



Drug Delivery Report

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***Nab* Technology**

**A Drug Delivery Platform Utilising
Endothelial gp60 Receptor-based
Transport and Tumour-derived SPARC
for Targeting**

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Neil Desai is Vice President of Research and Development at Abraxis Bioscience, Inc. (ABI), in Los Angeles, CA. Dr Desai is an inventor of Abraxis' nanotechnology and nanoparticle-albumin bound (*nab*[™]) drug delivery platform and discovered its novel targeted biological pathway. He was primarily responsible for the development of the nanotechnology drug Abraxane[®], which was approved by the FDA in January 2005 as the first in a new class of nanotherapeutics for the treatment of metastatic breast cancer. Prior to joining ABI, Dr Desai was Senior Director of Biopolymer Research at VivoRx, Inc., where he developed novel encapsulation systems for living cells and was part of the team that performed the world's first successful encapsulated islet cell transplant in a diabetic patient. Dr Desai has more than 17 years' experience in the research and development of novel drug delivery systems and biocompatible polymers. He holds over 60 issued US and foreign patents and has authored over 40 peer-reviewed publications. Dr Desai holds an MS and a PhD in Chemical Engineering from the University of Texas at Austin and a BS in Chemical Engineering from the University of Bombay.

Introduction

Despite intense research and recent advances in drug delivery, the effective and non-toxic delivery of hydrophobic therapeutic compounds remains a major challenge for the pharmaceutical industry. The use of solvents and surfactants in formulations often impairs drug distribution and is associated with increased toxicity from these components. As an example, paclitaxel, a potent chemotherapeutic agent, is widely used against multiple tumour types. Due to its poor water solubility, the conventional paclitaxel formulation (Taxol[®], made by **Bristol-Myers Squibb Co.**) contains a high concentration of Cremophor-EL[®] (polyethoxylated castor oil, made by **BASF**), which is associated with significant toxicities including allergic, hypersensitivity and anaphylactic reactions that require premedication and prolonged peripheral neuropathy. In addition, paclitaxel is sequestered by Cremophor micelles, which prolongs the systemic exposure and increases drug toxicity. Several attempts have been made to create new, Cremophor-free formulations of paclitaxel, e.g. liposomal encapsulated paclitaxel (by **NeoPharm**), prodrug paclitaxel polyglumex (Xyotax[®], by **Cell Therapeutics**), polymeric-micellar paclitaxel (Genexol-PM[®] by **Samyang** and Nanoxel[®] by **Dabur Pharma**), paclitaxel vitamin E emulsion (Tocosol[®], by **Sonus Pharmaceuticals**) and a polymer microsphere formulation of paclitaxel (Paclimer[®], by **Guilford Pharmaceuticals**). None of these formulations has yet succeeded in obtaining approval from the US **Food and Drug Administration (FDA)**. The high risk in developing the novel paclitaxel

formulations is highlighted by the failure of Xyotax in Phase III trials in non-small cell lung cancer (NSCLC) and also the most recent failure of Tocosol in its Phase III clinical trial for metastatic breast cancer (MBC).

Abraxane: The First Prototype of Nab Technology

Nanoparticle albumin-bound (*nab*[™]) technology is a patented novel nanotechnology-based drug delivery platform developed by **Abraxis BioScience**, which exploits the natural properties of albumin to achieve a safe, solvent-free, efficient and targeted drug delivery. Abraxane[®] is the first successful example of *nab* technology-based drug delivery, and consists of paclitaxel protein-bound particles for injectable suspension (albumin bound). Abraxane, or *nab*-paclitaxel, is a Cremophor-free, albumin-bound 130-nm particle form of paclitaxel (see Abraxane package insert). Approved by the FDA in January 2005 for the treatment of breast cancer after a failure of combination chemotherapy for metastatic disease or a relapse within six months of adjuvant chemotherapy, Abraxane is recognised as the first nanotechnology-based drug¹ on the market.

Abraxane consists of particles of paclitaxel in the nanometre-size range, stabilised with human albumin. The paclitaxel and albumin are not covalently linked but rather associated through hydrophobic interactions. The particles of paclitaxel are in a non-crystalline, amorphous, readily bioavailable state, allowing for rapid drug release from the particles following intravenous administration (*Figure 1*).

¹ http://nano.cancer.gov/about_alliance/q-and-a.asp

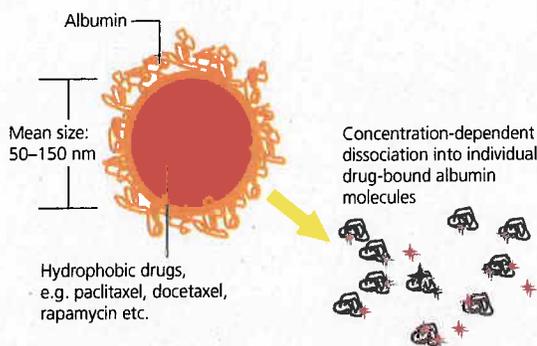


Figure 1 – Schematic of nanoparticles prepared by nab-technology.

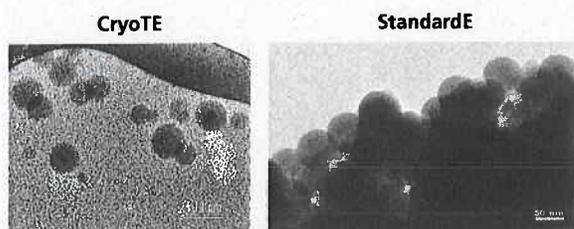


Figure 2 – Transmission electron micrographs of Abraxane (nab-paclitaxel) nanoparticles.

Upon reconstitution with a 0.9% sodium chloride injection to a concentration of 5 mg/mL, the paclitaxel particles are stable with an average size of 130 nm (Figure 2). *In vitro* and *in vivo* drug dissolution studies have shown that, once injected into circulation, paclitaxel nanoparticles quickly dissolve into smaller albumin-paclitaxel complexes whose size is virtually identical to that of endogenous albumin molecules in blood. Thus, the albumin-paclitaxel complexes are fully capable of utilising the natural albumin pathways, including gp60 and caveolae-mediated transcytosis and increased intratumoural accumulation, through association with tumour-derived SPARC protein (see below) to achieve enhanced drug targeting and penetration in tumours (Desai, Trieu, Yao *et al.* 2006).

Nab Technology: Exploiting the Transport Properties of Albumin

Albumin reversibly binds to and transports a wide range of molecules, including bilirubin, free fatty acids, hydrophobic vitamins, hormones, calcium and zinc, as well as many acidic and hydrophobic drugs. Human serum albumin constitutes approximately 60% of total plasma protein and is the most important drug carrier protein in plasma on account of its high abundance. Albumin can facilitate the diffusion of lipophilic drugs into the membrane lipid bilayer. In addition, various proliferating tumours are known to accumulate albumin and use it as a major energy and nitrogen source for *de novo* protein synthesis.

The transcytosis of albumin across the endothelium of blood vessels is mediated by gp60 and caveolae. Gp60 (albondin) is a 60-kDa glycoprotein localised on the endothelial cell surface that binds to native albumin with a high affinity in the nanomolar range (Schnitzer 1992). The

binding of albumin to gp60 induces gp60 clustering and association with caveolar-scaffolding protein caveolin-1, which leads to the formation of vesicles called caveolae that carry both gp60-bound and fluid phase albumin or albumin-bound drugs in a process known as transcytosis from the apical to the basal membrane, where the vesicle contents are released into the sub-endothelial space. The importance of gp60 and caveolae in albumin-drug transcytosis has been demonstrated in several studies. Studies in our lab have demonstrated that *nab*-paclitaxel increased the endothelial binding of paclitaxel by 9.9 fold ($P < 0.0001$) and the transport of paclitaxel across microvessel endothelial cell monolayers by 4.2 fold ($P < 0.0001$), as compared to Cremophor-based paclitaxel (Desai, Trieu, Yao *et al.* 2006). In contrast, Taxol cannot utilise and benefit from the gp60-mediated transcytosis, as the binding of paclitaxel to albumin and endothelial cells is inhibited by the presence of Cremophor even at low concentrations (Desai, Trieu, Yao *et al.* 2006). It is postulated that this inhibition of transcytosis occurs with other surfactants as well.

The accumulation of albumin and albumin-bound drugs in the tumour interstitium is further facilitated by SPARC (Secreted Protein, Acidic and Rich in Cysteine). SPARC, a secreted glycoprotein also referred to as osteonectin and BM 40, has been identified as an albumin-binding protein (Sage *et al.* 1984). We recently determined that the SPARC binding to albumin is saturable and specific and may play an important role in the increased tumour accumulation of albumin-bound drugs (Trieu *et al.* 2007). Over-expression of SPARC in multiple tumour types, including breast, prostate, oesophagus, gastric, colorectal, liver, lung, kidney, skin melanoma, bladder, head and neck, thyroid and brain tumours such as glioma, invasive meningioma, astrocytoma, etc., is associated with increased tumour invasion, metastasis and poor prognosis (Framson and Sage 2004). We have previously shown that Abraxane achieved 33% higher intratumoural paclitaxel concentration when compared with an equal dose of Taxol in SPARC-positive MX-1 tumour xenografts (Desai, Trieu, Yao *et al.* 2006) (Figure 3). More importantly, our studies demonstrated that increased SPARC levels in tumours correlate with enhanced response to Abraxane. The SPARC over-expressing line PC3/SP exhibited enhanced response to Abraxane compared

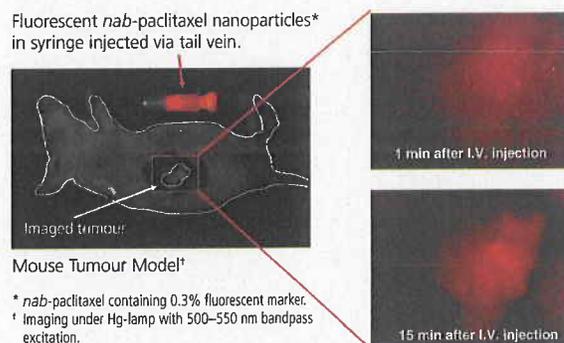


Figure 3 – Rapid uptake into tumours demonstrated by fluorescent labelled paclitaxel nanoparticles.

with wild type PC3 xenograft (Trieu et al. 2007). In head and neck cancer patients there was correlation between high levels of SPARC expression and tumour response to Abraxane (Trieu et al. 2006).

In summary, our research suggests that gp60 transport in tumour blood vessels and SPARC expression in tumours can enhance the transport and accumulation of albumin-bound paclitaxel in tumours, therefore improving its tumour targeting and efficacy. The transcytosis of albumin-bound paclitaxel across the endothelial barrier is facilitated by the binding to the gp60 receptor and caveolar transport. In the tumour interstitial space, albumin-bound paclitaxel complexes bind to SPARC and are rapidly internalised in tumour cells via a non-lysosomal pathway (Figure 4).

Clinical Results with Abraxane

The advantages of *nab* technology can be directly translated into clinical benefits for Abraxane. In a Phase I trial, the lower toxicities of Abraxane allowed the administration of 70% higher dose than the approved dose of Taxol (300 mg/m² vs 175 mg/m², q3w) over a shorter infusion time (30 minutes vs 3 hours), without the need for corticosteroid premedication (Ibrahim et al. 2002). In a randomised Phase III study in patients with metastatic breast cancer (MBC), compared with Taxol at 175 mg/m² q3w, Abraxane administered at 260 mg/m² q3w had statistically significantly higher response rates, longer time to tumour progression, and increased survival in the subset of patients receiving second-line or greater treatment. The incidence of grade 4 neutropenia and hypersensitivity reactions with Abraxane were significantly lower than in the Taxol group. Grade 3 neuropathy was higher for Abraxane due to higher dosage but was easily managed and improved quickly (Gradishar et al. 2005). These results were further supported by preliminary results from an open-label study of 210 Chinese patients with MBC, which suggested that Abraxane (260 mg/m² IV over 30 minutes, q3w) provided higher response rates and longer time to

tumour progression without increased toxicity compared to Taxol (175 mg/m² IV over 3 hours, q3w) (Guan et al. 2007). In a randomised Phase II clinical trial of first-line treatment of MBC in 300 patients, administration of Abraxane at 150 mg/m² weekly or 300 mg/m² q3w resulted in longer progression-free survival compared to Taxotere (100 mg/m² q3w) while the 100 mg/m² qw dose of Abraxane resulted in equivalent progression-free survival but a much improved toxicity profile compared to Taxotere (Gradishar et al. 2006). Preliminary clinical data with 40 patients with MBC showed that combination of Abraxane with bevacizumab (Avastin®, by Genentech) was well tolerated and resulted in an overall response rate of 48.5% (Link et al. 2007). In addition, preliminary findings from Phase II studies of Abraxane in combination with gemcitabine or capecitabine as first-line therapy for patients with MBC suggested that combination therapy was active in this patient population (Moreno-Aspitia and Perez 2005).

Besides breast cancer, Abraxane is also being researched in a variety of other solid tumours. In one recent multi-centre Phase II study of patients with non-small cell lung cancer (NSCLC), Abraxane administered as a single agent at a dose of 260 mg/m² q3w was found to be well tolerated and yielded a response rate of 16% and a disease control rate of 49% (Green et al. 2006), with median time to progression and median survival of 6 and 11 months, respectively. Abraxane administered at 125 mg/m² q3/4w as first-line, single-agent therapy in elderly patients with NSCLC resulted in objective response and disease control rates of 30% and 50%, respectively, with progression-free and overall survivals of 5 and 11 months, respectively (Rizvi et al. 2006). Other ongoing studies are exploring Abraxane in combination with platinum-based regimens, with and without bevacizumab, as first-line therapy in NSCLC (Reynolds et al. 2007). In a multi-centre Phase II study of patients with metastatic melanoma, preliminary data showed that Abraxane administered at 100 mg/m² q3/4w (previously treated patients) or 150 mg/m² q3/4w (chemotherapy-naïve patients) was

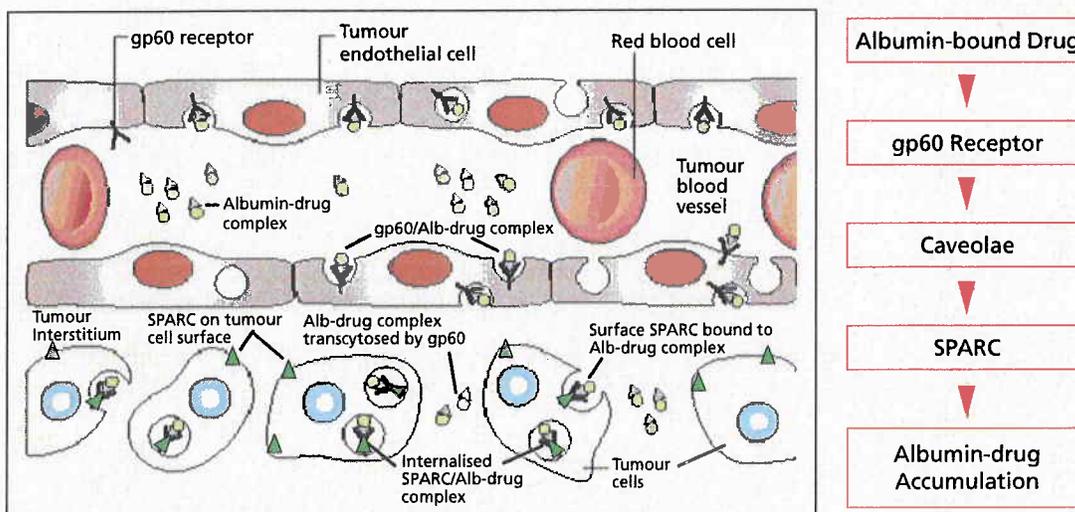


Figure 4 – Mechanisms for the transport and accumulation of Abraxane in tumours.

generally well tolerated except for incidence of peripheral neuropathy, with progression-free survival and overall survival of 3.5 and 12.9 months for the previously treated patients, and 4.5 and 9.6 months for the naïve patients, respectively. Preliminary data from an ongoing Phase II trial also highlighted the potential safety and efficacy for Abraxane as a single agent in platinum-sensitive patients with recurrent ovarian, peritoneal or fallopian tube cancer (Teneriello *et al.* 2007). Other preliminary data supported potential roles for Abraxane in carcinoma of the tongue and other head and neck cancers (Trieu *et al.* 2006).

Nab Technology: A Platform for Next-generation Drugs

With the validation of the *nab*-technology demonstrated by the success of Abraxane, Abraxis BioScience is developing other drugs based on the *nab* technology platform (Figure 5).

Nab-docetaxel (ABI-008, albumin-based nanoparticles of docetaxel), with a mean size of 130 nm, is the '*nab*' version of the active drug in Taxotere® (made by **sanofi-aventis**), which utilises polysorbate 80/ethanol as a surfactant/solvent to solubilise docetaxel. In preclinical studies, *nab*-docetaxel exhibited superior antitumour efficacy and decreased toxicity compared to Taxotere in the HCT-116 colon and PC-3 prostate tumour xenografts (Desai, Trieu, Yang *et al.* 2006). ABI-008 is currently in Phase I clinical trials.

Nab-rapamycin (ABI-009), with a mean particle size of 90 nm, is a *nab*-based injectable form of rapamycin. The mammalian target of rapamycin, mTOR, is a key regulator of cell proliferation and an important target in tumour therapy. The development of rapamycin as an anti-cancer agent has been hampered by poor solubility, low oral bioavailability, and dose-limiting intestinal toxicity. *Nab*-rapamycin was well tolerated in preclinical studies with no significant toxicity and no hypercholesterolemia and hypertriglyceridemia, a known side-effect of rapamycin. ABI-009 was highly effective against MX-1 (breast) HCT-116 (colon) and HT29 (colon) tumour xenografts (De *et al.* 2007) and is currently in Phase I clinical trials.

Nab-17AAG (ABI-010) is an albumin-bound form of the hydrophobic Hsp90 inhibitor 17-allylamino-17-

demethoxygeldanamycin (17-AAG) with a mean size of 110 nm. Hsp90 is an attractive therapeutic target as a chaperone for conformational maturation of oncogenic signalling proteins, including HER-2/ErbB2, Akt, Raf-1, Bcr-Abl and mutated p53 (Tao *et al.* 2005). ABI-010 clinical trials are planned for 2008.

Nab-5404 (ABI-011), with a mean particle size of 90 nm, is a nanoparticle albumin-bound form of a novel thiocolchicine dimer that possesses dual inhibition of tubulin polymerisation and topoisomerase I activities. In our studies, *nab*-5404 exhibits strong antiangiogenic and vascular targeting agent (VTA) activities. ABI-011 clinical trials are planned for 2008.

Abraxis BioScience is also applying its *nab*-technology to indications outside of oncology. Because of its low toxicity, Coroxane®, the albumin-bound particle form of paclitaxel used in cardiovascular applications, was well tolerated by systemic administration for the treatment of in-stent restenosis in coronary arteries (Margolis *et al.* 2007). Coroxane is being investigated in Phase II studies for the treatment of coronary restenosis and peripheral restenosis and in Phase I studies for hemodialysis graft failure.

Additionally, Abraxis BioScience is actively partnering with third parties to develop *nab* technology-based products for novel hydrophobic drugs.

Summary

Nab technology uses a proprietary manufacturing process to allow non-covalent association of hydrophobic drugs with albumin and the formation of nanoparticles that are readily water dispersible without any solvent and surfactant. *Nab* technology achieved improved and targeted drug delivery to tumours by exploiting the following natural properties of albumin:

- It acts as a drug carrier to enhance the solubility of hydrophobic drugs.
- It accumulates selectively and actively in tumours.
- It actively transports across the endothelium of blood vessels via gp60 and caveolae-mediated transcytosis.
- It increases retention in the tumour interstitium by association with the albumin-binding protein SPARC.
- It facilitates the diffusion of lipophilic drug across cell membranes.

Nab technology is a drug delivery system that turns the tumour nutrient albumin and cancer biology against the tumour itself by hijacking the biological pathways of albumin.

Following the successful spin-off in November 2007 from its generic drug business section **APP Pharmaceuticals, Inc.** (NASDAQ: APPX), the new Abraxis BioScience (NASDAQ: ABII) is now a fully integrated biotechnology company dedicated to delivering progressive therapeutics and core technologies that offer patients and medical professionals safer and more effective treatments for cancer and other critical illnesses. The Abraxis portfolio includes the world's first and only protein-based nanoparticle chemotherapeutic compound

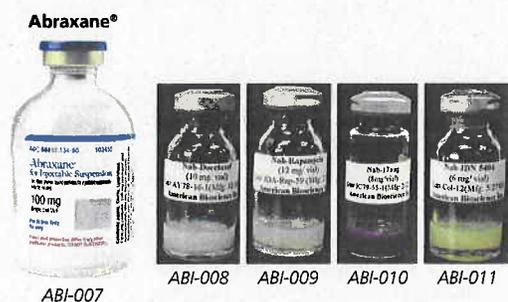


Figure 5 – Abraxane and other drugs in the *nab*-technology pipeline of Abraxis BioScience.

(Abraxane). Abraxane is approved for marketing in the US, Canada and India. Abraxis BioScience is actively expanding the use of Abraxane to other world markets including Europe, Japan, China, Australia, Russia and South Korea. Numerous clinical trials are testing the use of Abraxane in primary, neoadjuvant and metastasis settings for cancer types including breast cancer, non-small cell lung cancer, ovarian cancer, melanoma, prostate cancer, head and neck cancer, and pancreatic cancer, and in combination with various agents including bevacizumab, trastuzumab, lapatinib, sunitinib, epirubicin, cyclophosphamide, carboplatin, 5-fluorouracil, gemcitabine and rapamycin. The successful formulation of other hydrophobic drugs with *nab* technology demonstrates its broad application as a drug delivery platform. *Nab* technology-based chemotherapeutics could target multiple types of malignancies through exploitation of natural properties of albumin and tumour biology.

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