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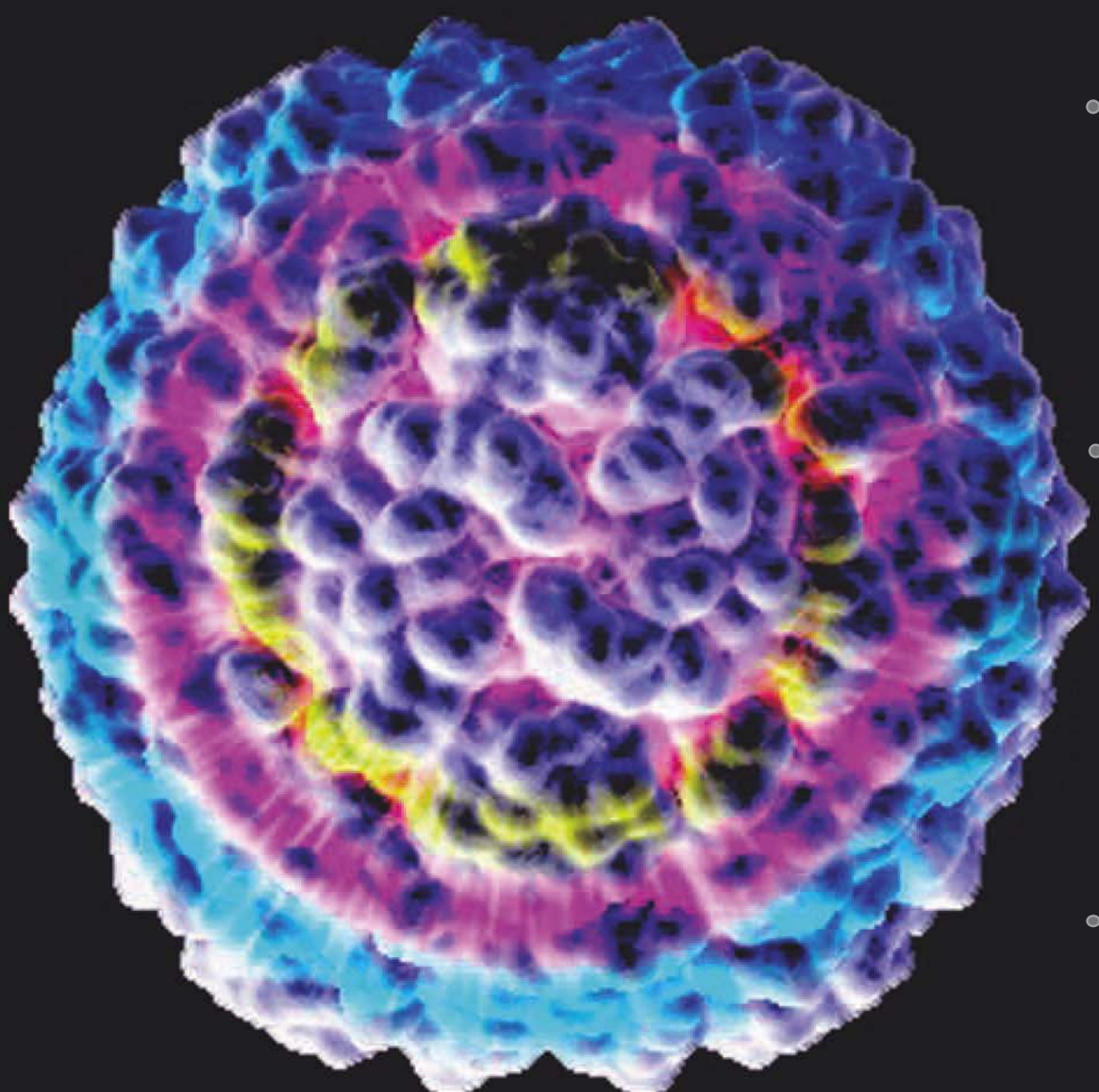

Oncolytic Virotherapy of Cancer

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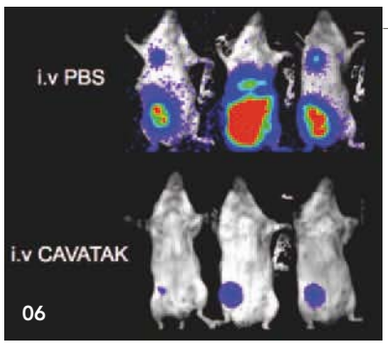

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Editor's Note

Michael Tham
Editor

Growth Response

The mass expansion of the middle class in countries like India and China appears to be fuelling growth in the pharmaceuticals industry. According to Nick Roelofs, VP and GM of the Life Sciences Solutions unit, Agilent, several million people in India are being added to the middle class every quarter. This demographic group is interested in food safety, water quality and better medicines.

Frost & Sullivan has predicted that the Compound Annual Growth Rate (CAGR) of China's pharmaceutical industry in the next seven years to be around 4-5 percent, of which the CAGR of the vaccine market is expected to be 14-15 percent.

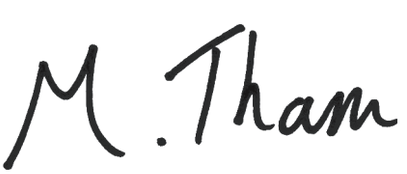
As Asia's pharmaceuticals engine continues to pull forward, the recent months have witnessed increasing cooperation within the industry. The US Pharmacopeial (USP) Convention has inked cooperative agreements with Chinese drug control authorities in Guangzhou, Beijing and Zhejiang – aimed at improving drug quality through initiatives such as scientist exchange programs, joint standards, testing, and other projects.

In India, Elsevier has formed a partnership with the Association of Biotechnology Led Enterprises (ABLE) to provide scientific content to Biotech SMEs (small and medium enterprises) for R&D. Kemwell is also working with German-based Boehringer Ingelheim to build a biopharmaceutical manufacturing plant in Bangalore.

Supporting industries such as automation and express delivery, seem to be riding on this growth. DHL has launched its medical express service – a temperature controlled service that caters to the clinical trials segment.

In June, Agilent opened its automation solutions facility in Singapore for the manufacture of instruments to automate laboratory sample-preparation processes, such as DNA extraction and cell screening.

Looking ahead, the pharmaceuticals industry in Asia looks set for an exciting time of growth and expansion. Many players have already moved into the region to lay claim to a piece of the pie – and we can expect more to respond in the coming months. **PA**



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Global News

RTS Life Science and Hall Analytical Laboratories Partner for Inhaler Testing Services

RTS Life Science has partnered with Hall Analytical Laboratories to provide analytical services and consultancy in the area of automation and inhaler testing. Initially focused on inhaled drug delivery devices, the two companies will share facilities, technology and resources to provide a range of services to help organizations improve efficiency in the development, adoption and use of automation.

Services that are to be provided in consultation with clients include:

- Method development for both manual and automated applications
- Equipment and analytical validation services
- Performance qualification of automation systems
- Canister content testing
- Emitted and delivered dose uniformity testing **PA**

AstraZeneca Receives Marketing Authorization for Lung Cancer Drug

AstraZeneca has announced that the European Commission has granted marketing authorization for an oral anti-cancer drug. Iressa is used for the treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of Epidermal Growth Factor Receptor-Tyrosine Kkinase (EGFR-TK) across all lines of therapy. The authorization is based on a submission package including two Phase III studies comparing the drug with chemotherapy, Ipass and Interest.

Iressa acts by inhibiting the tyrosine kinase enzyme in the EGFR, thereby blocking the transmission of signals involved in the growth and spread of tumors. A mutation in the EGFR is a characteristic occurring in 10-15 percent of lung cancers in non-Asians, and studies have shown that these types of tumors are particularly sensitive to the drug.

AstraZeneca will work with clinicians and pathology groups on a country-by-country basis to facilitate appropriate access to EGFR mutation diagnostic testing.

The company has agreed to conduct a follow-up measure study to generate further data in a Caucasian NSCLC patient population and is currently in discussion with the European Medicines Agency (EMEA) to finalize the study design and endpoints. **PA**

Quotient Clinical Receives MHRA Supplementary Accreditation

Quotient Clinical has been awarded Supplementary Accreditation from the Medicines and Healthcare products Regulatory Agency (MHRA). This confirms that the company is qualified to perform the full range of Phase I trials, including First-in-Human (FIH) studies for low molecular weight chemical entities and biologics. **PA**

Watson Receives Approval for Nicotine Gum

Watson Laboratories has received approval from the US Food and Drug Administration (FDA) to market its over-the-counter Nicotine Polacrilex Gum USP, 2 mg and 4 mg strengths in the coated fruit and cinnamon flavors.

Nicotine Polacrilex Gum coated fruit and cinnamon flavors are the generic equivalent of GlaxoSmithKline Consumer Healthcare's Nicorette Fruit Chill and Cinnamon Surge Coated gums, which are used as an aid to smoking cessation. The market for over-the-counter nicotine gum had annual sales of over US$305 million for the twelve months ending March 2009, according to IRI sales data. **PA**

Agilent Opens Manufacturing Facility in Singapore

Agilent Technologies officially opened its life sciences manufacturing facility in Singapore in June to produce liquid-handling and laboratory robotic instruments.

The instruments manufactured here are used by pharmaceutical companies for the mass commercial production of drugs. These instruments automate laboratory sample-preparation processes such as DNA extraction and cell screening.

This is the company's first facility outside of the US that manufactures precision laboratory automation instruments.

"We are pleased that Agilent Automation Solutions has chosen to establish this operation in Singapore," said Dr Beh Swan Gin, MD, Singapore Economic Development Board. "It testifies to the competitiveness of our precision manufacturing capabilities. Beyond manufacturing, the growing base of public and private sector R&D activities in Singapore also offers a good environment for research instrumentation and scientific tools companies to develop new products and solutions for the global market."

"This manufacturing operation will expand our presence in Singapore and the region," said Nick Roelofs, VP and GM of the Life Sciences Solutions unit.

"We can now more quickly offer an enhanced set of comprehensive workflow solutions to our customers in this region, including major pharmaceutical and biotechnology companies as well as genome centers and academic institutions."

"We're seeing growth in Asia. China for example, has been investing heavily in proteomics, food safety and testing. Our equipment are being used to test about 70 percent of their dairy products for melamine. In India, several million people are being added to the middle class every quarter. This group of people is interested in food safety, water quality and better pharmaceuticals," continues Roelofs.

"With the close proximity to our Asia supply chain, the Automation Solutions facility will complement the Singapore government's strategic investments in the life sciences area," said Gooi Soon Chai, president of Agilent Technologies Singapore.

"We see the opportunity to bring together a portfolio of life science tools in the form of a workflow. This workflow spans from collecting, handling, manipulating, separating and analyzing a sample, and turning that sample into data – basically transforming the analog world of cells and tissue into information," says Roelofs. **PA**

Cover Story

Oncolytic Virotherapy of Cancer

Modern day studies reveal that oncolytic viruses may be an effective therapy for dealing with cancer tumors.

Erin Haley and Darren Shafren,
University of Newcastle, and Viralytics

Currently, oncolytic viruses are being evaluated in the pre-clinical and clinical settings. The acceptance of oncolytic viruses in the clinic has increased, following the publication of clinical trial results, reporting safety and efficacy data. Moreover, China has recently granted approval for the clinical use of the oncolytic virus, adenovirus H101, specifically for the treatment of head and neck cancer .

Targeted Destruction

Oncolytic viruses are defined as those viruses that are capable of specifically targeting, and subsequently destroying tumor cells without causing excessive damage to surrounding normal tissue. These viruses are able to replicate in the target tumor cells, thereby producing high levels of infectious progeny virus and subsequently enabling the infection of additional malignant cells (Figure 1). To be employed successfully and safely as an anti-cancer therapeutic, it is desired that an oncolytic virus displays a number of attributes:

i) Relatively low pathogenicity
ii) Able to replicate specifically in malignant cells
iii) Easily genetically manipulated
iv) Relatively well characterized in terms of viral genome and protein function
v) Possess a rapid life cycle
vi) Well characterized in terms of mechanism of oncolytic action and tumor cell specificity
vii) Able to be delivered systemically
viii) Display susceptibility to an antiviral drug
ix) Not cause serious side effects following administration

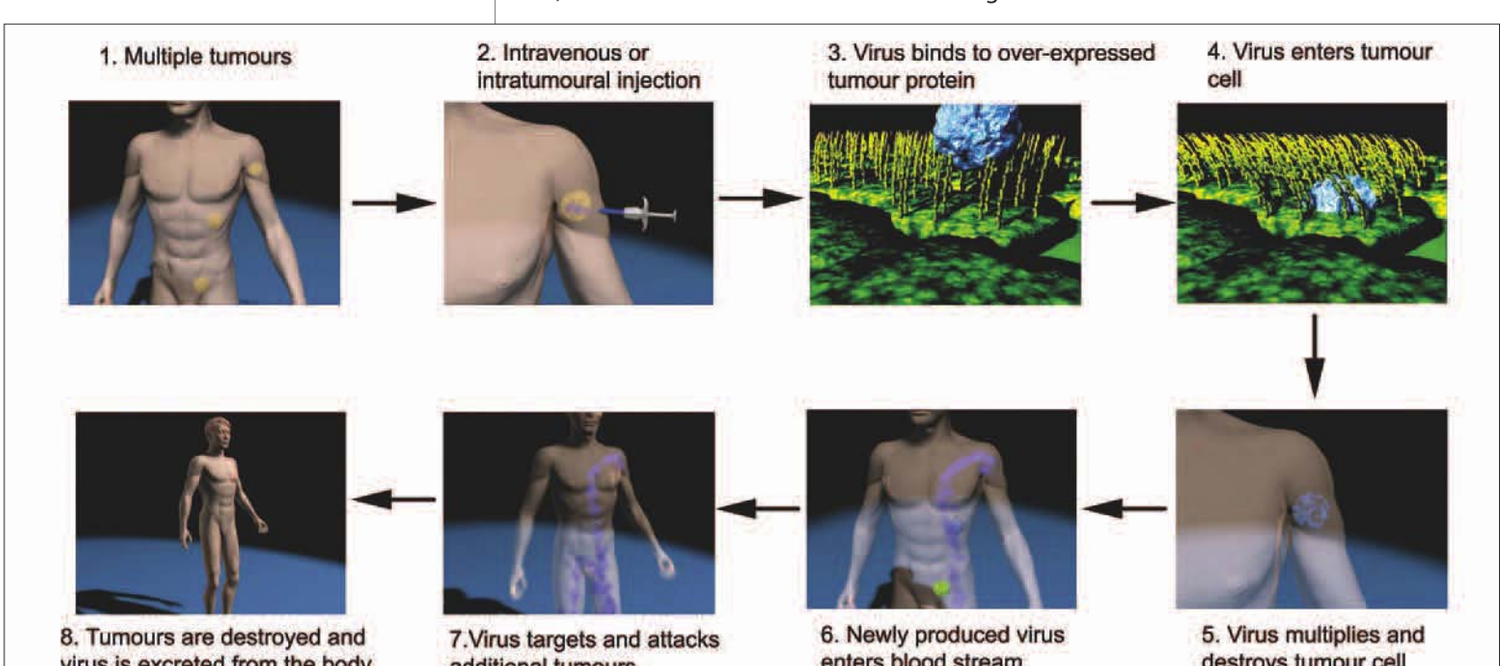


Figure 1: Schematic representation of oncolytic virotherapy. (Source: Viralytics)

Some oncolytic viruses are naturally occurring, whilst others are genetically engineered to reduce pathogenicity, enhance tumour cell selectivity and encode therapeutic genes. Naturally occurring oncolytic viruses include: Newcastle Disease Virus (NDV), Vesicular Stomatitis Virus (VSV), myxoma virus, reovirus, Seneca Valley virus, Coxsackie A viruses and echoviruses. Engineered oncolytic viruses encompass backbones from adenoviruses, vaccinia viruses, Herpes Simplex Virus (HSV) and poliovirus.

Oncolytic virus infections are believed to induce tumor cell death in three main ways. In the first instance (i), viruses infect and replicate in malignant cells, (ii) may induce apoptotic induction, followed by (iii) cell lysis and the expulsion of numerous progeny viral particles. This can subsequently infect additional surrounding malignant cells, thereby enabling further lytic destruction within the tumor micro-environment.

In addition, oncolytic viruses may induce immunotherapy, involving the substantially more complicated mechanism of oncolytic viral killing of malignant cells via the stimulation of the host immune system. In general, the immune system plays the natural role of immune surveillance via the detection of Tumor Associated Antigens (TAAs) and the elimination of neoplastic cells prior to tumor development.

Oncolytic viruses can contribute to this process through the direct lysis of malignant cells and the subsequent presentation of TAAs to the immune system. The viruses themselves are capable of evoking strong immune responses. Such a theory is behind the utilization of oncolysates for therapy. Oncolysates, comprising of tumor cells that have been infected ex vivo, when administered, elicit strong antiviral and anti-tumoral immune responses and have shown promise in both animal models and human clinical trials.

Furthermore, some oncolytic viruses are modified to encode immune-stimulatory cytokines, including interleukin (IL)-12 and granulocyte macrophage-colony stimulating factor (GM-CSF) encoding HSVs (BioVex), adenoviruses (Cell Genesys) and vaccinia viruses (Jennerex Biotherapeutics).

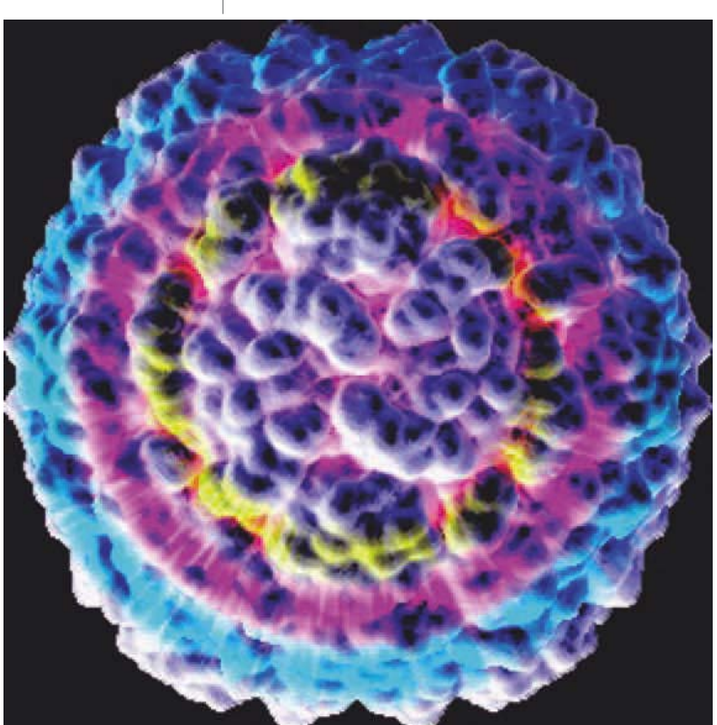
Mechanisms of Oncolytic Virus Tumor Cell Selectivity

(i) Elevated Surface Expression of Viral Receptors

Cancer cells undergo clonal evolution and acquire mutations during this process that are beneficial for the growth and invasive capabilities of the tumor. Many of these cancer-specific, beneficial mutations result in the over-expression of molecules on the cell surface, which are expressed at low levels, or absent, on corresponding normal cells. The elevated surface expression of the integrin a2b1 on ovarian and prostate cancer cells is exploited by the naturally occurring human enterovirus, echovirus type 1 (EV1), for cell attachment, internalization and lytic infection.

Another naturally occurring enterovirus, Coxsackievirus A21 (**CVA21**) utilizes Inter-Cellular Adhesion Molecule 1 (ICAM-1) and/or Decay-Accelerating Factor (DAF), which are over-expressed on the surface of a variety of malignant cells, for cell entry.

The prototype strain of the "common cold" causing, naturally occurring, genetically unmodified, human C-cluster enterovirus, CVA21 (Kuykendall) displays oncolytic activity in multiple malignancies. In particular, CVA21 displays in vitro and in vivo lytic activity in cell cultures derived from melanoma (Figure 2), multiple myeloma, breast cancer and prostate cancer cell lines. The systemic administration of this strain induces efficient tumor regression in immune-compromised melanoma, breast cancer and prostate cancer xenograft models.



A three-dimensional image of the CVA21. (Source: Viralytics)

Cover Story

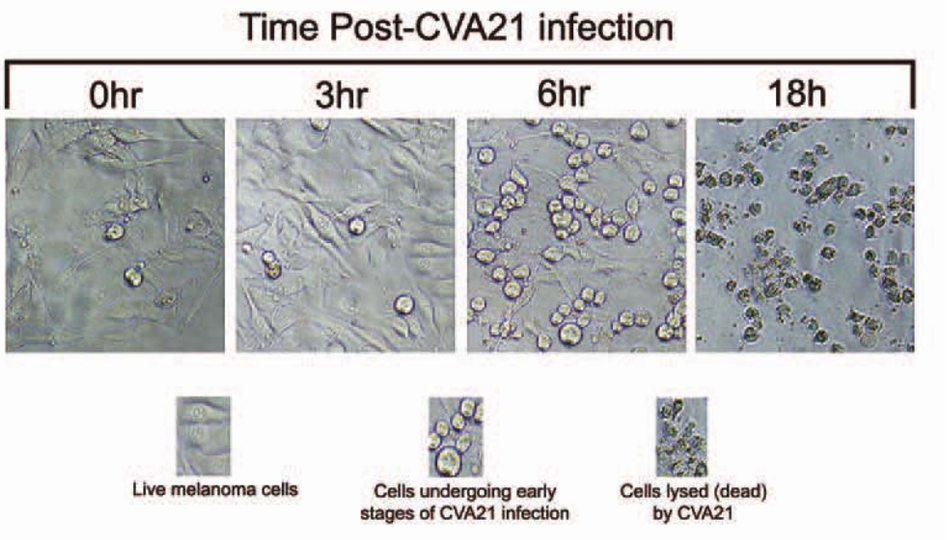


Figure 2: Rapid oncolysis of human melanoma cells by CVA21 (CAVATAK). The 0 hour picture was taken before the addition of CVA21, while the next three pictures were taken at 3, 6 and 18 hours post addition of CVA21, respectively. (Source: Viralytics)

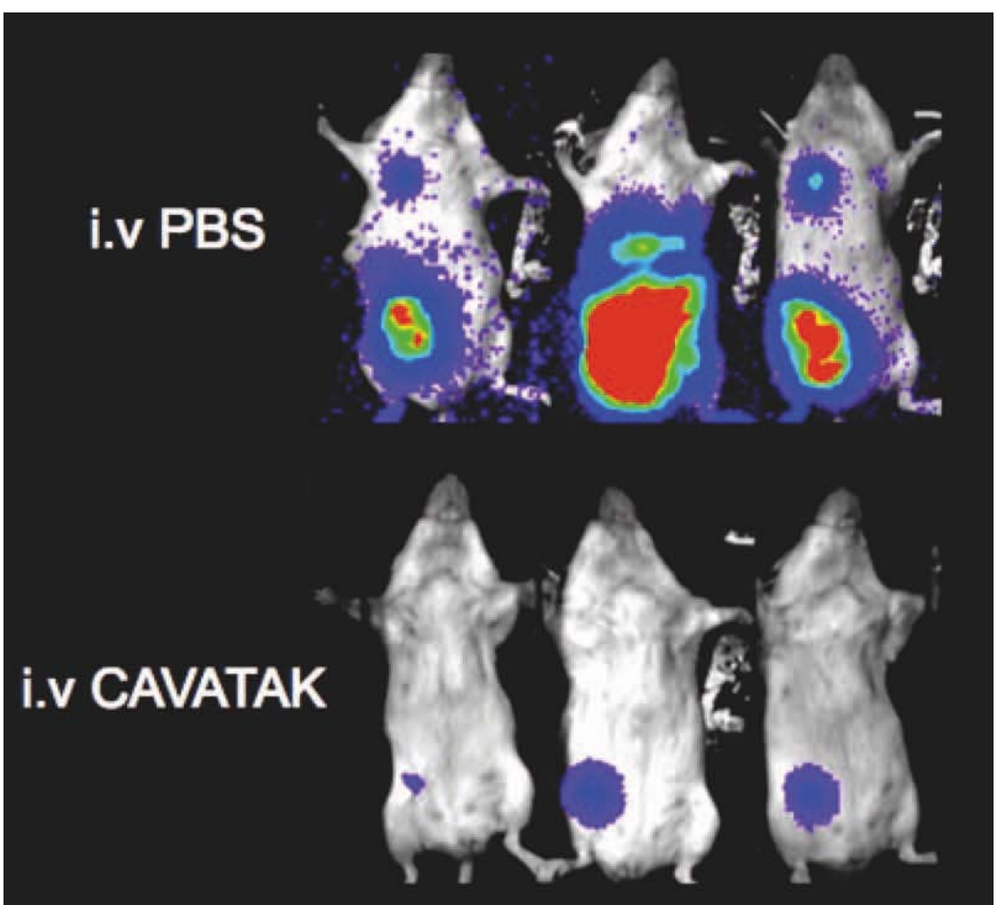


Figure 3: Regression of human breast cancer xenografts in immune-compromised mice following intravenous infusion of CVA21 (CAVATAK) compared to injection of a saline solution (PBS). Note that the reduction in the area and intensity of the colored image represents reduction in tumor size.
(Source: Viralytics)

Moreover, the intra-tumoral administration of CVA21 in a melanoma xenograft model induced regression of a second non-injected tumor. Its systemic administration in a metastatic breast cancer model, resulted in the elimination of primary tumors and metastases. This indicates that CVA21 is capable of disseminating and targeting secondary tumors (Figure 3).

In addition, preliminary studies suggest that the efficacy of oncolytic CVA21 therapy is enhanced when it is combined with chemotherapeutic agents and radiation therapy. Oncolytic CVA21 therapy is licensed as CAVATAK, and is currently under Phase I clinical evaluation in patients with late stage melanoma, prostate cancer, breast cancer and head/neck cancer .

In a similar fashion to CVA21 and EV1, engineered attenuated and vaccine strains of PV target the Poliovirus Receptor (PVR)/ CD155 on the surface of cancer cells. In addition, the selectivity of Seneca Valley Virus (SVV: Neotropix) is also believed to be via receptor over-expression. Although the specific receptor is yet to be reported, it is postulated to involve interaction with integrin a4b1. Furthermore, the targeting of the high affinity Laminin Receptor (LAMR), which is elevated on tumor cells, is utilized by Sindbis virus vectors for cell entry. Meanwhile, the Edmonston strain of measles virus targets the upregulated molecule, CD46, which is expressed at high density on the surface of malignant cells. Measles virus has also been engineered for enhanced selectivity via the targeting of CD38 and Epidermal Growth Factor Receptor (EGFR).

(ii) Defective Antiviral Pathway

The major cellular response to viral infection is mediated via the induction of type I interferons (IFN-a/b). The presence of viral Deoxyribonucleic acid (DNA), single-stranded RNA (ssRNA) or replication intermediates such as double-stranded RNA (dsRNA), are recognized by extra-cytoplasmic Toll-Like Receptors (TLRs) or other cytoplasmic sensors such as the helicases encoded by Retinoic-acid Inducible Gene-I (RIG-I) and

Melanoma-Differentiation-Associated gene 5 (MDA-5). These proteins initiate various signaling cascades, stimulate transcription factors and lead to the initial production of IFN-a/b. The IFNs act in a positive feedback loop on the secreting cells, inducing an "antiviral" state in the surrounding cells. Numerous Interferon-Stimulated Genes (ISGs) are transcribed, including the Protein Kinase PKR, Myxomavirus Resistance 1 (MX1), ISG-20, RNAseL and 2'5' Oligoadenylate Synthetase (OAS) genes, which act via various mechanisms to inhibit viral replication and to protect the host.

The IFN pathway also plays a role in cancer, primarily through the actions of IFNs and IFN stimulated proteins including PKR, Interferon Regulatory Factors (IRFs) and activated Ribonuclease (RNAse) L, having tumor suppressor functions. Some of these factors also contribute to the induction of apoptosis. Additionally, activated Ras signaling inhibits PKR. Predictably, the genes that are directly involved in the IFN pathway are mutated in many neoplastic cells, presumably conferring a selective advantage for tumor development.

Such characteristics of malignant cells are exploited by multiple oncolytic viruses, as cancer cells are permissive to viral infection whilst the surrounding normal cells, boasting intact IFN responses, are protected from infection. This is the major mechanism of selectivity for NDV (Wellstat Biologics), VSV, Myxoma virus, Reovirus (Oncolytics Biotech) and an engineered Influenza A strain.

(iii) Cellular Proliferation State

Malignant cells actively divide due to their being self sufficient in growth signals and insensitivity to regulatory anti-proliferation signals – a characteristic that is exploited by a number of oncolytic viruses. A replication-competent retrovirus vector that is based on the Moloney Murine Leukaemia Virus MLV (ACE-CD) can replicate only in actively dividing cells due to the absence of nuclear localization signals in its capsid, and displays a selective effect in studies of glioblastoma and liver metastases.

Looking Back...

Virotherapy is the therapeutic use of viruses, both naturally occurring and genetically altered for the selective destruction of cancerous cells.

For many years it has been hypothesized that the declining environmental exposure to bacterial and viral pathogens in the community, due to the increasing availability of immunizations and improved health care, may be contributing to a rising incidence of cancer. Circumstantial evidence contributing to this hypothesis is the numerous cases of spontaneous tumor regression that have been documented throughout history. Many of these cases occurred subsequent to viral or bacterial infections or following an episode of fever, a symptom often indicative of infection.

In 1904, a case was reported of a woman with leukemia that was dramatically reduced following an episode of presumed, but never proven, influenza. In 1912, the regression of uterine cervical carcinoma following the inoculation of an attenuated rabies vaccine was reported. Measles virus infections have appeared in a number of reports, causing the regression of lymphoblastic leukemia and Burkitt's lymphoma. More recently, cases of spontaneous remission of chronic lymphatic leukemia were documented, following virus infection in some instances. The remission of chronic lymphocytic leukaemia following small pox vaccination has also been described.

In addition, acquired infections may have a protective effect against the occurrence of cancer later in life. A number of studies have been carried out, in which viral infection and/or the presence of fever early in life, have been correlated with the occurrence of cancer. Early studies on the protective effects of colds and the occurrence of cancer later in life offered conflicting results. A number of larger studies however, have since shown that a protective effect of common cold/influenza infections is conferred against the development of cancer.

A study in 1991 showed that a history of common colds or gastro-enteric influenza was associated with a decreased risk of cancer, and a specific association was found between febrile abdominal influenzas and a decreased risk of carcinomas of the colon and rectum. In this study, it was also noted that chicken pox infections during childhood were significantly related to a decreased risk of breast cancer later in life.

Meanwhile, Herpes Simplex Virus (HSV) infections and cases of influenza/common cold during life substantially reduced the risk of melanoma. Although not documented, this phenomenon is possibly attributed to the stimulation of anti-tumor immune responses following the immune surveillance and early detection and destruction of neoplastic cells.

Early Clinical Evaluations of Oncolytic Viruses

The oncolytic activity of a number of viruses was investigated in humans during the first half of the 20th century. In 1940, an attenuated rabies vaccine was used in humans as a treatment for melanoma. By the middle of the century, large numbers of patients were being treated for a variety of cancers with various, and in some cases multiple viruses including; myxovirus, paramyxovirus and arbovirus. During this time, oncolytic virus research grew in popularity. However, towards the end of the century, oncolytic virotherapy trials in humans waned, most likely due to ethical and safety issues.

Rodent parvovirus H1 is able to infect both resting and proliferating cells. However, it requires the entry of the cell into the S-phase and the activation of the P4 promoter for the occurrence of a productive viral cycle, and has therefore been evaluated for its oncolytic potential. An engineered HSV-1, HSV1716, attenuated via the deletion of the neurovirulence gene, g34.5, replicates conditionally in proliferating cells and has demonstrated oncolytic efficacy in murine melanoma brain metastases.

(iv) Cell-Specific Transcriptional Control

Neoplastic cells often display differences in the types of active promoters present, compared to non-malignant cells. Oncolytic viruses can be engineered to ensure that viral gene transcription is controlled by cancer cell-specific promoters. Adenoviruses are widely engineered in this way. The adenovirus E1 gene has been placed under the control of multiple cell-specific promoters.

This includes the prostate specific antigen promoter, rendering the virus specific for prostate cancer cells, and the carcinoembryonic antigen promoter, rendering the virus specific for Carcinoembryonic Antigen (CEA) producing cells such as colorectal cancer cells. Oncolytic HSVs are also engineered to be controlled by the CEA promoter and the cell cycle regulated B-myb promoter. The naturally occurring rodent parvovirus H1 is also under the control of the cellular P4 promoter.

Another engineered adenovirus, AdTop-PUMA, is under the control of a b-catenin/Tcf-responsive promoter, thereby allowing replication to occur only in cells in which the b-catenin/Tcf pathway is activated, such as colorectal cancer, gastric cancer and hepatocellular carcinoma cells. This is also an example of an oncolytic virus that exploits the proliferation state of a cell, as an activated b-catenin/Tcf pathway results in increased cellular proliferation.

An additional mechanism of oncolytic virus tumor cell tropism is attributed to the cell type-specific control of viral protein synthesis. The Internal Ribosome Entry Site (IRES) of a picornavirus is used to initiate viral protein translation. An engineered oncolytic PV containing the rhinovirus 2 (RV2) IRES, PV-RIPO, demonstrates inhibited neuropathogenicity due to the inhibition of translation in cells of neuronal origin. This tissue type specific control of IRES function is regulated by viral 3'-terminal sequence elements, with the virus specifically infecting glioma cells.

The tolerance profiles of cancer patients to oncolytic virotherapy are quite impressive when compared to those of cyto-toxic chemotherapeutics and some targeted monoclonal antibody therapies – with toxicity being limited to reports of "flu-like" symptoms following viral administration.

(v) MicroRNA Regulated Tropism

A relatively new mechanism by which oncolytic virus tumor cell selectivity may be regulated, is through viral encoded targets for microRNAs (miRNAs). miRNAs are short (≈ 22 nt) regulatory RNAs that act post-transcriptionally to influence numerous cellular processes. Through complementary base pairing with short sequences, usually located within the 3' Untranslated Region (UTR) in cellular messenger Ribonucleic Acid (mRNA), miRNAs act to suppress mRNA translation, and depending on the degree of complementarity, degrade mRNA. Furthermore, some host-encoded miRNAs target viral RNA , contributing to the host immune response to infection.

As the expression of many miRNAs is highly tissue specific, viruses may be engineered to encode particular miRNA target sequences, thereby regulating tissue tropism and decreasing pathogenicity. An oncolytic adenovirus that is engineered to encode the target sequence for the liver-specific miRNA 122T, markedly reduces viral replication in normal hepatocytes in vitro, thereby potentially reducing the liver toxicity associated with oncolytic adenovirus administration.

Furthermore, the virus (VSV $^{let\text{-}7wt}$) was engineered to encode the target sequence for the let-7 tumor suppressor miRNA, which is often expressed at low levels in tumor cells, thereby eliminating replication in normal cells whilst retaining oncolytic activity in tumor cells in *vivo*.

Current Clinical Evaluation of Oncolytic Viruses

The genetic modifications and pre-clinical studies of oncolytic viruses outlined above have enabled the initiation of the clinical evaluation of an array of oncolytic viruses throughout the world. There are currently more than 10 different oncolytic viruses in various Phase I and II clinical evaluation studies. Comprising this panel of oncolytic viruses are both naturally occurring and genetically altered viruses, with routes of viral delivery including single/multi-intravenous and intra-lesional injections.

In some clinical evaluation programs, oncolytic viruses are administered in combination with standard chemotherapeutic regimes and immune-suppressive agents. The tolerance profiles of cancer patients to oncolytic virotherapy are quite impressive when compared to those of cyto-toxic chemotherapeutics and some targeted monoclonal antibody therapies – with toxicity being limited to reports of "flu-like" symptoms following viral administration. The lack of statistical significant data from randomized clinical trials of oncolytic viruses against standard care agents, has historically cast a shadow as to the clinical future of this biologically targeted therapy.

In this environment however, two oncolytic virus companies, BioVex and Oncolytics Biotech have recently announced that they are undertaking pivotal randomized Phase III clinical trials with their lead candidates in late stage melanoma (OncoVexGM-CSF) and refractory head and neck cancers (Reolysin), respectively. Favorable outcomes from these trials should establish oncolytic virotherapy as an accepted targeted anti-cancer therapy, open the regulatory door for further pivotal oncolytic virus trials and finally, attract interest from pharmaceutical companies. **PA**

Enquiry code: 095E01

Drug Discovery

Cancer Research: Epigenetic Mechanisms

Understanding Epigenetics and its role in cancer development can help scientists to discover ways to deal with the disease.

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Cancer accounted for approximately 13 percent of all deaths in 2004, according to the cancer factsheet published by the World Health Organization (WHO) in February 2009. The term cancer (malignancy) describes a diverse class of diseases characterized by uncontrolled cell growth, which frequently culminates in the invasion into and the destruction of adjacent tissue – and subsequent metastasis to other locations in the body via lymph or blood. It is these malignant properties that differentiate cancer from normal cells and benign tumors that tend to be self-limited, noninvasive and do not metastasize.

Nearly all cancers arise gradually, resulting from the accumulation of abnormalities (mutations) in the cell's genetic material due to the effects of carcinogens, ionizing radiation, viral infection, errors in Deoxyribonucleic Acid (DNA) replication, or inherited defects (Figure 1). This accumulation of mutations in cells contributes to the invasive and metastatic properties of cancer cells as well as their ability to take up residence in an array of tissue environments. Genetic abnormalities resulting in cancer frequently occur in oncogenes (genes that cause the transformation of normal cells into cancerous tumor cells) or in tumor suppressor genes.

Proto-oncogenes (eg, ras, wnt, myc and erk) code for proteins that help to regulate cell growth and differentiation, and are often involved in the signal transduction and the execution of mitogenic signals. Mutations in these genes result in their activation and lead to hyperactive cell growth and division, or a newfound protection against apoptosis.

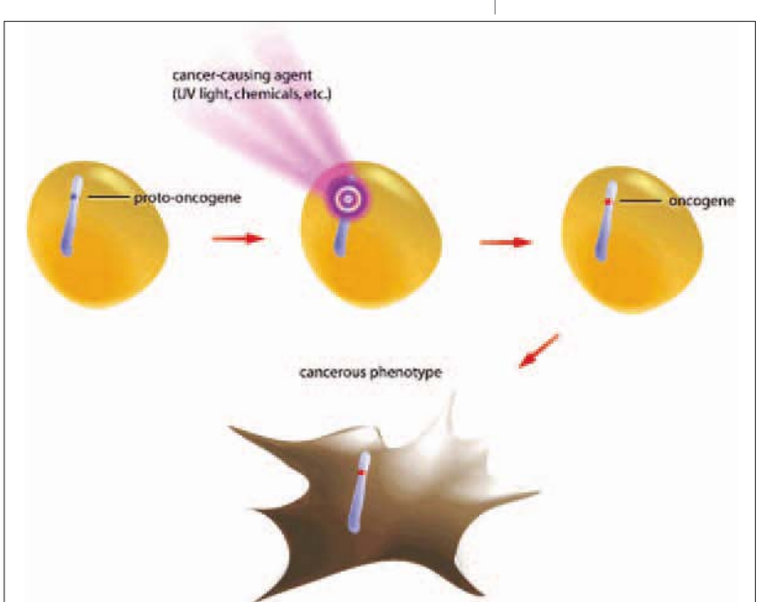

Figure 1: Oncogene Formation
Cancers arise gradually, resulting from the accumulation of mutations in the cell's genetic material due to the effects of cancer causing agents. These mutations result in the activation of oncogenes and contribute to the development of a cancerous phenotype. (Source: Jiang Long, *The Science Creative Quarterly*)

An additional cause of cancer results from mutations occurring in tumor suppressors such as p53 and the retinoblastoma protein. The down-regulation of these proteins has a dampening or repressive effect on the regulation of the cell cycle or promotes apoptosis, and sometimes does both, according to Sherr, 2004. Usually in combination with other genetic changes, these mutations result in a loss or reduction in gene function and enable the cell to progress towards cancer.

Identifying Candidate Genes for Activity in Cancer Progression

While the study of the whole organism often provides the most data, it is also complex due to the interactions between tissue types and the organism's endocrine and paracrine pathways. Many stages of the progression of cancer can also be modeled at the cell-based level, allowing the elucidation of the genetic mechanisms underneath many of the overlying layers of cell-type interaction. There is a large number of molecular interactions that lead to the causal phenotype within a given system, pathway or disease.

To better understand this complexity, screening to identify the major candidates causally involved in these pathways, often lies at the beginning of most discovery research. Researchers are now

moving toward large screening projects, often genome-wide studies, to identify the candidate genes involved in the biological question of interest. Discovering these biological interactions leads to a host of characterization and validation studies, requiring further evaluation.

The flexibility of its applications has made Ribonucleic Acid inhibition (RNAi) a valuable tool for researchers who are interested in gene function characterization, signaling pathway analysis and drug target validation. RNAi utilizes a sequence-specific inhibition of gene expression to allow a targeted approach to identify the role of gene activity, based on the resulting loss-of-function phenotypes. The ease of use allows the generation of whole genome screening tools. Both short interfering RNA (siRNA) and short hairpin RNA (shRNA) platforms have been utilized in screening.

The primary advantages of using synthetic siRNAs for screening are found in their ease of use and the greater availability of established delivery methods. Available siRNA libraries targeting nearly every annotated gene have been extensively validated and provide robust gene silencing, as described in an article by Zhou, *Cell Host Microbe*, 2008.

More recently, an alternative RNAi pooling method by Ding in *Cell Stem Cell*, 2009 – enzymatically synthesized RNA (esiRNAs) (Figure 2), has been used in whole genome screening in mammalian cells. The initial discovery of esiRNAs took place in the laboratory of Michael J Bishop and was subsequently developed by Frank Bucholz for screening applications at the Max Planck Institute in Germany. This technology involves the generation of endoribonuclease-prepared siRNAs (esiRNAs) by the in vitro transcription of a 300–600 bp gene specific double-stranded RNA (dsRNA), followed by enzymatic digestion using Ribonuclease (RNases), ie, RNase III. This digest produces complex pools of siRNA-like molecules and these multiple silencing triggers lead to specific and effective gene silencing.

For stable long term silencing, shRNAs are the RNAi platform of choice for complex pathway analysis and screening. Delivering the shRNAs via a lentiviral particle provides numerous features that are useful for screening studies as well, including broad tropism, stable integration, and negligible interferon response upon transduction. With lentiviral delivery, the shRNA sequence stably integrates into the host chromosome for the long-term reduction of messenger RNA (mRNA), thereby extending the assay time and allowing for the measurement of protein reduction.

The RNAi Consortium (TRC), a public/private consortium led by the Broad Institute of MIT and Harvard has developed lentiviral-based shRNA libraries that provide coverage of the murine and human genomes. This library has been used in a number of screens as described by Root, Nature Methods, 2006. A variety of RNAi screening tools based on the TRC genome-wide libraries are now commercially available, including both pooled or pre-arrayed, to allow for more flexible methods to screen whole genomes.

These processes have become increasingly significant in drug R&D and RNAi can be used to facilitate the identification and the validation of drug targets. In cancer research, RNAi is useful for characterizing molecular targets, screening

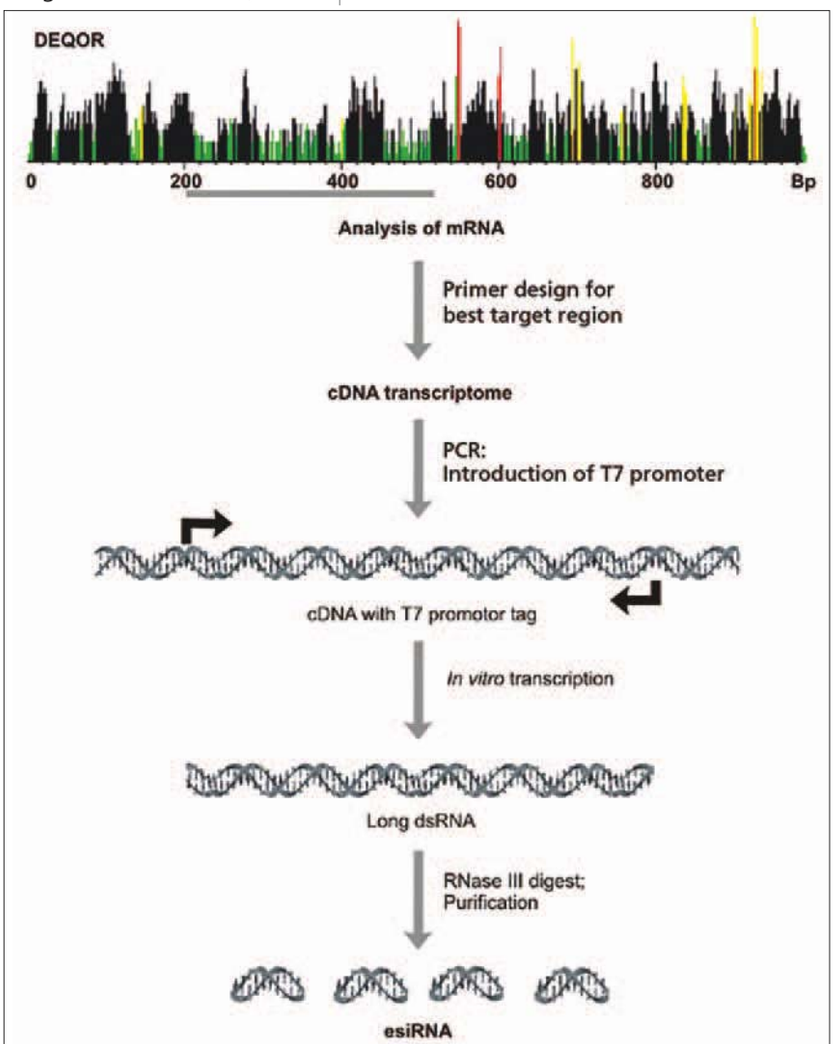

Figure 2: Overview of Misson esiRNA production.
A cDNA transcriptome is generated from a region of mRNA. The region to be amplified is selected based on the highest possible number of highly effective siRNA based on the Deqor siRNA design program. PCR is used to introduce T7 promoters for the in vitro transcription of long dsRNA. Finally, the long dsRNA is enzymatically digested to short dsRNAs producing complex pools of siRNA-like molecules. The digestion is then purified to remove any remaining DNA template, unincorporated nucleotides, and dsRNAs longer than approximately 40 bp. (Source: Sigma Life Science, Sigma-Aldrich)

genes and looking at gene interactions with specific drugs – indispensable to the field of pharmacogenomics.

Epigenetics and Cancer

Although genetic lesions have been the focus of cancer research for many years, it has been increasingly recognized that aberrant epigenetic modifications also play a major role in tumorigenesis. Epigenetic changes, referring to heritable changes in gene expression occurring without alteration in a DNA sequence, contribute to the pathogenesis of cancer by altering gene expression, according to *Gronbaek*, 2007. Furthermore, both genetics and epigenetics cooperate at all stages of cancer development. While the accumulation of genetic lesions and aberrant epigenetic regulation are causative agents in the formation of cancer, RNA (in particular microRNA or miRNA) is a final player that necessitates mention. MicroRNA comprises a network that controls gene expression and protein production throughout the body and is intimately involved in the formation of a repressive chromatin state as described by Djupedal and Ekwall, *Cell Research*, 2009. Scientists believe miRNAs play a major role in controlling overall gene expression and the cancerous process.

Nearly all cancers arise gradually, resulting from the accumulation of abnormalities (mutations) in the cell's genetic material due to the effects of carcinogens, ionizing radiation, viral infection, errors in Deoxyribonucleic Acid (DNA) replication, or inherited defects

Epigenetics refers to all heritable modifications to genes other than changes in the DNA sequence itself. The Greek prefix "epi-" implies features that are on top of, or in addition to genetics. Epigenetic modifications influence the appearance and structure of DNA and regulate gene expression. An example of an epigenetic mechanism – DNA methylation, refers to the addition of a methyl group to cytosine in a Cytosine-phosphate-Guanine (CpG) dinucleotide.

Once a cell has an established DNA methylation pattern, these sites are inherited by daughter cells and can have important implications in normal cellular function and development. Additionally, aberrant epigenetic modifications play a major role in the development of cancer and other conditions in which cell and tissue growth are abnormal. Incorrect epigenetic changes to tumor suppressor genes and oncogenes are some of the first steps in cancer initiation. In cancer, some tumor suppressor genes are mistakenly turned off, preventing the growth-limiting protein from being made. Likewise, many oncogenes, or growth-promoting genes, are mistakenly turned on, resulting in abnormal cell proliferation.

In cancer cells, genes can be modified by mutations, which alter the function of the proteins that the genes encode. Through epigenetics, modifications to chromosomes take place and alter gene-expression patterns. Epigenetics changes occur through DNA methylation, and the methylation, acetylation, or phosphorylation of histones and other proteins around which DNA is wound, to form chromatin. The theory of epigenetics in cancer pathogenesis is that non-mutational changes to DNA lead to alterations in gene expression. In a normal cell for example, an oncogene may be silent as a result of DNA methylation, and the loss of that methylation may induce the aberrant expression of a gene, contributing to cancer progression. Likewise, tumor suppressor genes may be silenced by DNA hypermethylation during cancer development. Current epigenetic therapy takes advantage of the reversibility of these "epimutations".

Both genetics and epigenetics cooperate at all stages of cancer development. To date, most of the mutations that have been identified as contributors to cancer formation are associated with tumor initiation. In contrast, few specific genetic mutations have been linked to tumor progression, suggesting that epigenetic changes may be involved. In this scenario, a genetic mutation initiates the cancer but epigenetic changes including DNA methylation and histone modification promote its progression. However, this does not mean that epigenetic changes do not participate in cancer initiation as well. For instance, a decrease in methylation can result in the loss of imprinting to genes, which participate in the regulation of growth, which can lead to cancer. Furthermore, changes within the epigenome may "prime" cells in such a way as to promote cellular transformation upon a subsequent DNA mutagenic event.

DNA Methylation

DNA methylation is an essential part of normal development and is associated with imprinting, X-chromosome inactivation, suppression of repetitive elements and carcinogenesis. DNA methylation involves the addition of a methyl group to DNA, for example, to the number-5 carbon of the cytosine pyrimidine ring. Like other epigenetic mechanisms, it is heritable and does not alter the underlying DNA sequence. In humans, DNA methylation occurs at CpG dinucleotides and 60-90 percent of CpG sequences are methylated in the genome of adult somatic tissue. The maintenance methylation activity catalyzed by DNA methyltransferase (DNMT) preserves DNA methylation on daughter strands after DNA replication.

Methylation is repressive to transcription and serves to enhance genome stability. DNA methylation impacts gene transcription in two ways. First, the methylation of DNA physically impedes the binding of transcriptional proteins to the gene and secondly, methylated DNA is often bound by Methyl-CpG-Binding Domain (MBD) proteins. MBD proteins recruit additional proteins, including chromatin-remodeling proteins such as Histone Methyltransferases (HMTs) and Histone Deacetylases (HDACs) to the locus. The net result is compact, inactive chromatin.

DNA methylation was the first epigenetic alteration to be observed in cancer cells, according to Feinberg and Tycko, Nature Reviews Cancer, 2004. The 5' regulatory regions (promoters) of many genes contain "CpG islands" that escape DNA methylation (Figure 3). In some cancers, these CpG islands acquire abnormal hypermethylation, resulting in heritable transcriptional silencing by this process. The reverse is also true as some CpG islands, which are normally methylated, acquire abnormal hypomethylation resulting in gene activation.

A general tendency affiliated with aging, is for the genome to become hypomethylated while some CpG islands become hypermethylated. The net result is an increase in the incidence of cancer with age. Based on what is known about methylation, it is easy to appreciate how this process may facilitate tumorigenesis. For example, the hypermethylation of CpG islands in tumor suppressor genes switches off these genes, whereas global hypomethylation

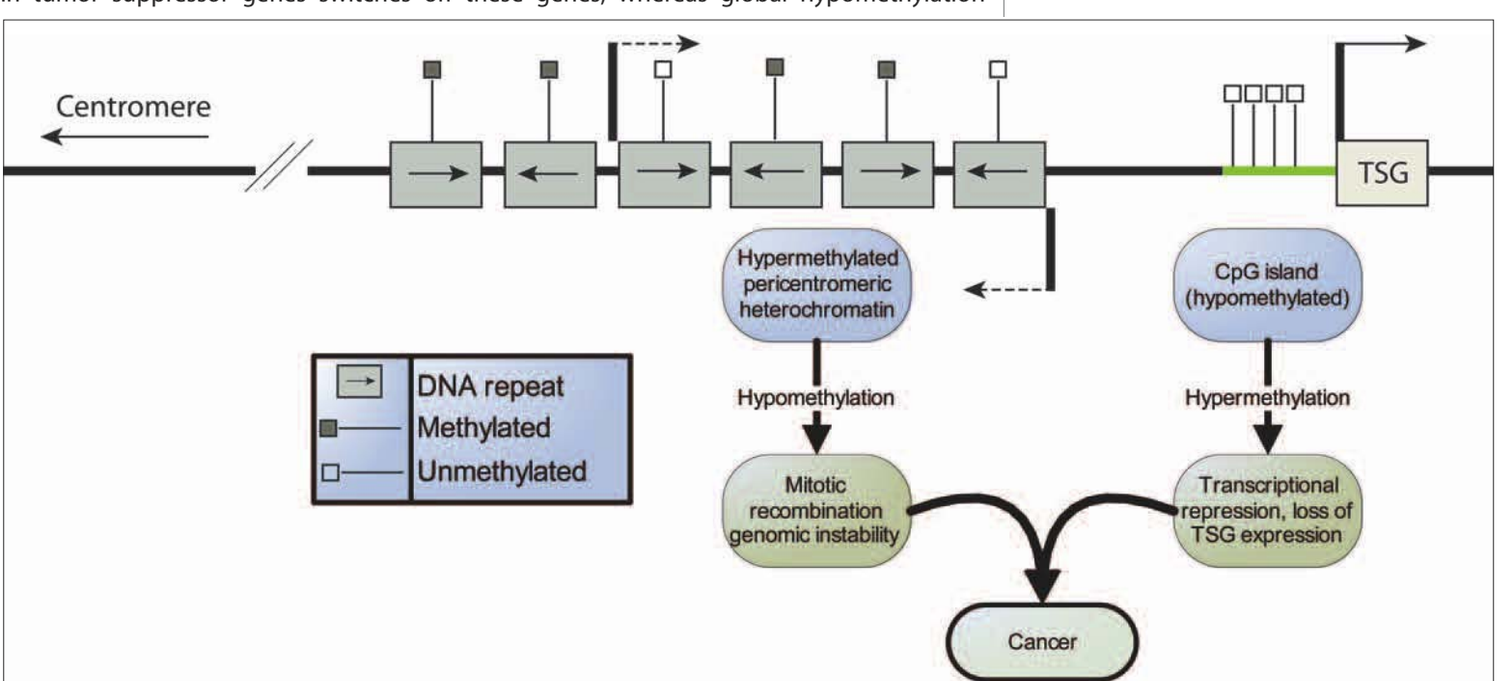

Figure 3: DNA Methylation and Cancer
This region of genomic DNA contains hypermethylated heterochromatin and an actively transcribed Tumor Suppressor Gene (TSG). A hallmark of tumor cells is the conversion of repeat rich regions from hypermethylated to hypomethylated, culminating in genomic instability resulting from increased mitotic recombination. Additionally, the CpG island located upstream of the TSG is hypomethylated, allowing for transcription. However, during oncogenesis, the CpG islands become hypermethylated, resulting in a loss of expression and a progression towards cancer. (Source: Sigma Life Science, Sigma-Aldrich)

promotes genomic instability and the subsequent activation of oncogenes and transposable elements (transposons are mutagens).

DNA methylation is also the principal epigenetic factor governing allelic imprinting. Genomic imprinting is a genetic phenomenon by which certain genes are expressed in a parent-of-origin-specific manner independent of classical Mendelian inheritance. For the majority of autosomal genes (ie, genes found on any of the chromosomes other than the gender-determining chromosomes), expression occurs from both alleles simultaneously. However, a small proportion (less than one percent) of genes are imprinted and expression occurs from only one allele.

Imprinted genes are either expressed only from the allele inherited from the mother (eg, H19 or CDKN1C), or in other instances from the allele inherited from the father (eg, IGF2). The regulation of imprinted genes is largely dependent on methylation marks, which are laid down during the embryological development of germ cells. The stability of these methylated regions in somatic cells is maintained through each cellular replication by DNMT1. The aberrant regulation of imprinted gene expression (Loss of Imprinting or LOI) is seen frequently in a variety of human tumors, and may be considered the most abundant and precocious alteration in cancer, as described by Jelinic and Shaw in *Journal Pathology* in 2007.

There are two primary outcomes resulting from LOI. These are the activation of a normally silent copy of a growth-promoting gene, such as the insulin-like growth factor -2 (IGF2), or the silencing of the normally active copy of a growth-inhibitory gene, such as p57 KIP2. Medical scientists are studying DNA methylation and human disease to determine the connections between methylation abnormalities, gene expression or silencing. They are also examining various diseases such as cancer, lupus, muscular dystrophy, and a range of birth defects that appear to be caused by defective imprinting mechanisms.

Hypomethylating Drugs

According to Gronbaek, APMIS, 2007, the current approach to cancer treatment – a direct result of hypermethylation, is to employ hypomethylating drugs. For example, the drug Dacogen (5-aza-CdR) has been approved by the US Food and Drug Administration (FDA) for use in the treatment of certain hematopoietic cancers. When this deoxycytidine analogue is incorporated into DNA, it covalently binds to DNMTs, sequestering the enzymes.

Consequently, DMNT is no longer available for maintaining the methylation pattern in newly synthesized DNA strands during replication, resulting in the successive loss of the methylation signature. More importantly, the demethylation activity occurs in actively dividing cells and because the growth rate of cancer cells is typically higher than that of normal cells. This activity does not affect the epigenetic silencing patterns of normal cells, which is important, as the demethylation of oncogenes in normal cells would lead to cancer.

Histone Modifications

Eukaryotic genes are located on multiple linear chromosomes that are packed into a complex with histone proteins to form chromatin. The structure of chromatin is dynamic, existing in either a heterochromatin (condensed) or euchromatin (extended) state. The basic unit of chromatin is the nucleosome, which is folded through a series of successively higher order structures to eventually form a chromosome. Nucleosomes are composed of 146 bp of DNA around a histone octamer, consisting of two copies each, of the core histones H2A, H2B, H3, and H4 with a linker H1. In the absence of linker histones, the nucleosome adopts a less condensed, or “relaxed” form of chromatin, commonly referred to as "Beads-on-a-String". A plethora of covalent post-translational modifications of the histone tails have been documented including, but not limited to acetylation, methylation and phosphorylation.

Histones undergo post-translational modifications that alter their ability to interact with DNA and nuclear proteins. The H3 and H4 histones have long tails protruding from the

nucleosome that are covalently modified, principally by methylation, acetylation, phosphorylation, and ubiquination. Each of these histone modifications participate in transcriptional regulation. Consequently, each has the potential to be oncogenic if deregulated. The manner in which DNA is stored on the histone and the chemical modifications of the histone itself, are both regulatory mechanisms that determine whether a particular region of DNA is accessible for gene expression.

Under normal cellular conditions, histones contain N-terminal lysine residues which are positively charged on their epsilon amino groups. This positive charge enables histones to interact with the negatively charged phosphates in DNA. Acetylation neutralizes the positive charges on the histone, thereby decreasing the latter's ability to bind to DNA, and enables chromatin expansion (relaxation) which facilitates the process of transcription by allowing transcription factors to gain access to regulatory elements in the DNA. Conversely, HDACs remove acetyl groups, increasing the positive charge of histone tails and encourages binding between the histones and the DNA backbone. This process condenses the DNA structure, preventing transcription. Accordingly, histone acetyltransferases (HATs) tend to be transcriptional activators whereas HDACs tend to be repressors.

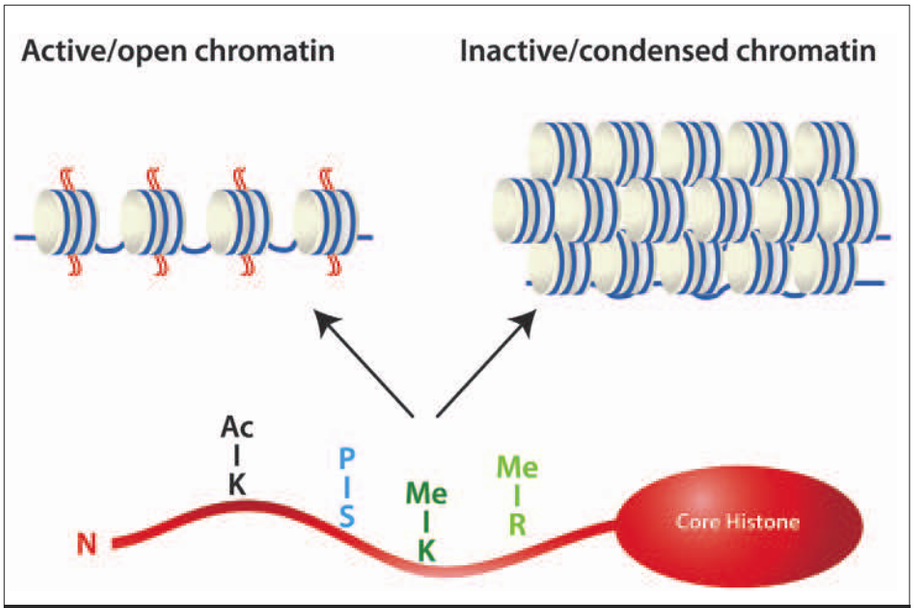

Figure 4: Chromatin
Eukaryotic genes are located on multiple linear chromosomes packed into a complex with histone proteins to form chromatin. Histones are the primary regulator of the chromatin structure, which is dynamic, existing in either a heterochromatin (condensed) or euchromatin (open) state. Whether chromatin is active or inactive is largely dependent on the post-translational modifications of the histone tails including acetylation, methylation and phosphorylation. (Source: Sigma Life Science, Sigma-Aldrich)

The over expression or mutation of HAT genes is a component of a variety of cancers, especially those of hematological and epithelial origin. For example, the p300 HAT gene is mutated in a number of gastrointestinal tumors. Changes affecting the normal function of HDAC genes as a causative agent in cancer formation are far less common. However, the aberrant targeting of HDACs is associated with the transcriptional silencing of tumor-suppressor genes, including the cyclin dependent kinase inhibitor p21 that blocks cell cycle progression.

In this example, histones are improperly deacetylated and bind more tightly to the regulatory elements of the p21 gene, preventing the latter's transcription and resulting in the inhibition of the p21 expression. The outcome is uncontrolled cell division. HDAC inhibitors can reactivate the p21 expression and thereby prevent tumor cell proliferation. HDAC inhibitors are performing well in the clinic as anti-cancer drugs and have significant anti-tumor activity, as described by Pan, *Cellular Molecular Immunology*, 2007.

Histone methylation is more complex than acetylation as both lysine and arginine residues can be methylated on side-chain nitrogen atoms by histone methyltransferases, and one or more methyl groups can methylate each amino acid residue. This complexity provides regulatory potential as each event may affect the chromatin structure and the ability to interact with regulatory proteins. Histone methylation is generally associated with transcriptional repression. However, the methylation of some lysine and arginine residues of histones results in transcriptional activation. Examples include methylation of lysine (K) 4 of histone 3 (H3K4), and arginine (R) residues on H3 and H4.

The Supressor of variegation-Enhanser of zeste-Trithorax (SET) domain protein methyltransferase super family methylate histones on lysine and numerous SET domain-containing proteins are implicated in cancer. For example, SUV39 is a SET domain-containing methyltransferase that catalyzes the methylation of K9 in H3. Mice that carry deletions of

SUV39 and its family members, suffer genome instability that is associated with a substantial loss of H3K9 methylation. Transgenic mice devoid of this enzyme are susceptible to cancer, especially B cell lymphomas.

Several histones are subject to phosphorylation (the addition of a phosphate to a protein or an organic molecule) and this modification is associated with large-scale chromatin reorganization during processes such as mitosis, apoptosis, and DNA repair. Phosphorylation of the linker histone H1 by CDK2 is associated with cell-cycle progression, and H1 phosphorylation has long been a marker for mitotic cells. However, while elevated H1 phosphorylation is observed in many cancer cells, this may be an artifact of the enhanced proliferation of these cells. Nevertheless, the improper regulation of the kinases mediating histone phosphorylation can be oncogenic. For example, the Aurora kinases normally phosphorylate H3 and control a number of mitotic (cell division) events. All three family members (Aurora A, B, and C) are over expressed in many aggressive human cancers, resulting in defective chromosome segregation and aneuploidy.

DNA methylation may be the best characterized epigenetic process, largely due to the fact that it is the easiest to study with existing technology. Methods for DNA methylation analysis can be roughly divided into two types: global and gene-specific methylation analysis.

Studying the Epigenome

Epigenetic gene silencing is a major driving force in cancer, and the study of epigenetic mechanisms in the disease, such as DNA methylation, histone modifications, and micro-RNA expression, have revealed factors that contribute to the neoplastic phenotype. The methylation of cytosine in promoter regions and the covalent modification of chromatin proteins such as histones cause the suppression of transcription. Many of these silenced genes are tumor suppressors and promoter/CpG island hypermethylation is frequently associated with poor disease prognosis. Understanding the trigger for these epigenetic changes will be essential to reduce or prevent them from occurring. DNA methylation may be the best characterized epigenetic process, largely due to the fact that it is the easiest to study with existing technology. Methods for DNA methylation analysis can be roughly divided into two types: global and gene-specific methylation analysis.

The overall methylation status of a genome can be a useful measure of global regulatory changes. Methods for measuring global methylation include High-Performance Liquid Chromatography (HPLC), mass spectrometry, and methyl accepting capacity assays. These methods measure the overall level of methyl cytosines in the genome. Enzyme-Linked Immunosorbent Assays (ELISA) are a fourth method for determining global methylation. Some commercially available kits utilize a sandwich ELISA-based method to quantify methylated DNA colorimetrically. The amount of methylated DNA present in the sample is proportional to the absorbance measured. The advantage of this method over HPLC and mass spectrometry is that the format is easier to implement in the lab.

A number of techniques have been developed for gene-specific methylation analysis. Most early studies used methylation sensitive restriction enzymes to digest DNA, followed by Southern detection or Polymerase Chain Reaction (PCR) amplification. Bisulfite reaction-based methods have become popular – such as Methylation Specific PCR (MSP) and bisulfite genomic sequencing PCR. Methylated Cytosine (meC) is stable with bisulfite while cytosine is converted to uracil.

Therefore, bisulfite treatment is employed to introduce specific changes in the DNA sequence that depend on the methylation status of individual cytosine residues. There are numerous commercially available kits containing the necessary components to treat DNA with bisulfite to convert cytosine residues to uracil, while leaving 5-methylcytosine residues unaffected. Converted DNA is suitable for a variety of downstream applications including MSP, methylation sequencing, and Pyrosequencing. Additionally, genome-wide screen methods have been developed, such as Restriction Landmark Genomic Scanning for Methylation (RLGS-M) and CpG island microarray to identify unknown methylation hot-spots or methylated CpG islands in the genome.

Another significant epigenetic process is chromatin modification. Histone modifications change the chromatin structure, and are an early indicator of epigenetic regulation. One way to study this phenomenon is via Chromatin Immunoprecipitation (ChIP). This technique starts with cells, and uses a cross linking agent to chemically link the DNA and the latter's interacting proteins. The resulting DNA is isolated, sheared, and precipitated from the bulk, using a protein specific antibody (eg, acetylated histone). The cross-links are reversed, and the precipitated DNA, now enriched for sequences that interact with the protein of interest, is examined to determine which sequences are present. Detection can be via PCR when looking for a few genes, or can be performed using microarrays (ChIP-chip) or parallel (deep) sequencing (ChIP-sequencing). There are commercially available kits on the market for ChIP analysis including kits using a 96 well format for high throughput analyses.

ChIP-chip requires the amplification of the enriched DNA sample, as immunoprecipitation does not supply the amount of DNA that is required for microarray analysis. Whole genome amplification has been successfully applied to ChIP DNA amplification, and is a method for generating more DNA from a fragmented DNA sample, according to O'Geen, *BioTechniques*, 2006.

Discovery and Validation of Epigenetic Drugs

Unlike genetic alterations, epigenetic changes are potentially reversible and the large-scale development of small molecule inhibitors of DNA and histone-modifying enzymes is in full swing. The utilization of epigenetic targets is emerging as an effective and valuable approach to chemotherapy as well as the chemoprevention of cancer. The success of HDAC inhibitors and DNA demethylating agents like 5-aza-CdR as anti-cancer drugs, demonstrates proof-of-principle of this approach and provides hope for the development of a more comprehensive portfolio of "epigenetic drugs" in the future.

Until a decade ago, research programs were focused on identifying and quantifying the environmental and inherited factors that are associated with cancers. By utilizing improved screening tools such as RNAi and small molecules, a basic understanding of the mechanisms have been attained as well as a glimmer into the increasingly intricate interactions between genes. However, it is increasingly being recognized that aberrant epigenetic modifications also play a major role in tumorigenesis. More than 600 genes have been identified that are regulated by epigenetic mechanisms, including tumor suppressor genes, oncogenes, and cancer-associated viral genes.

Epigenetic mechanisms driving cancer formation include changes in primary DNA methylation, modifications to the histone code related to DNA methylation, or abnormalities in specific histone modifying enzymes. The field is rapidly moving towards clinical applications for the treatment of patients with cancer, or evaluating a patient's level of risk for developing cancer. Assays for aberrant DNA methylation, bisulphite modification, high-throughput bisulfite genomic sequencing, quantifying global DNA methylation, combinations of histone deacetylase inhibitors and DNA methyltransferase inhibition assays, chromo-immunoprecipitation and RNAi interference, address the role of epigenetics in cancer.

With next generation genomic platforms and methods of screening whole genomes and the subsequent analysis of drug target candidates, scientists are able to cost-effectively assay individual cancer genomes. These genomes can be characterized in terms of global genetic, epigenetic, and transcriptional changes. The development of drug discovery tools like RNAi and continued improvements in high-throughput robotics, data processing, control software, and liquid handling devices will accelerate this process. In-depth characterization of these events and the interdependent relationships between them will lead to a better understanding of the mechanisms of tumorigenesis, metastasis, and therapeutic response.

PA

Enquiry code: 095E02

Managing Cold Chain Storage and Distribution

The process of transporting temperature sensitive pharmaceutical products involves the consideration of various factors that range from warehousing to regulatory compliance.

Pearlyn Wang,
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DB Schenker

When dealing with temperature-sensitive high-value critical products, experience counts – the cold chain management process should include: R&D, sourcing, validation, Standard Operating Procedures (SOPs), storage and warehousing, process management, distribution, transportation, regulatory compliance, training, and monitoring.

Such a complexity of logistics and distribution has often posed a challenge to supply chain managers in the balancing of the stringent requirements of the US Food and Drug Administration (FDA). It entails audit trails for the complete validation and monitoring of temperature-sensitive products – from manufacture, to delivery to patient – with a constant emphasis on cost containment.

The start of the supply chain must always begin with R&D, or the sourcing of raw material supplies. The pharmaceutical industry shake-up has seen some major mergers. With the takeover of Wyeth, Pfizer's CEO, Jeffrey Kindler, explained that the combined company will include "two distinct, but complementary, research organizations," with one specializing in small-molecule compounds and the other in biotechnology drugs. The main attraction of Wyeth is its research and concentration on large molecules, creating a broad and deep pipeline in vaccines, antibodies, proteins, peptides, nucleic acids and other modalities.

The announcement by Merck's CEO, Richard Clark, remarked that the merger agreement with Schering-Plough "is about size, it's about the growth of in-line products and it's about diversity from a global standpoint." The focus is on the latter's vaccine pipelines for arthritis and allergy problems.

The third merger is the partnership between Roche and Genentech, where the primary objective was to develop the combined organization to become one of the most effective companies in research in biotechnology. Genentech, in keeping its company name in the US, will continue to focus on developing peptides for biopharmaceutical firms.

Another development is the discussion between GlaxoSmithKline and Stiefel Laboratories, where the takeover will increase the former's revenues by US$3 billion.

As the industry moves to develop pharmaceuticals to better treat and combat new diseases, a different set of requirements in the distribution and transportation of these products is also needed. (Source: DB Schenker)

Meeting Needs

As the movers and shakers of the industry move into another era of biopharmaceutical products (mostly vaccine-formulated) to better treat and combat new diseases, a different set of requirements in the distribution and transportation of these products is also needed.

The success of efforts against vaccine-preventable diseases is attributable in part to the proper storage and handling of vaccines. Exposure of these vaccines to temperatures outside the recommended ranges can adversely affect their potency and efficacy.

With the allure of revenues and profitability, physicians, surgeons, specialists and hospitals' staff, are often the key audiences that are targeted for product education and training by healthcare companies. This is not so for Logistics Service Providers (LSPs), most of which are untrained in understanding the purpose and nature of these potent treatments for chronic diseases such as arthritis, dementia, diabetes, hyperlipidemia, osteoporosis and cancer. A clear mapping of the methodology to handle these products is often neglected. This means that the possibility of mishandling such transportation and storage is high.

Besides biopharmaceutical products, there is also a growing trend in the receiving and handling of medical diagnostics, consumables, devices and re-agents (which have different temperature requirements), in accordance to their individual unique properties.

Strategic Approach Towards Healthcare Development

The evolution of healthcare focuses on biologics, bio-pharmaceutical and medical diagnostics, involving international companies such as GSK, Novartis, Lonza, Genentech and Roche Diagnostics. There are few global LSPs that have the expertise and the necessary business tools that are required to create a hybrid line of logistics solutions for the emerging healthcare requirements.

In addition, the shift of manufacturing sites from the West to the East has also created an increasing demand for inventory movement within Asia and globally. Such growth, only when supported by the right global operating models, which includes a growth-centric global agenda, will then achieve supply chain efficiency. This is essential since supply chain excellence is directly tied to a company's financial performance.

In reality, many traditional pharmaceutical companies have not been able to catch up with the newer, smaller biotechnology companies – with the latter having effectively reengineered their own supply chains and related infrastructure. Slow supply chain reengineering is often due to an organisation's the strong focus on other aspects of the business such as R&D productivity; training and educating internal staff to physicians to patients; complying regulatory standards; obtaining new drug licenses in various countries to gain entry etc.

With overwhelming operating tasks at hand, it is challenging to focus on growth at a strategic level. A good method is the setting up of a steering committee to carve out a roadmap, especially in emerging markets like Asia. In an efficient supply chain, a top-down approach is necessary to ensure operational excellence.

Cold Chain Logistics – What is it?

Cold chain logistics refers to the movement of temperature-sensitive products from the point of origin to end customers in the best possible quality. With greater emphasis on new drugs that are made of relatively larger molecular structures for better efficacy of treatment, these drugs are often sensitive to environmental changes. Such products require temperature-control and can only accept a certain range of temperature fluctuations during transportation and storage. Maintaining the temperature within the desired range for every shipment is the challenge of cold chain logistics.

Close monitoring at periodic stages is essential and such audits help to identify areas of weakness where logistics professionals can implement and devise the right tools to support and maintain the cold chain from "paddock to plate".

Humidity, Temperature and Environment Monitoring

Present day technological devices can drive full monitoring platforms, which include the management of requirements such as humidity, temperature and environment measurement from wall-to-wall and floor-to-ceiling. In addition, remote monitoring is possible via Global Positioning Systems (GPS), along with online or web-based systems for rapid alert functions. Such technologies, of course do not come cheap.

The shift of manufacturing sites from the West to the East has also created an increasing demand for inventory movement within Asia and globally.

Drug Delivery

Maintaining the temperature within the desired range for every shipment is the challenge of cold chain logistics. (Source: DB Schenker)

Facilities operate on strict budgets, while striving to meet industry standards and regulations. There is often a need to decide on whether to invest in additional equipment or a new facility, and if it is time to institute an electronic monitoring capability.

Depending on each organization's needs, technology like mobile refrigeration units, incubators, clean/ redressing rooms, dangerous-goods and/or poison-drug storage cabinets, key-lock cage and etc, are just examples of such investments – together with an extensive on-site evaluation to include protocols, validation, Standard Operational Procedures (SOPs), process improvements, etc.

Regulatory Compliance

Ensuring stringent environmental assessment for storage, in compliance with regulatory bodies globally is another complex topic as different countries have their own standards and regulations. In order to maintain the quality of products manufactured, these pharmaceutical companies often design different sets of standards and requirements based on the nature of their products. Such protocols add to the complexity of compliance with transportation and storage activities.

A key checklist for Quality Control (QC) managers, maintenance personnel, disease management teams, nurses, physicians, and pharmacists, includes assessments such as:

- Identifying deficiencies and allowing companies to make informed, calculated decisions to rectify problems.
- Demonstrating due diligence to ensure that the unit operates within the prescribed temperature parameters.
- Achieving compliance with USP 797 temperature guidelines, Joint Commission on Accreditation of Healthcare Organizations (JCAHO) MM.2.20 & EC.6.10 standards, CDC standards, US FDA 21 Code of Federal Regulations (CFR) (Part 11, Part 210, Part 211) guidelines.
- Eliminating vaccine/ medication loss due to compromised storage temperatures.
- Ensuring Process Improvement Programs (POP) as part of a continuous Quality Assurance (QA)/QC effort.

It is critical to undertake complete assessments, and maintain communication between three key parties, namely, healthcare firms, LSPs and regulatory bodies. It is vital to ensure that all compliance requirements are agreeable and are standardized for the purpose of maintaining drug efficacy and timely delivery – from manufacturing sites to patients.

Seamless Cold Chain Transportation

The transportation of cold chain products poses the greatest challenge. Any major movements in handling, adverse weather conditions and shock can result in "upsetting" the products' state of conditions. Using the appropriate packaging materials and careful labeling to indicate the delicate nature of such products will help operators to take extra care

when handling these items. In certain long-haul journeys, operators may be required to be equipped with gel packs or dry ice to perform re-icing operations to the products, in order to avoid temperature shock.

Another important factor is the ability to handle large volumes via specially approved containers. These containers are accepted by commercial air carriers that are able to ensure better control of maintaining the temperatures within the acceptable range.

Internationally, many organizations engage third party LSPs to provide flexible air, ocean, customs compliance and logistics solutions for highly perishable products with time-critical delivery from the US and throughout Asia Pacific, Europe and Latin America.

A few specialized third party LSPs are able to provide critical transportation solutions with zero tolerance for service failure. This is in addition to the complete automated customer visibility for complicated temperature-controlled product movement, including cold chain management. With the consolidation of such shipments in larger quantities from different healthcare companies, economies of scale can be achieved – which translates back into cost savings for the companies.

The Need to Innovate

R&D in cold chain logistics, refers to ways and methods to reduce waste (in absolute dollar or time-savings) using innovations. Supply chain professionals need to understand the nature of the product and the supply chain, and also adapt and apply other existing best-practices. Such activities are part of continuous improvement practices which encourage an environment to "invent" new logistics methodology or tools for the future. It is through these concerted efforts that LSPs provide value-adds to their existing and/or potential customers, as well as gain market share.

With increasing globalization and environmental awareness, the constant need to reduce cost and address evolving public health issues is likely to shape the cold supply chain of the future. (Source: DB Schenker)

Viable and sustainable Cost Optimization

With increasing globalization and environmental awareness, the constant need to reduce cost and address evolving public health issues is likely to shape the cold supply chain of the future. This should lead to the further integration of many pharmaceuticals and healthcare companies to work closely with global service providers who have the right capabilities. These service providers should be equipped with business tools and skilled professionals to offer both technological expertise and advice on supply chain optimization models, over a sustained period if required.

It is important that the companies are satisfied with their selected LSP's business resourcefulness in consolidating efforts to bundle lower rates for transport distribution (domestically and worldwide). Global transportation involves different modes of movement via air, ocean, truck, rail and possible hybrid modes which combine more than one single mode of transport for a single shipment. Such services allow freight savings as well as shorter lead times.

Consolidation efforts in the arena of global logistics include increasing storage capacity as well as a complete logistics solution; from custom clearance to order management, pick-and-pack, repackaging, orders delivery, goods return handling, batch control, labeling and logistics information analysis and reporting.

Understanding the complex pharmaceutical supply chain concept and achieving the lean process of logistics and distribution flow, requires strong strategic planning. Each process, through professional in-depth analysis or with the support of business tools, will reveal areas of either process optimization or waste reduction.

With each stage of improvement or elimination of waste, the combined savings can be significant and may allow cost optimization. The journey is challenging but achieving a complete and lean logistics distribution system will be invaluable to any organization. **PA**

Enquiry code: 095E03

Cold Chain Management: The Next Level

With the rapid expansion of Asia Pacific's pharmaceuticals industry, demand for reliable and effective supply chain solutions is on the rise

Karel van de Pijpekamp,
sales & marketing director,
TNT Asia

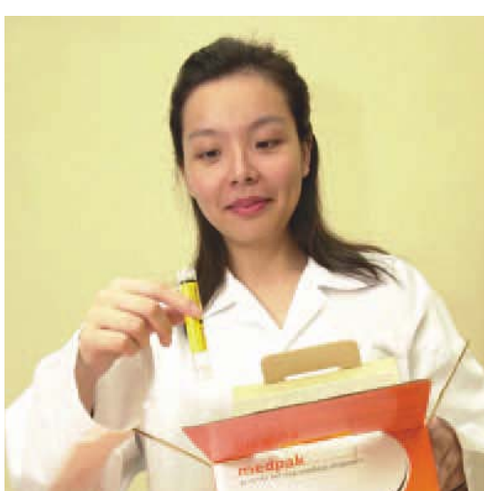
Asia Pacific is in the race to own the lion's share of the global pharmaceutical industry. This brings about a challenge: how to best manage the transportation, shipment and handling of specialized treatments and technologies. Cold chain supply management looks at the process of moving goods in a temperature controlled environment – and the solutions which guarantee that the goods, whether vaccines or blood samples, are transported efficiently and safely.

Growth in China, India and Singapore has led to Asia Pacific becoming the largest market in the world for drugs. A rapidly ageing population, downward pressure on public healthcare costs and growing patient demand for leading-edge medical technology is forcing hospitals and medical products manufacturers to adjust.

Several pharmaceutical companies are moving their manufacturing and research activities into the region. In November 2007, US drugmaker Pfizer announced its plans to double its outsourced manufacturing from 15 to 30 percent, mostly to Asia. Likewise in 2006, AstraZeneca announced investments of US$100 million over three years in R&D in China. GlaxoSmithKline opened a US$415 million vaccine plant in Singapore in June 2009. Even Asia Pacific's own pharmaceutical companies are increasing their share of the international market.

Along with this growth, the regulatory requirements in this sector are also becoming more stringent. This has forced companies to re-look at their processes and supply chains to maintain their competitiveness and product integrity as well as to preserve quality and regulatory compliance.

These pharmaceutical com-panies, as well as their stake-holders such as hospitals and clinics, need to transport their products, whether urine samples, cord blood or temperature-sensitive drugs, both within Asia Pacific and internationally. They require the assurance that their goods will arrive at their destination in a timely manner and in the same condition in which they were dispatched at. So what are the factors that can affect the integrity of products and how can express providers address them?



Companies need to re-look at processes and supply chains to maintain competitiveness and product integrity as well as to preserve quality and regulatory compliance. (Source: TNT)

Environment Management

Temperature control is of prime importance in cold chain management. There is a large and growing community of manufacturers that have products which require temperature-control. For instance, maintaining the temperature range at 2 - 8°C is critical if the diagnostic reagents for laboratory testing are to perform their intended function. It is therefore critical to sustain the temperature of such products for several hours, whether in the back of a truck or in the cargo section of a plane.

Contract Research Organisations (CROs) and pharmaceutical companies are working closely with express services providers – for the development of temperature-precise packaging for moving and storing clinical test kits and clinical samples. The aim is to decrease the discrepancy in test results (which delays product launch) that arise from samples that are exposed to temperatures that are outside the prescribed requirements.

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Drug Delivery

The side effect is that this also ensures service-level improvements. Express service providers can help manufacturers to comply with government regulations that hold the latter accountable for temperature management and product integrity.

Speedy Delivery

Time is also of the essence. Drug manufacturers and research labs want to know if their products are going to be delivered on time and on target. For instance, drugs, devices and reagents can be held by customs authorities for several days. On other occasions, incorrect documentation can stall the transfer of goods. Even when in-country distributors do take ownership, the controls on product handling and expirations can be uneven at best, and even dangerous in the worst case scenario.

An important part of a freight offering is to provide flexibility for customers. Some items need to be moved quickly, while others are less urgent. (Source: TNT)

It is therefore necessary to use an express provider that can offer swift customs clearance, especially through the filing of proper documentation before the products even reach the customs checkpoint.

Ideally, the provider should also be able to offer expert advise on regulatory matters relating to customs and import/ export permits.

Apart from a speedy customs clearance, an extensive network is also critical. As clinical trials extend into rural areas, the need to reach remote hospitals poses fresh challenges as well.

This may mean that the service provider needs to have access to efficient road transportation networks in the region, eg, linking countries like Singapore, Malaysia, Thailand, Indochina and China.

An important part of a freight offering is to provide flexibility for customers. Some items need to be moved quickly, while others are less urgent. With integrated air-road networks, customers have the option of choosing a seamless combination of road and air transportation to deliver their goods. This combination allows businesses to use air transportation where speed is critical, and road transportation when it is not. The integrated service, as opposed to only air transportation, also provides cost savings for the customer.

Keeping Track

Especially with time and temperature sensitive goods, customers want to know the location of their goods in transit. More importantly, the question is whether the delivery is on schedule and if it is being maintained at the right temperature.

While manufacturers typically take charge of moving a product from a factory location to an Asian port of entry, the efficient handling of a product thereafter could be a question mark.

There are however, service solutions and IT platforms that are available to track and safeguard products from point-to-point. Radio Frequency Identification (RFID) has been identified as one of the best solutions keeping track of the supply chain. It has enabled express delivery providers to track, monitor and report on the products' temperature integrity from

point-of-origin to point-of-destination.

Centralizing a manufacturer's inventory in a single warehouse, rather than in multiple storage facilities also helps to reduce delivery times. Using advanced cold chain management technology, goods ranging from medical devices, clinical diagnostics to pharmaceuticals and biotechnology can be stored safely.

For example, a pharmaceutical manufacturer's inventory can be consolidated in Singapore. The products can then be distributed to various countries in the Asia Pacific region through a combination of integrated air and road networks.

With this concept, the manufacturer benefits from faster order-to-delivery cycle times, reduced inventory holding costs and a reduced risk of product obsolescence. At the same time, full information visibility and improved end-customer (hospitals, laboratories and healthcare providers) satisfaction can also be acheived. **PA**

Centralizing a manufacturer's inventory in a single warehouse, rather than in multiple storage facilities also helps to reduce delivery times. (Source: TNT)

Enquiry code: 095E04

A Paradigm Shift in Vaccine Production

Subunit vaccines that do not require cold chain support and which can be produced quickly in large quantities, may be an attractive option for less-capital intensive drug manufacturers in Asia.

Kenneth Carpenter,
chairman and CEO,
MediVas

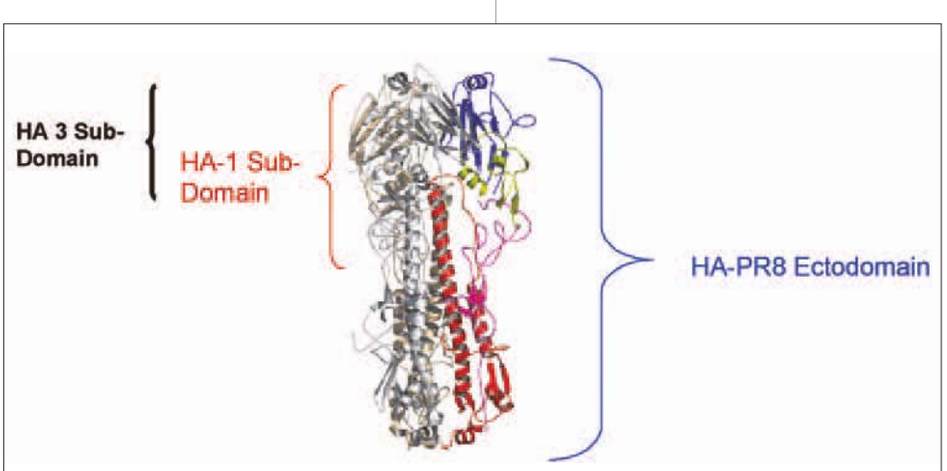
Vaccines have been designed and manufactured in essentially the same manner for more than 200 years. In fact there are indications that primitive forms of vaccination were practiced in China and India from as early as 2000 years ago. Modern vaccinations are generally credited to Edward Jenner for his cowpox vaccine against smallpox in 1796.

Vaccines work by inducing an immune response via the introduction of a foreign antigen. This can be accomplished in a variety of ways, four of which now present the basis for modern vaccines.

Vaccinations against infectious diseases have traditionally involved the use of the entire virus of a pathogen, either inactivated or attenuated. Inactivated vaccines involve the production of the infectious virus, which is then killed so it cannot replicate. This method presents certain risks if not all of the virus are killed, as it can cause the vaccine to induce an infection from the virus.

In more recent times, live viral pathogens have been genetically attenuated to remove or reduce their virulence. Attenuation is achieved by replacing virulent genes with similar but less virulent genes. Injecting a whole attenuated virus is an effective method to induce immunity against the pathogen since the body's antibody and T-cell responses to the vaccine are comparable to that of the infectious pathogen. This is because the immunogenic surface proteins of the attenuated virus which induce the immune response, retain the three-dimensional structure found in the infectious virus.

Two methods to produce vaccines have gained attention. Virus-Like Particle (VLP) vaccines are made from small immunogenic portions of the viral protein – which self-assemble into particles resembling the infectious virus but lack certain key components of the virus which allow it to replicate. In this way, VLP vaccines are safe because they cannot replicate. A limitation of VLP vaccines is that not all human pathogens have self assembling immunogenic proteins.



Subunit segments of the influenza Puerto Rico 8 Hemagglutinin. Representation of Trimeric HA (Source: Palese: Fields, 5th edition)

The second method is recombinant protein subunit vaccines. Subunit vaccines are similar to VLP vaccines in that they contain only small immunogenic portions of the viral protein (antigens) which induce the immune response to the virus. Unlike VLP, these antigens do not need to self assemble. This makes subunit vaccines applicable for a wider range of pathogens. However, segments of the antigens tend to be unstable.

This has led to the common belief that subunit

vaccines are not sufficiently immunogenic since the antigens fail to retain the precise three-dimensional structure of the virus' surface proteins. They may induce an immune response but not one that is protective against the target pathogen.

The production of vaccines has traditionally taken place in large, complex and expensive vaccine plants. Production of a whole virus inactivated or attenuated vaccine can be a long process, especially for rapidly mutating viruses such as the influenza virus. Growing whole viruses efficiently requires first optimizing the virus and growth conditions in order to achieve acceptable levels of viral production. The production of live, infectious pathogens also present a risk and requires a high level of safety containment for the production process – which adds to the cost of the manufacturing process.

The development of mammalian cell lines has enabled whole virus manufacturers to reduce the time to optimize and produce their virus from several months to just a few.

Technological Considerations

Two factors have limited the potential of subunit vaccines to supplant whole virus vaccines. One is the difficulty in growing properly folded small immunogenic portions of the viral protein in a large-scale, cost efficient manner. It was previously believed that cell-based growth media, whether mammalian, insect or bacteria, could not be used to mass-produce the subunit proteins due the former's inability to maintain the proper folding or glycosylation of the antigens outside the context of other viral components. Without the ability to mass produce the antigens, large quantities of subunit vaccines were commercially impractical.

This problem has been solved by researchers who have developed subunit protein constructs that can be successfully grown in bacteria. Because bacteria are the fastest growing recombinant protein media, massive amounts of properly folded antigen can be produced without inclusion bodies.

Mammalian cells and insect cells double in number every 24 hours, while bacteria double every 40 minutes. This means that with a starting base stock of 100,000 mammalian or insect cells, there would be 200,000 cells available after 24 hours to produce recombinant proteins. In comparison, starting with 100,000 bacteria, there would be nearly 70 billion bacteria after the same period of time, each producing a recombinant protein subunit.

By maintaining a plasmid bank of various strains of infectious pathogens such as influenza, it is possible to produce a plasmid for an emerging pathogen within a few days after the identification of the Deoxyribonucleic Acid (DNA) structure of the new subunits. The production of vaccine antigens can begin within a few weeks. The first batch of the subunit vaccines against a new strain of flu can be ready for testing and market approval in less than six weeks using these techniques.

The second factor that was thought to limit the viability of subunit vaccines was the belief that subunit vaccines could not provide efficient levels of immunity against a pathogen. The denaturing of the antigen caused by organic solvents or the harsh processing conditions that are required to attach the protein fragments to polymers, often resulted in the loss of the precise three-dimensional structure required of the protein subunits. Furthermore, antigens that had been injected without a stabilizing moiety also lose their desired three-dimensional confirmation. The result of these failures was a belief that an immune response against the desired pathogen could not be achieved by a subunit vaccine.

This problem has been overcome by the use of a protein-like synthetic polymer that binds the antigenic proteins and maintains their three-dimensional conformation. This is achieved through the use of an ion-chelating property of the polymer and by processing in a mild solution which produces antigen-bound nanoparticles that are similar to VLPs.

Because of the polymer's ability to maintain the bound water that is necessary for the proper folding of the antigens, the vaccine nanoparticles can be dried, stored, transported

The production of live, infectious pathogens also present a risk and requires a high level of safety containment for the production process – which adds to the cost of the manufacturing process.

An Xcellerex FlexFactory installation. (Source: MediVas)

and administered at ambient temperatures. This technology eliminates the cold storage and therefore the entire cold chain that is required of virus-based vaccines. This makes subunit vaccines viable for much of the world's population.

The Economics

Whole virus vaccine plants tend to be large, costly to build and operate. This is primarily due to the high levels of risk that are associated with the production of live viruses and the infrastructure that are necessary to provide the economies of scale – in order to be cost effective. The cost of traditional vaccine plants often runs into several hundred million dollars. Such costs make locating a vaccine plant in a small or less economically developed country prohibitive.

The result is that these countries often find themselves at the end of a long line of buyers for vaccines. In addition, the vaccines that they buy may not even be the best vaccine for their local needs, as the strains included in the vaccine may have been determined as being those that are the most appropriate for the large, Northern Hemisphere markets such as the US, Europe and Japan. The decision to make the world's supply of the H1N1 (swine flu) vaccine from the A/California/07/2009 strain may be appropriate for the US market but may be inappropriate for markets in Asia.

Small or less economically developed countries, especially those in the tropical zones, may also have special vaccine requirements that are not met because such vaccines are not cost effective for pharmaceutical companies to produce, since the disease may not exist in the latter's primary markets.

A different type of vaccine plant may solve that problem and may bring the local production of vaccines to virtually every country. Small recombinant protein production facilities which use disposable (single-use) technology can be the cornerstone of a highly efficient and low cost vaccine plant. Companies such as Xcellerex (Marlborough, Massachusetts) produce modular recombinant protein production lines such as the FlexFactory that are Good Manufacturing Practice (GMP) approved for manufacturing within one year after ordering the equipment.

Since recombinant protein subunit vaccines do not involve the production of dangerous pathogens, the cost of the vaccine facility is a fraction of that of a traditional vaccine plant. Since the subunit vaccines that utilize the proprietary polymer technology do not require cold storage or cold transportation, this also provides a reduction in the cost of building and maintaining the vaccine production facility.

Another advantage of a subunit approach to vaccines using a single-use production line is that it is capable of producing relatively small amounts of a variety of vaccines efficiently. The production of a new antigen can begin within hours after the completion of the production of a previous antigen. This allows the vaccine plant to produce a variety of subunit vaccines to meet more local needs.

The ability to produce vaccines quickly in large quantities, provides another financial advantage. Vaccines such as those for influenza, have a short life such that they must be changed each year. This means any vaccine that has been produced but not sold, must be destroyed at a loss to the company. Conversely, if too small a quantity of influenza vaccine is produced, the company will be unable to meet the local demand. This is the ongoing dilemma that faces influenza vaccine manufacturers.

With a recombinant protein-based subunit vaccine technology and a rapid production method using bacteria, it is possible to produce vaccines closer to the time when they are needed, so that quantities of vaccines do not need to be stockpiled in advance. This advantage can mean the difference between making or losing money each year. **PA**

Enquiry code: 095E05

Talent Acquisition in Emerging Markets: Making the Move ...or Not *(Part Three)*

The concluding segment of this three-part series looks at the factors that play a pivotal role in an executive's decision to join a company.

Martin Reynolds,
CEO,
Sharpstream Life Sciences

Given that a company's good reputation plays such a small part in attracting leading talent, it is perhaps surprising that, in both of the regions studied, a bad reputation is one of the most important elements that would discourage individuals from joining a company. In Asia Pacific, some 39 percent of in-market executives cite a Company's Reputation, if poor, as being a major turn-off, compared to 31 percent in Latin America. This result confirms the belief of corporate leaders that reputation is important, but perhaps not in the way that they expect it to be. It seems that, while a good reputation is of little value, a bad reputation can repel ambitious executives.

Far less surprising, given the results, is that a lack of Learning and Development Opportunities ranks high in Latin America, although it only ranks seventh in Asia Pacific, below other elements such as Company Culture and a Poor Product Portfolio.

It is notable that, in Latin America at least, a company's Ethical Approach ranks third in the table, which supports the view that a bad reputation can act to discourage potential talent.

Table 3.2: Top three factors that would discourage in-market executives from joining a company. (Source: Sharpstream Life Sciences)

Rank	Asia-Pacific	Latin America
1	Reputation of the Company	Lack of Learning & Development Opportunities
2	Company Culture	Reputation of the Company
3	Poor Product Portfolio	Company's Ethical Approach

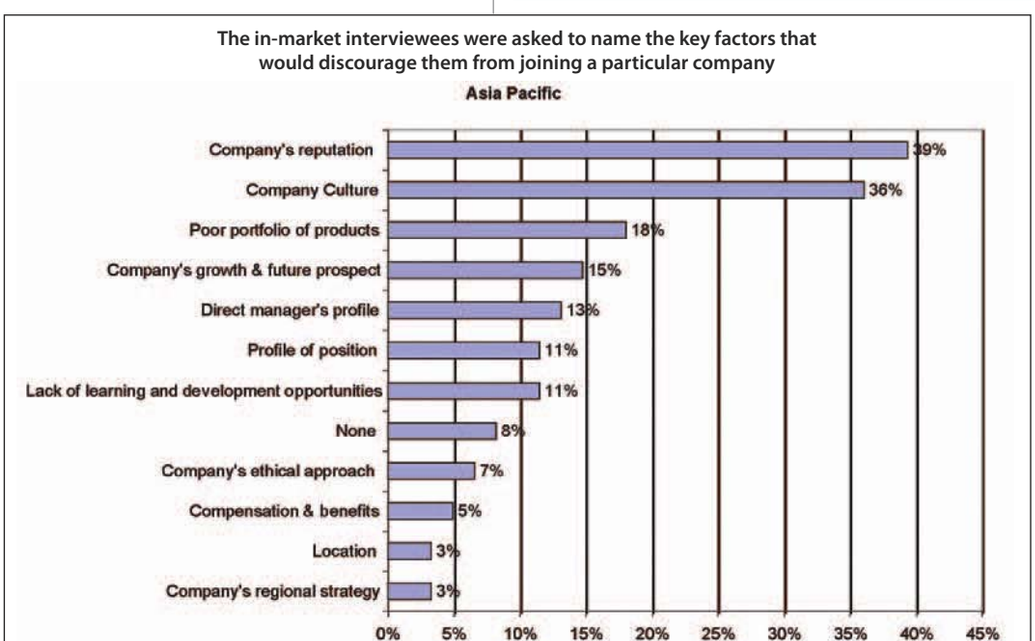


Figure 3.12: Leading factors that would discourage in-market executives in Asia Pacific from joining a company. (Source: Sharpstream Life Sciences)

It is notable also that Compensation and Benefits ranks low in both regions, with less than 5.0 percent of Asia Pacific interviewees and just 3.0 percent of Latin America interviewees citing it as a concern.

- **Readiness to Relocate for a New Position**

To an increasing extent, globalization requires a healthy trade in people as well as capital and goods, and successful individuals often achieve their potential in places other than the country of their birth. The pharmaceutical industry is no less globalized than any other, and international mobility has become one of the key characteristics of its top management talent. This is borne out in

Drug Manufacturing

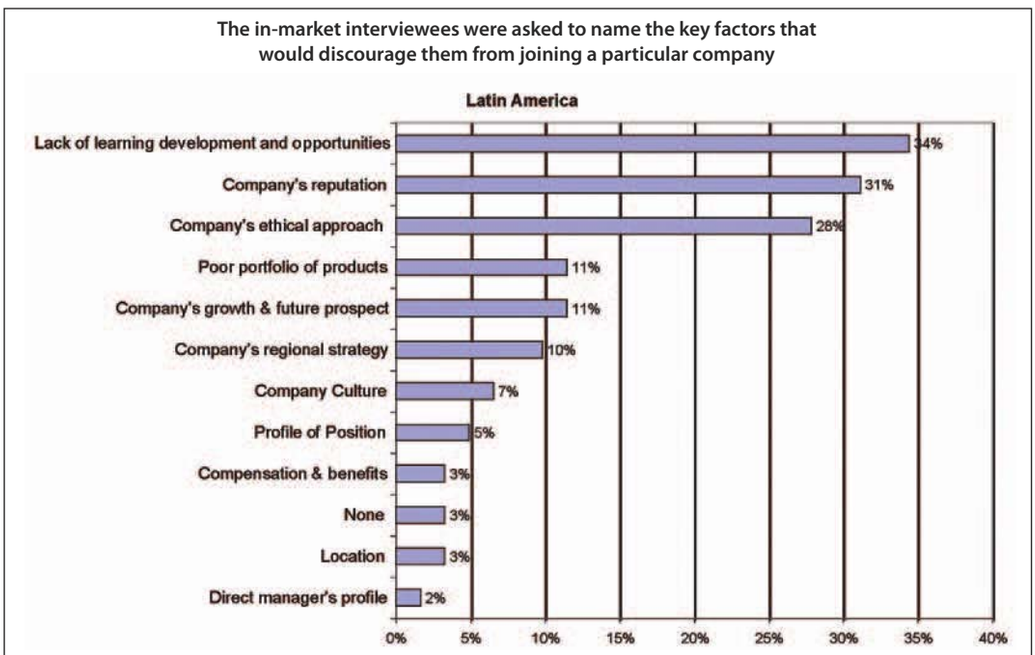


Figure 3.13: Leading factors that would discourage in-market executives in Latin America from joining a company. (Source: Sharpstream Life Sciences)

the survey; in both regions, only a small minority (13 percent in Asia Pacific and seven percent in Latin America) rule out completely the possibility of relocating to another country to pursue their career.

There are clear differences between the regions however. It appears that executives in Latin America are significantly more open to an international move, with 82 percent responding with a Yes to the question, "Would you relocate for a new position?", and 11 percent with a Maybe. In Asia Pacific, the executives surveyed are a little less sure of this answer, with just 55 percent responding with a Yes, and 32 percent with a Maybe.

- **Main Decision-Maker in Foreign Relocation**

This result may be partly explained by another finding from the survey, in which the interviewees were asked who the main decision-maker would be in regard to a foreign relocation. There are marked differences between the regions, with only 19 percent of executives in Asia Pacific saying that they are the sole decision-maker, compared with 30 percent in Latin America. An individual's spouse is also an important decision-maker when it comes to relocation, particularly in Latin America.

Perhaps more significantly, 59 percent of those in Asia Pacific claim that their family would have the main say in any relocation, compared to just 37 percent in Latin America. The strong family bonds felt by executives in Asia Pacific may well explain their apparent reluctance (at least in comparison to their peers in Latin America) to move to another country to further their career.

- **Regions that Talent Would Consider Moving to**

The strength and importance of family ties to the interviewees in Asia Pacific is supported by the response to the question, "Which regions would you consider moving to?" The Asia Pacific interviewees are much less open to a move outside of their home region, with 53 percent ruling out such a move, compared to just 22 percent in Latin America.

For those that would consider a move, Europe is the favorite destination for both groups (30 percent in Latin America and 20 percent in Asia Pacific), followed by North America (25 percent in Latin America and 11 percent in Asia Pacific). It is unsurprising that executives in Latin America might prefer a move to Europe over North America, given the existing language and cultural ties, but more surprising that Europe should be so much more attractive to those in Asia Pacific.

It is also worth emphasizing that the desire of many of the Asia Pacific executives to remain in Asia cannot simply be put down to family or cultural ties; it may also be motivated by the perception that Asia is becoming the engine of growth in the pharmaceutical industry.

With the US and European markets growing at less than 5.0 percent per annum and China growing at over 20 percent, the center of gravity of the industry is moving east, and interviewees might just prefer to stay where the action is. This is partly supported by the fact that 7.0 of executives want to move from Latin America to Asia, while none want to move in the other direction.

Of course, the international mobility of these executives, and their willingness to move to other regions, particularly the more developed markets, could well exacerbate the talent shortages that are currently a feature of the emerging regions. This perhaps indicates a worsening outlook for Latin America, whose talent is more keen on an extra-regional move than that of Asia Pacific.

Likelihood of Changing Jobs in the Next Two Years

The inherent mobility of these high-performing executives, whether internationally or domestically, is reflected in the fact that over 30 percent of them in both regions indicated that they were Most Likely to switch jobs sometime in the next two years, with just 20 percent saying that such a move was unlikely (Less Likely or Least Likely).

This is a somewhat startling result, particularly in the light of the fact that their superiors at corporate headquarters, when asked to estimate their company's employee retention rate in Asia Pacific and Latin America, produced an average figure of close to 90 percent (although note that by far the most common answer to this question was Don't Know, an indication of the extent to which some corporate headquarters are out of touch with the facts on the ground in emerging markets).

Compare and Contrast

The survey has found many similarities between top-level executives working in Asia Pacific and Latin America when it comes to career expectations and motivations, but there are also important differences.

- **Similarities between Asia Pacific and Latin America**

► In both regions, multinational pharmaceutical companies are dependent on expatriate and repatriate managers. The holders of many key management positions are foreign, due in part to a shortage of local talent at both executive and entry levels.

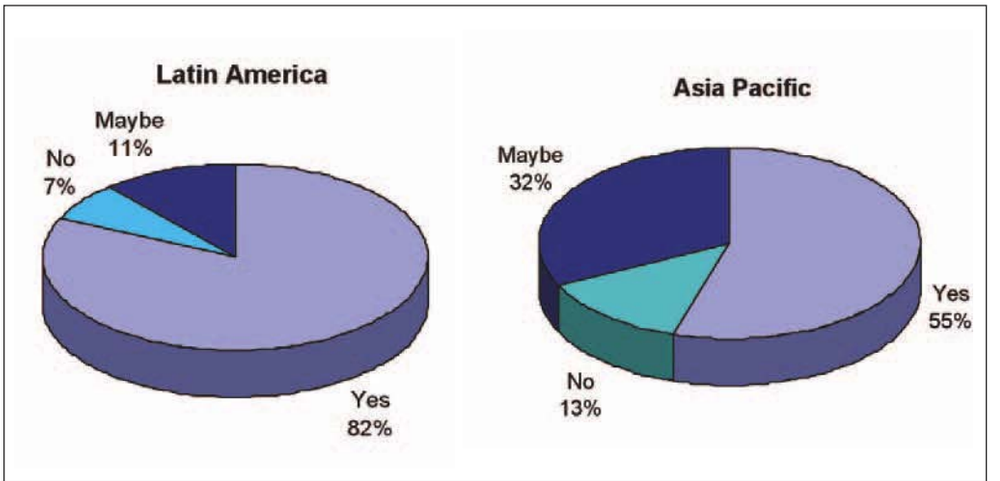


Figure 3.14: Executives in Latin America are more open to an international move than those in Asia Pacific. (Source: Sharpstream Life Sciences)

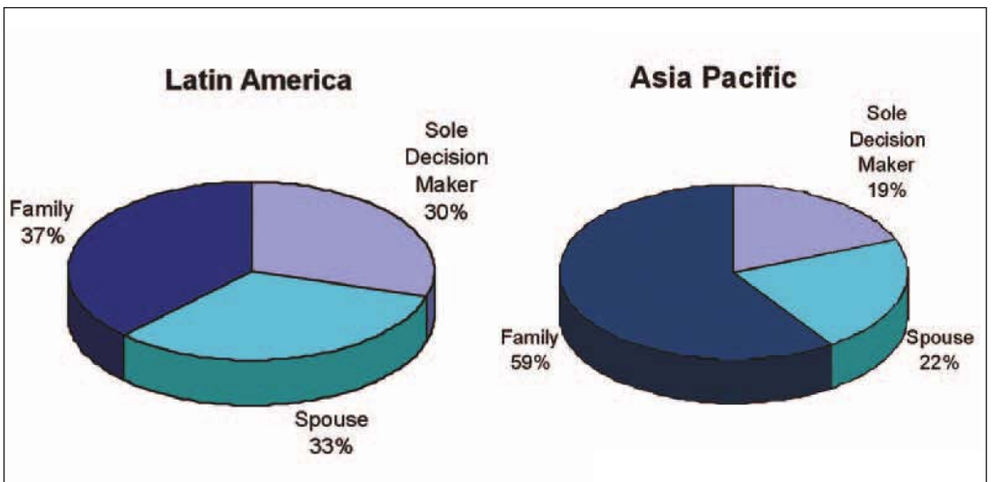


Figure 3.15: The family plays a more important role in relocation decisions in Asia Pacific than in Latin America. (Source: Sharpstream Life Sciences)

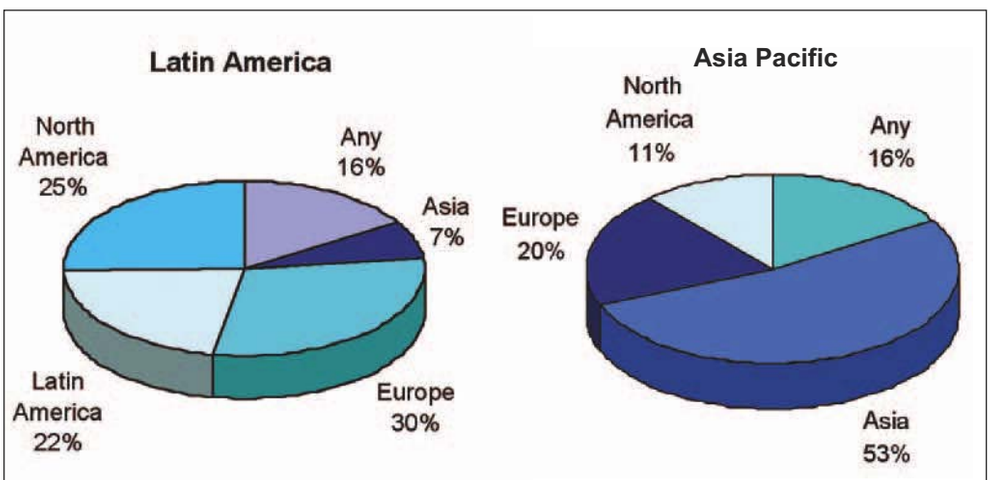


Figure 3.16: Executives in Latin America would consider a more diverse range of relocation destinations than those in Asia Pacific. (Source: Sharpstream Life Sciences)

Drug Manufacturing

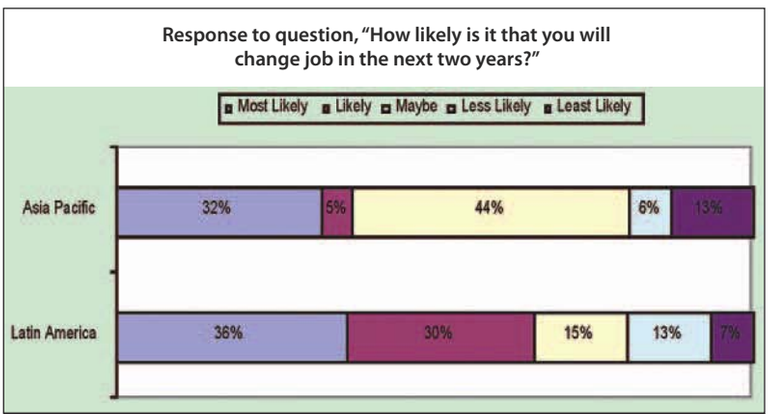


Figure 3.17: Just 20 percent of in-market executives in both regions rule out a move in the next two years. (Source: Sharpstream Life Sciences)

► With demand for talent outstripping supply, salary expectations have soared. As a result, companies in both regions are suffering the effects of salary inflation. This is seen across the board, in each job function studied – Marketing, Clinical, and Medical.

► The in-market executives in both regions see the profile of the position as being of paramount importance in any future job, with this ranking first in both regions.

► The in-market executives in both regions are concerned with being given the opportunity to learn and develop, and expect this to be a key component of any future move.

► Both groups are highly mobile, and are willing to work in many parts of the world; only a small minority is against relocating to another country to pursue their careers. Just 20 percent in both markets rule out the possibility of a job change, either locally or internationally, in the next two years.

- **Differences between Asia Pacific and Latin America**

While the talent shortage is an issue in both regions, it is more pressing in Asia Pacific. This is evidenced by its top ranking in the list of market challenges there, and also by the number of executives in each region citing salary inflation as a problem (86 percent in Asia Pacific, 71 percent in Latin America).

► There are also several underlying differences with regard to individual career expectations and motivations, the most notable being the importance of the profile within the company of the potential recruit's direct manager. This is highly important to individuals in Asia Pacific, but is relatively insignificant in Latin America.

► Executives in Latin America are more open to an international move than those in Asia Pacific, and would consider a wider range of locations. The opinions of family members with respect to a move are more important to Asia Pacific executives than to those in Latin America.

► The executives in Asia-Pacific are more demanding than their peers in Latin America when it comes to relocation support, although this may be just another symptom of the more severe salary inflation in Asia-Pacific in comparison to Latin America.

There is somewhat of a disconnection between the perceptions on the ground and those at corporate HQ. This pertains to the motivations and career expectations of in-market executives and the factors that most influence their career choices. Executives in both regions agree that although it could be improved, most corporate HQs have a reasonable degree of awareness of the operating environment in each market. Nevertheless, the distance of corporate HQ from the market, in terms of knowledge and understanding of the motivations of its staff, becomes clear in the survey. For instance, whereas the in-market individuals attach a high level of importance to the potential for learning and development opportunities at work, those at HQ greatly underestimate its significance. The corporate leaders have not recognized that top performers see the pursuit of personal and professional development as a key component of their future career path.

On the other hand, many at corporate HQ overestimate the strength of a company's reputation as an attraction for talent. This actually has relatively little importance to the in-market executives – except where it is perceived as being poor, in which case many would not consider working for the company.

Therefore, although a company cannot use a strong reputation to attract talent, it must ensure that its reputation is good enough not to repel them. This can perhaps be summarized by saying that reputation is not a factor that will swing the deal – it is instead a baseline requirement that must be present before top talent will consider accepting a position at a company.

Most strikingly however, is that the corporate leaders attach very little weight to the most important factor of all for in-market executives: the profile of the position. Although this is of importance to executives in both emerging regions, it is not recognized at the corporate level. Similarly, although the profile of direct management is highly important for in-market executives in Asia Pacific, this is not reflected in the responses of their corporate leaders.

This points towards something of a Catch-22 situation: if corporate managers do not recognize the importance of the direct manager in meeting potential recruits' expectations, there will be an inherent difficulty in developing and attracting top people, which means that the quality of future management will suffer, and so on.

Consequences of Talent Management

The factors that attract or discourage top talent are relevant not only to those companies trying to recruit, but also to those trying to effectively manage existing talent. If people are not offered the learning and development opportunities they expect, or are unhappy with the profile of their position, then no matter how good their current employer's reputation or growth prospects are, they will leave.

These latter attributes simply will not be enough to make them want to stay. This is a real risk, bearing in mind that people in both markets are open to the prospects of a career change; only 20 percent in each region rule out the possibility of a job change in the next two years. And although the survey suggests that salary is not a major factor when it comes to a career move, the prospect of a 20-30 percent raise for a lateral move, and 30-50 percent for a position offering an increase in responsibilities, may be very tempting.

Of course, there is another side to the salary inflation story: that of the companies that are offering these substantial increases in compensation to bring in the top talent. There is a question mark over whether companies can continue to deliver such large salary and benefit packages without disrupting their existing salary structures and creating resentment within the workforce.

The results of the survey point towards a dynamic market for talent in emerging markets going forward, and there seems little doubt that pharmaceutical companies face a challenge in minimizing senior staff turnover. If even a small proportion of those who intend to move actually do so, there will be many people changing jobs over the next few years, driven by the desire for development and tempted by the prospect of large salary increases. This movement will put pressure on staffing and HR functions, and companies must be sure that they have the internal processes and systems in place to move quickly and deliver results.

Opportunities exist to attract the best talent, not least for smaller companies, which will

be able to compete on a level playing field with Big Pharma – if they can offer an attractive employee value proposition that encompasses an industry-leading reputation, effective management and excellent learning and development opportunities. But these smaller companies must ensure that they can reach the talent and draw them in before they get lost amongst the competition.

Recommendations

Money is not everything. In fact, compensation is one of the least important components in a strategy to attract the best people; it is far more important to offer the prospect of growth for the individual, in both personal and professional terms. To achieve this, the following actions are recommended, which can improve the recruitment, retention and management of top talent in emerging markets in the future:

Money is not everything. In fact, compensation is one of the least important components in a strategy to attract the best people; it is far more important to offer the prospect of growth for the individual, in both personal and professional terms.

- Invest more senior leadership time in HR to ensure that talent management and acquisition strategy links clearly with overall business aims. Identify where the key skills gaps are in the business and what areas are the most critical to business performance and success.

- Make high profile appointments into key positions in order to draw talent into the company. Choose a core number of key appointments and focus on getting these filled successfully with the best candidates that can be attracted. They will be an expensive but sound investment in the long term.

- Salary expectations are high, so address this head-on. What are you willing to pay? Is the company prepared to compete for talent? If so, choose the key positions where the company will pay higher and those where it will not.

- Create "development opportunities", not just jobs. Development paths should be created for key positions. Interesting and dynamic job challenges should form part of this. Offer financing for external executive education.

- Move people around laterally to expose them to different functions or businesses, but keep them in each position long enough for them to perform effectively. If necessary, create new roles and incentives to retain the best managers.

- Establish global training programs, so that locals have the opportunity for training and exposure abroad, and to build personal relationships within the company.

- Build and maintain a company culture that encourages strong personal relationships between direct managers and their teams. People stay in the company for these; they are loyal to the immediate individual, not the company.

- Build a strong ethical foundation to engender pride in the company and commitment to being a part of the company's future.

- Always be aware of differences between markets, cultural and otherwise. Develop a unique strategy for each market; be flexible, listen and tailor it to local needs.

- Do not rely on the company's reputation as a sure fire way of attracting talent. It will not be enough. What is the company's reputation like in the market? If it is not strong, then there is a need to factor this into talent acquisition plans and to take appropriate action. **PA**

Enquiry code: 095E06

Product Focus
Packaging/Process Components

Freeze-Drying Sample Extractor for Effective Cycle Development

SP Industries has introduced another generation of the Sample Thief sample extractor accessory for its Virtis Genesis range of freeze-dryers.

The extractor is used to remove samples from the freeze dryer without disturbing the process facilitates. It is constructed from clear acrylic and provides scientists with improved visibility throughout the product chamber, enabling unhindered rapid and safe removal of samples during the freeze-drying process. Offering stable fine control, the claw removal device facilitates the extraction of even small-sized vials and eliminates errors caused by disturbing adjacent vials and stoppers.

Several samples can be removed and stoppered (under an inert Nitrogen blanket if desired) at once. In addition, the sealing has been improved so that there is virtually no pressure excursion in the product chamber upon opening the inner antechamber door. Vial removal has been improved so that the operator simply breaks vacuum on the outer antechamber, lowers the outer door and reaches in to remove the sample.

SP Industries, www.spindustries.com

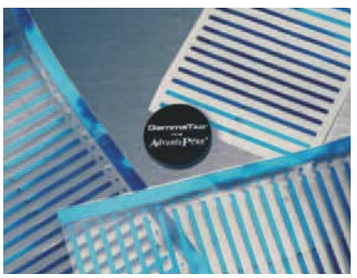
Enquiry code: 095P01

► See more products & equipment at www.PharmaAsia.com.

AdvantaPure: Radio Frequency Tag for Process Components

AdvantaPure has introduced the GammaTag 500 for high volume items requiring repeated gamma sterilization. It is developed for single-use process components and other critical parts, for pharmaceutical and biotech applications. The tag is used to identify, record, and access the current status of process components on the spot. Information such as manufacture date, part number, lot number, gamma sterilization date, and other data may be retrieved from the tag's memory.

The tag handles typical doses of 25 kGy (kilograys) and a cumulative amount of at least 500 kGy with no loss of data. The read-only tag uses the globally available 2.45 GHz radio frequency and is available as a bare inlay or can be converted into various finished tag constructions.



It works well for identifying high volume items such as cleanroom supplies (garments, mop heads, and instruments); pharmaceutical vials; and biotech processing equipment.

AdvantaPure, www.gammatag.com

Enquiry code: 095P02

Allegheny Bradford: Easy Cleaning, Draining

The Opti-Clean filter housing from Allegheny Bradford is designed for maximum drainability. Unlike traditional housings with a collection chamber under a flat cartridge plate, this housing's one-piece design eliminates the collection chamber and features an integrated sloped cartridge plate to aid in drainability.

All the cartridge sockets drain to individually machined and sloped slots that lead directly to the central outlet port. The same integrated cartridge plate is sloped so that any unfiltered product drains out of the inlet nozzle. The result is a faster, more efficient draining process, no spills or mess during disassembly, and greater output volume.

The housing eliminates manual cleaning while cutting product loss from hold-up volumes. Customization is offered with a variety of surface finishes, socket configu-rations, and optional features, including hand wheels that eliminate the use of tools.

Allegheny Bradford, www.alleghenybradford.com

Enquiry code: 095P03

Efficient Monitoring of Controlled Environments

Veriteq's browser-based monitoring and alarm system, viewLinc deploys easily on an existing network, saving time and cost for installation. Temperature and humidity conditions can be monitored and reports generated via standard internet browsers. There is no need to install or validate software on individual workstations; with viewLinc, the user can see live graphical data from any selected logger channel with one click.

The system sends notifications by text, email, phone or pager to alert the pertinent personnel for each monitored area. The system can be customized with reports by area, logger description, date and time. Also featured is an audit trail that is fully 21 CFR Part 11 compliant. The data loggers are powered by a 10-year battery and on-board memory.

Veriteq , www.veriteq.com

Enquiry code: 095P04

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Sheraton Towers, Singapore
www.ibc-asia.com/regulatory

Aug 26 – 27, 2009
OTC Pharma Asia: Capitalizing on New Market Development & Building a Sustainable Growth Strategy
Singapore
www.abf-asia.com

Sep 7 – 9, 2009
BioProcess International China 2009
Beijing, China
www.ibclifesciences.com/BPIChina

Sep 13 – 15, 2009
ISPE Australasia Conference 2009
Sydney, Australia
www.ispe2009.com

Sep 14 – 15, 2009
Thermo Fisher Scientific – Spectroscopy User Meeting
Stratford, UK
www.thermo.com/ukscievents

Sep 16 – 18, 2009
Bio Korea 2009
Seoul, South Korea
www.biokorea.org/info/bio_korea_01.html

Sep 16 – 18, 2009
World Pharmaceutical (China) Summit 2009
Shanghai, China
www.cfeci.com/wpcs2009

Sep 22 – 23, 2009
In-Vitro Diagnostics Technologly Congress
Marriott Hotel Hongqiao, Shanghai, China
www.ivdtechcongress.com

Sep 23 – 25, 2009
World Pharma Trials Asia 2009
Shanghai, China
www.terrapinn.com/2009/pharmatrials

Sep 24 – 25, 2009
Medical Devices Summit 2009
Shanghai, China
www.ibc-asia.com/medicaldevices

Sep 28 – 29, 2009
2nd Pharma Marketing Asia Summit
Sheraton Towers, Singapore
www.ibc-asia.com/pharmamarketing

Oct 5 – 7, 2009
Stem Cells & Regenerative Medicines Asia 2009
Singapore
www.terrapinn.com/2009/stemcellsasia/

Oct 6 – 8, 2009
Biotechnica
Hannover, Germany
www.biotechnica.de

Oct 8, 2009
Clinical Outsourcing Alliances in India
Boston, Massachusetts, USA
https://www.nextlevelpharma.com/events/view/clinical_outsourcing_alliances_india

Oct 16, 2009
RNAi Market Analysis and Business Tutorial
Kunshan/Shanghai, China
www.selectbiosciences.com/conferences/RazviLondon/RNAi_Tutorial.aspx

Oct 19, 2009
Stem Cells in Drug Discovery and Regenerative Medicine
Tokyo, Japan
www.selectbiosciences.com/conferences/Razvi_19OCTpm/

Oct 19 – 20, 2009
Wyatt Technology Corporation - 20th Annual International Light Scattering Colloquium
California, US
www.wyatt.com/events/colloquium/

Oct 20, 2009
MicroRNA and Epigenetics
Tokyo, Japan
www.selectbiosciences.com/conferences/Razvi_20OCTam/?utm_source=SBTrngJune09

Oct 20, 2009
Nucleic Acid Diagnostics and Therapeutics
Tokyo, Japan
www.selectbiosciences.com/conferences/Razvi_20OCTpm/?utm_source=SBTrngJune09

Oct 22 – 25, 2009
BIT's 7th Annual Congress of International Drug Discovery Science and Technology (IDDST)
Shanghai, China
www.iddst.com

Oct 27 – 28, 2009
4th Annual Generics Asia Summit 2009
Hilton Hotel, Singapore
www.ibc-asia.com/generics

Nov 1 – 3, 2009
HUGO Symposium on Genomics and Ethics, Law and Society
Geneva, Switzerland
www.hugoevents.org/gels/

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