, 2010*). This high profile deal, coupled with upcoming pivotal data from the leading candidates, mean interest in this novel approach to targeting tumours is set for a major resurgence.

The concept of using oncolytic viruses has been around for several decades but the first wave of clinical candidates foundered due to delivery and efficacy constraints, which in turn dampened big pharma's interest in the technology. However, the current crop of oncolytic viruses offer hope that these hurdles can be overcome, and Amgen's move on BioVex indicates renewed expectation. All of which offers encouragement to the likes of Oncolytics Biotech, Jennerex Biotherapeutics, Oncos Therapeutics and Neotropix in their quest for funding and partnerships (see table below).

Harnessing virus power

Oncolytic viruses, viruses which preferentially infect and kill cancer cells, are a natural phenomenon, known for more than a century now and researched in clinical trials for decades.

Promising research in the 1960s, using naturally-occurring viruses such as poliovirus, adenovirus and coxsackie virus, demonstrated the potential in harnessing the power of viruses to attack cancer cells, but safety concerns and the lack of sustained or consistent responses hampered subsequent research efforts.

As such, only the relatively recent breakthroughs in DNA engineering and a greater understanding of cancer and virology have propelled the technology, now that researchers are able to design and engineer these viruses to try and maximize safety and efficacy.

First wave: safe but not effective

The first wave of engineered oncolytic viruses was spearheaded by Onyx Pharmaceuticals' ONYX-015 (lontucirev), a modified adenovirus which targeted cancer cells with an abnormal p53 pathway.

ONYX-015 made it as far as phase III studies in head and neck cancer but the trial failed to complete due to manufacturing constraints given the trial size and very high doses of the virus required to illicit a response. Onyx scrapped ONYX-015 in 2002 along with a number of follow-on candidates.

Other leading candidates, particularly those being developed by Cell Genesys, were also ditched around the same time.

Although most of this first wave of engineered oncolytic viruses fell by the wayside, they did at least achieve two significant milestones: demonstrating safety and attracting interest from big pharma.

Demonstrating safety, such that flu–like symptoms are now the only real concern, was important given prior experience with using naturally-occurring viruses. Matt Coffey, chief scientific officer and co-founder of Oncolytics Biotech, acknowledges the work carried out by the likes of Onyx.

"They (Onyx) did a lot to educate the regulatory environment and did a fantastic job of getting it out into the public, although ultimately they were not successful," says Mr Coffey.

At the same time big pharma interest in the space was piqued, with Pfizer and Novartis establishing broad collaborations with Onyx and Cell Genesys, respectively.

Unfortunately these collaborations folded as the lead candidates, having established a decent safety record, were simply not effective enough in combating tumours. And until Amgen's acquisition of BioVex this week, big pharma had turned their backs on the technology.

"It was not surprising the pharma industry became a little tired of oncolytic viruses, so the field retracted into: 'we need to make better products, which then might be more attractive'", says BioVex's founder and chief

technology officer, Robert Coffin, speaking to *EP Vantage* prior to the Amgen deal.

New wave: efficacy building, interest returning

It is hardly surprising therefore that the current pipeline of oncolytic viruses, displayed in the table below, is mostly being developed by small biotechs and academic institutions; and of the biotech companies, it is interesting to note that most are privately-held.

The retraction of the field, a relatively modest-looking pipeline and lack of big pharma interest, especially when compared to other novel technologies such as cancer vaccines, RNAi and gene therapy, makes Amgen's move on BioVex all the more significant for the space.

Clinical stage pipeline for oncolytic viruses						
Status	**Product**	**Virus type**	**Company**	**Originator**	**Launch**	**Lead Indications**
Phase III	OncoVEX (talminogene laherparepvec)	HSV + GM-CSF	BioVex (Amgen)	BioVex	2012	Melanoma [Phase III]; Head & neck cancers [Phase III]
	Reolysin	Reovirus Serotype 3 Dearing	Oncolytics Biotech	University of Calgary	2013	Head & neck cancers [Phase III]; Non-small cell lung cancer (NSCLC) [Phase II]; Melanoma [Phase II]
Phase II	JX-594	Vaccinia virus (poxvirus) + GM-CSF	Jennerex Biotherapeutics + Transgene + Green Cross (Korea)	Jennerex Biotherapeutics	2015	Hepatoma, liver cancer [Phase II]; Colorectal cancer [Phase II]; Head & neck cancers [Phase I]; Melanoma [Phase I]; Lung cancer [Phase I]
	NTX-010	Seneca Valley virus-001	NCI + Neotropix	Novartis	-	Small cell lung cancer (SCLC) [Phase II]; Neuroendocrine tumours [Phase I]
	CGTG-102	Adenovirus type 5	Oncos Therapeutics	Oncos Therapeutics	-	Solid tumour indications [Phase II]
	MTH-68H	Newcastle Disease Virus (NDV)	Hadassah Medical Organization	Hadassah Medical Organization	-	Solid tumour indications [Phase II]
Phase I	GL-ONC1	Vaccinia virus (poxvirus)	Genelux	Genelux	-	Lung cancer [Phase I]; Mesothelioma [Phase I]; Solid tumour indications [Phase I]; Pancreatic cancer [Pre-clinical]
	PV701	Newcastle Disease Virus (NDV)	Wellstat Group	Wellstat Group	-	Colorectal cancer [Phase II]; Cervical cancer [Phase II]; Head & neck cancers [Phase I]; General cancer indications [Phase I]

	JX-929	Vaccinia virus (poxvirus)	Jennerex Biotherapeutics	Jennerex Biotherapeutics	-	Solid tumour indications [Phase I]
	Cavatak	Coxsackievirus A21	Viralytics	Viralytics	-	Melanoma [Phase I]; Head & neck cancers [Phase I]
	HF10	HSV type 1	Takara Bio	Nagoya University	-	Head & neck cancers [Phase I]
	HSV1716	HSV type 1	Children's Hospital Medical Center, Cincinnati	Children's Hospital Medical Center, Cincinnati	-	Non-CNS solid tumours [Phase I]
	CG0070	Adenovirus type 5	Cold Genesys	Cell Genesys	-	Bladder cancer [Phase I]

BioVex's lead candidate is OncoVex, a genetically altered strain of herpes simplex virus (HSV) designed to only enter tumour cells. It is injected directly into the tumour, causing cell death as the virus replicates and spreads, while a GM-CSF component helps to stimulate a patient's immune system to attack other cancerous cells.

Inducing an immune response, when tumour antigens are released following viral oncolysis, is a feature common to a number of other candidates, such that the technology is often also referred to as a cancer vaccine. No bad thing given Dendreon's breakthrough FDA approval for Provenge which seems to have given the whole sector a major boost.

Following highly encouraging phase II data in melanoma, BioVex initiated a phase III trial in 2009 in 360 patients with metastatic melanoma, comparing OncoVex to subcutaneously administered GM-CSF; Leerink Swann analysts note this control approach has not historically resulted in tumour responses, suggesting the trial design, which has been agreed with the FDA under a special protocol assessment (SPA), heavily favours OncoVex; "Even if the Phase II activity was cut in half, the (phase III) study would still likely be positive," wrote Leerink Swann analysts in a note today.

Results from the melanoma trial are due by the end of 2011, hence the timing of Amgen's acquisition of BioVex is somewhat surprising, albeit the full deal value is contingent on regulatory and commercial milestones being met. Meanwhile Biovex recently initiated a second phase III trial as a first line treatment in 528 patients with squamous cell head and neck cancers.

Oncolytics seeking partner

The only other phase III candidate is Oncolytics' Reolysin, an engineered form of the human reovirus which targets tumour cells with an activated Ras pathway. Oncolytics is the only publicly-listed biotech developing a clinical stage oncolytic virus.

A number of phase I and II studies were conducted across a range of solid tumours before a phase III trial was initiated in 2009, also under SPA from the FDA, to assess Reolysin in combination with paclitaxel and carboplatin in patients with platinum-refractory head and neck cancers.

The overall trial is adaptive, meaning data from the first 80 patients enrolled will be revealed before deciding whether to expand the trial, which according to Mr Coffey's estimates will require 173 patients to meet its primary endpoint of overall survival.

A look at this critical data from the first 80 patients will be announced in the first half of the year, with positive results likely to help accelerate any partnership discussions. Mr Coffey says a partner could be secured any time although it seems most likely only after this interim phase III data has been revealed.

Oncolytics' shares gained just 4% yesterday to C$6.55 following the Amgen-BioVex news; the stock has more than doubled in the past 12 months and currently trades at around a six-year high. Oncolytics is currently valued at $445m and expectations around Reolysin and partnerships, possibly now even a takeover, appear to be building.

Delivery advantage

Of the phase II candidates, Jennerex's JX-594 is on the verge of entering phase III and made headlines last year when Transgene licensed European rights to the product for an undisclosed equity investment in Jennerex, $116m in development and regulatory milestones, and double digit royalties.

JX-594 is an engineered poxvirus, or vaccinia virus, which also has a GM-CSF component like OncoVex. Phase III trials are expected to start this year in liver cancer.

Although JX-594 is slightly behind OncoVex and Reolysin in developmental terms, Jennerex's chief executive officer, David Kirn, believes its candidate holds a technological advantage over its rivals.

Whereas nearly all other candidates in the class need to be injected directly into the tumour – they would otherwise be cleared from the bloodstream by a patient's immune system – pox viruses have evolved to be stable in the blood which means JX-594 can be delivered by intravenous (IV) injection and generate systemic efficacy.

Although phase II trials were conducted with intra-tumour injections of JX-594, a phase I dose escalation trial of an IV formulation has successfully completed, while a phase Ib in colon cancer with the IV formulation was recently initiated.

"Despite clear safety and localised efficacy with oncolytic viruses, a major hurdle that had not previously been overcome was the ability to deliver these products intravenously in order to get systemic efficacy", says Mr Kirn. "We believe this field will see an explosion of interest and eventually the involvement of large pharmaceutical companies".

In the spotlight

With the rest of the oncolytic virus pipeline in development at small and private biotech companies, as well as academic research institutions, it is hardly surprising that many of these candidates remain under the radar.

The Amgen-BioVex deal however is likely to throw the spotlight on the remaining candidates and the companies could start to field enquiries from big pharma.

Neotropix is conducting a phase II trial of NTX-010 in small cell lung cancer which should report in early 2012, while Oncos Therapeutics is running a phase I/II study with CGTG-102. Genelux is conducting a phase I trial of GL-ONC1, which uses a poxvirus similar to Jennerex's technology, which therefore also has the potential for IV delivery. Wellstat also claims its candidate, PV701, can be delivered intravenously.

Antibody parallels?

Amgen's purchase of BioVex, following Transgene's deal with Jennerex, indicates interest is returning to the oncolytic virus space and could gather momentum.

Unsurprisingly, all proponents of the technology draw parallels to the long and arduous developmental history of monoclonal antibodies, which finally hit the jackpot when Rituxan gained approval in 1997.

Assuming efficacy can be established, coupled with a relatively benign safety profile by most cancer drug standards, oncolytic viruses certainly have potential commercial and therapeutic value on a par with antibodies.

Oncolytic viruses have the potential to be used across the spectrum of cancer treatment, from early to late stages of disease, as a monotherapy or in combination with chemotherapy, or in an adjuvant setting.

The proof will ultimately be in the pudding of positive pivotal data from large randomised clinical trials, a validation step that the technology has yet to breach, for all the excitement created by the Amgen-BioVex deal.

The sense is that this second wave of oncolytic viruses needs to deliver if the technology is ever to realise its potential.