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Contents

• Page 2 - **Unravelling the mysteries of CA Analytes**

Knowledge gained about the structure and function of mucins found in a number of cancer types has enabled the development of new generations of antibodies to track them. Better understanding about these molecules is the reason why this progress has been made. Here we look at what efforts have been taken by researchers to unlock the secrets behind this important class of molecules.

• Page 5 - **Gaining the coveted CE mark**

• Page 6 - **On Display**

Phage display is a promising technique for the identification of effective cancer markers. It has proved to be a powerful enabling technology in proteomics and drug development. Christian Fermér, senior research scientist at CanAg Diagnostics explains the significance of this technology in the company's hunt for new products.

Page 8 - **Company News**

The Smile project.
The latest additions to the global distributor network
Two step to one- shortening assay times.

Conference information

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Welcome to the first issue...

Welcome to the first issue of our newsletter which we hope will help our customers learn more about CanAg Diagnostics.

Since its establishment, CanAg Diagnostics has launched a broad range of immunological products for serological cancer diagnosis, which has created a stable and profitable base for the company's further growth.

The CanAg brand name has become associated with competence and high quality. This reputation is one of the company's core assets. In order to maintain and nurture the high standing of the CanAg brand name, the company and all its employees are committed to serving customers in a way that meets our standards of Competence, Innovation and Quality.

Our ambition is to be a leading company within our chosen market niches, and this should be achieved through increased market presence and product development.

Mainly, our focus will be on developing a comprehensive and innovative product range in the field of serological cancer diagnosis embracing clinically validated antibodies and antigens and Enzyme Immuno Assay, EIA, kits. In addition, to our own R&D activities, the aim is to extend our collaboration with other academic and commercial partners. The "SMILE project" reported on page 8 is one example of our strategy to co-operate with external partners to find solutions for the development of innovative diagnostic tools.

Our newsletter is part of our desire to share our knowledge and experience of working in this challenging area. We believe that sharing information with users is of vital importance in ensuring that the best clinical results can be achieved. If there is any particular topic that you would like us to cover in future issues, please let us know.

Our first issue focuses on two topics which are of main interest for the present and future product portfolio - CA Analytes, which are some of our most important products, and the use of the key research tool, phage display, in identifying promising antibodies for further product development and commercialisation.

Olle Nilsson
Managing Director

Exploding the myths about CA analyte determination

Introduction of hybridoma technology during the 1970s resulted in the identification of a number of novel tumour associated markers from the end of that decade onwards through their reactivity with monoclonal antibodies.

The majority of these monoclonal antibodies were raised against tumour cell lines and/or membrane fractions from tumour tissue. The specificities of the established monoclonal antibodies were based mainly upon preferential reactivity with tumour tissues compared to normal tissue. The antigens recognised were also shown, in many cases, to be elevated in serum from cancer patients, and thus allowed serological determination of tumour markers for different cancer forms. The first and most commonly used markers of the new "hybridoma defined" markers were CA19-9, CA125, CA15-3, CA50, CA242, CA72.4 etc.

Further biochemical characterisation of the "CA-analytes" revealed that they recognised highly glycosylated heterogeneous proteins, commonly known as mucins. Mucins are notoriously difficult to characterise and detailed knowledge about the antigens as well as the epitopes recognised in the "CA-analytes", has been poor. There has also been a considerable myth and mystery about what actually is determined and how to determine the "CA-analytes".

However progress in the knowledge of the biochemistry of mucins and characterisation of antibodies for determination of the "CA-analytes" has provided considerable insight and knowledge about the CA-antigens as well as the CA-assays.

The understanding of mucins has dramatically increased during the 80-ies and 90-ies through the biochemical characterisation and cloning of the genes of several common mucins. Over the past three years, the mucin-like superstructure of the CA125 gene has also been revealed (ref.2).

The initiative of ISOBM (International Society of Oncodevelopmental Biology and Medicine) to conduct International Workshops in order to characterise monoclonal antibodies towards common tumour markers has also provided much new knowledge about the CA-analytes and monoclonal antibodies for their determination. It is an important forum that seeks to explode many of the myths that have grown up around the issue of tumour markers and antibody performance.

CanAg Diagnostics has participated in all the ISOBM workshops. According to Olle Nilsson, founder of CanAg Diagnostics,"These workshops clearly demonstrate that there are a number of antibodies that may be used to determine the CA markers, that different antibody combinations may be used as long as they are well characterised and the detailed reactivity of the antibodies used are known."

Based on the ISOBM efforts to understand the molecules new generations of antibodies may now be identified. Through improved knowledge, the hunt for more appropriate antibodies is made easier.

Back to basics

In particular, considerable efforts have gone into the characterisation of the CA15-3 found in breast cancer, CA 125, indicative of ovarian epithelial cancers and CA19-9 which suggest the presence of pancreatic and colo-rectal cancer. These markers were amongst the first CA-analytes to be discovered using monoclonal antibodies.

CA19-9, CA15-3 and CA125 are interesting because they represent three different types of immunoassays for determination of tumour associated mucins. In the CA19-9 assay, a single determinant assay format is used. In the assay a sialylated carbohydrate epitope (S–Lea) is determined that is expressed on several different mucin core proteins. Thus several different mucins may be determined in the CA19-9 assays.

In the CA15-3 assay, antibodies directed against the MUC-1 mucin core protein are used in combination with an antibody directed against a carbohydrate epitope associated with MUC-1 of breast cancer. Thus, a double determinant assay format is used, determining a carbohydrate epitope in combination with a protein epitope.

In the CA125 assay, two monoclonal antibodies directed against different protein determinants in the CA125 protein core are used. As a result, the CA125 assay is less influenced by differences in glycosylation between different individuals and conditions.

Mucins are epithelial glycoproteins, having a high content of O-linked carbohydrates. In addition, it has been found that they have a protein backbone containing tandem repeats that are specific to each mucin.

Mucins may be classified according to whether they are secreted, or bound(fig.1). MUC-7 is an example of a secreted monomeric mucin, though other mucins can be dimeric or multimeric, such as MUC-2. Epithelial membrane mucins are typified by MUC-1.

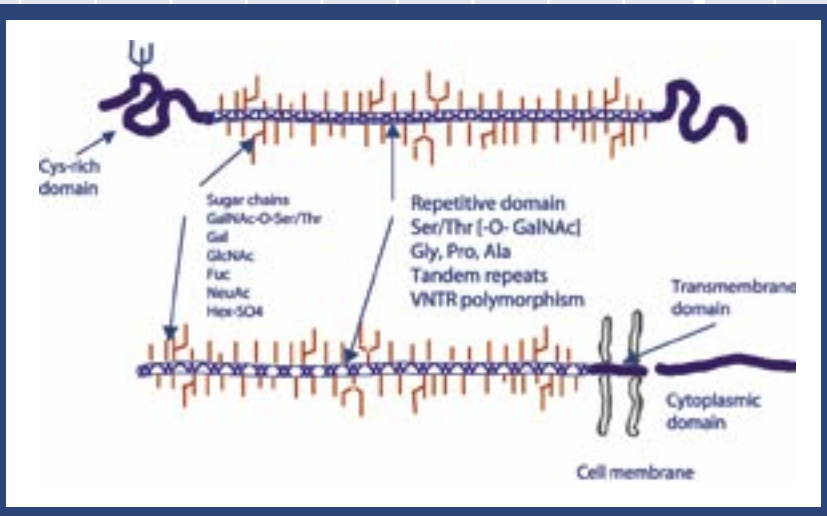

Fig.1: General structure of secreted and membrane bound mucins.

Function and structure

The functions of mucins are not understood but a number of possible functions have been suggested: a first line defence against environmental attack; lubricants; and, as cell adhesion or repellant molecules.

Mucins are normal constituents in most epithelial tissues and the same mucin may be found both in normal and malignant tissues. However, certain distinct differences in the expression and general cellular architecture and tissue organisation may explain why presumably normal substances may act as good serological markers of the presence or absence of cancer disease. Normal epithelial tissue shows an apical expression of the mucins and mucins are shedded into the ductal lumens (Fig.2). In cancerous tissue, however, there is a loss of apical expression of mucins, degradation of the basal membrane and increased vascularisation that may lead to shedding of mucins into the blood. There are also other both qualitative and quantitative differences in the expression of mucins in normal and malignant tissues. However, the mechanism shown above is important in order to explain why mucins may be good serological tumour markers.

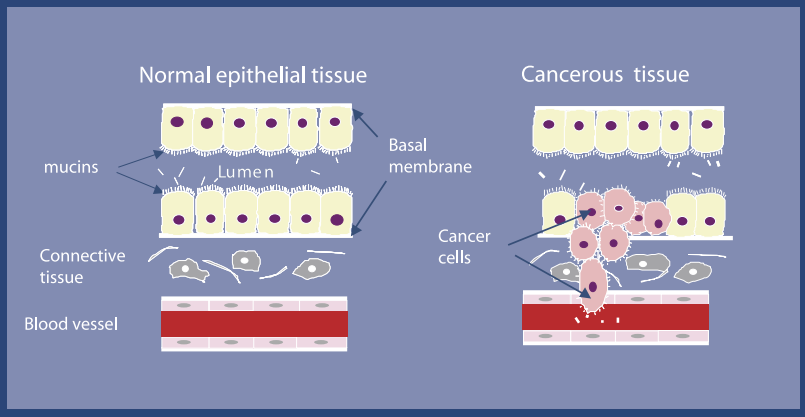

Fig.2: Shredding of mucins in normal and epithelial tissues.

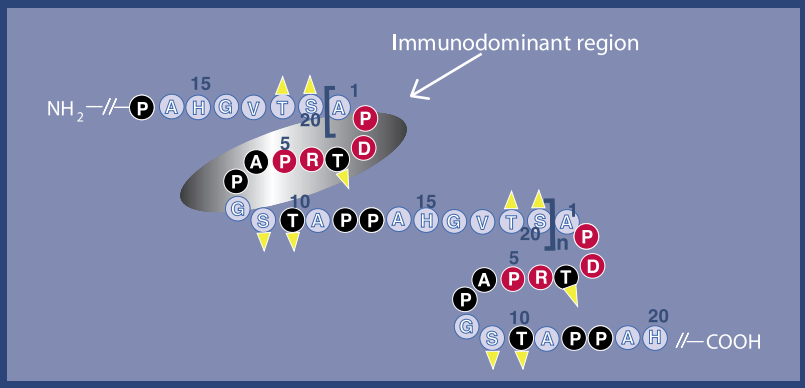

Fig.3: MUC1 Epitopes

Considering CA125, which was originally identified in 1981, we now know that it is expressed in normal endometrial tissues, epithelial lining of pleura, pericardium, and in the abdominal cavity. This molecule was originally identified by its reactivity with the Oc125 monoclonal antibody, and was characterised as a high molecular weight mucin-like glycoprotein complex.

Looking more closely at the CA125 antigen. It has an extracellular superstructure that is dominated by repeat sequences (Fig.4)(ref.2). It comprises:

- A transmembrane glycoprotein
- Tandem repeat units (> 60), 156 amino acids
- Conserved disulphide bridged Cystein- loop containing the Oc125 and M11 epitopes
- Heterogeneity in the tandem repeat sequence
- N-terminal highly glycosylated domain (O-linked CHO)
- Short cytoplasmic tail
- Phosphorylation site

At the first ISOBM International TD workshop for the characterisation of monoclonal antibodies, (MAb), 26 coded MAb against CA125, were characterised by a number of independent research groups. The consensus result identified two main antigenic domains: domain A was defined by the Oc125 MAb, Domain B defined by the M11 MAb. A third domain, Domain C, was identified by the Ov197 MAb (ref.1).

This knowledge led to the conclusion that the most robust assays are obtained by combining antibodies from Domain A[/C] and antibodies from Domain B. Today, all commercially available CA125 assays use antibodies directed against protein determinants located in the same region of the tandem repeat of CA125.The epitopes for the antibodies used in CA125 assays seem to be less influenced by glycosylation, and this, in combination with the use of MAb against two protein determinants, may explain why different assays for CA125 show very good correlation to each other, irrespective of the source of antibodies or technology.

MUC-1 (CA15-3) breast cancer assays

A similar workshop has been carried out on the breast cancer associated mucin, MUC-1. MUC-1 is known in the literature under several different names e.g Episialin, PEM, PUM, ETA, EMA, HMFGM, PAS-O, Epitectin and DUPAN-2. It is an epithelial membrane antigen with a

Exploding the myths about CA analyte determination

cytoplasmic domain, a transmembrane domain, and an extra-cellular carbohydrate rich domain. Its structure is characterised by VNTR polymorphism (Variable Number of Tandem Repeats) in the extra-cellular domain

• 20 - ≈ 100 repeats of a 20 amino acid sequence [-APDTRAPAPGSTAPPAHGVTS-]

Several breast cancer assays are used to determine the presence of this antigen including:

• CA15-3 (115D8 MAb and DF3 MAb)
• BRMA (Ma695 MAb and Ma552 MAb)
• CA27/29, CA549, MCA, MSA, BCM, TAG12

At the 4th ISOBM international TD workshop Mabs against MUC-1 were characterised. In the workshop a total of 55 MAb were submitted for consideration. The results showed that 35 MAb reacted with the tandem repeat region of MUC i.e "true" MUC-1, 12 MAb reacted with carbohydrates and 2 MAb recognised Sialic acid containing CHO associated with MUC-1 of breast cancer [Ma695 and 115D8], while a further 8 MAb proved not to be associated with MUC-1(ref.3). The immunodominating region of the tandem repeat was found in the region [-PDTRA-PAP-] of the MUC-1 tandem repeat, and the majority of the MAb against the MUC-1 was directed against this part of the tandem repeat. The region contains a potential glycosylation site –T- and subtle differences in the binding specificity of different MAb may be influenced by the glycosylation of this site (Fig.3).

The two MAb against a sialylated carbohydrate associated with MUC-1 of breast cancer submitted to the workshop were similar to each other. The Ma695 MAb inhibits the binding of MUC-1 antigen to 115D8 MAb suggesting that the Ma695 and 115D8 MAbs have similar specificity.

MUC-1 assays

Larger differences are generally found between different MUC-1 assays when compared to the results obtained for CA125 owing to the fine specificity of the antibodies used. These differences become more apparent, if only MAb against the MUC-1 protein core are used as compared to the CA15-3 assay that uses a MAb against the MUC-1 protein core in combination with a MAb against a carbohydrate associated with MUC-1.

CA19-9

An additional antigen to be studied by the ISOBM TD workshop was the CA19-9 tumour associated carbohydrate antigen and related eptiopes, e.g. CA50 and CA195 (ref.4). The CA19-9 is an epitope originally identified by the MAb designated 1116-NS19.9. This epitope has been identified as Sialylted Lewis a, S Le^a, i.e. the Lewis a blood group substance containing an additional sialic acid. The CA19-9 antigens are associated with pancreatic and colo-rectal cancer. Both CA19-9 and CA50 have been found to be useful in the management of patients with suspected or known pancreatic cancer. However, the assays are not very specific and false positivity may be found in patients with benign pancreatohepatobiliary diseases.

MAb against S Le^a

The focus of the Workshop was on the characterisation of MAb against S Le^a. In this instance 20 MAb were submitted to the workshop for scrutiny.

CanAg Diagnostics has developed a number of monoclonal antibodies specific for S Le^a. C192 MAb (given the ISOBM code #251) was included in the ISOBM Workshop on MAb related to S Le^a. The "original 1116-NS-19.9 MAb was also included in the workshop (coded #246). The 1116-NS-19.9 MAb has a peculiar reactivity with S Le^a in that the binding at acidic pH is stronger than the binding at neutral pH. The C192 MAb also shows the same behaviour. The reactivity at different pH can be explained by the fact that though many MAbs are highly specific for S Le^a, they recognise S Le^a from different orientations. S Le^a is expressed on mucins and a large number of S Le^a epitopes are expressed on the same mucin. It is proposed that the "side" of S Le^a that is recognised by 1116-NS-19.9 (and C192) is more exposed if the mucins are

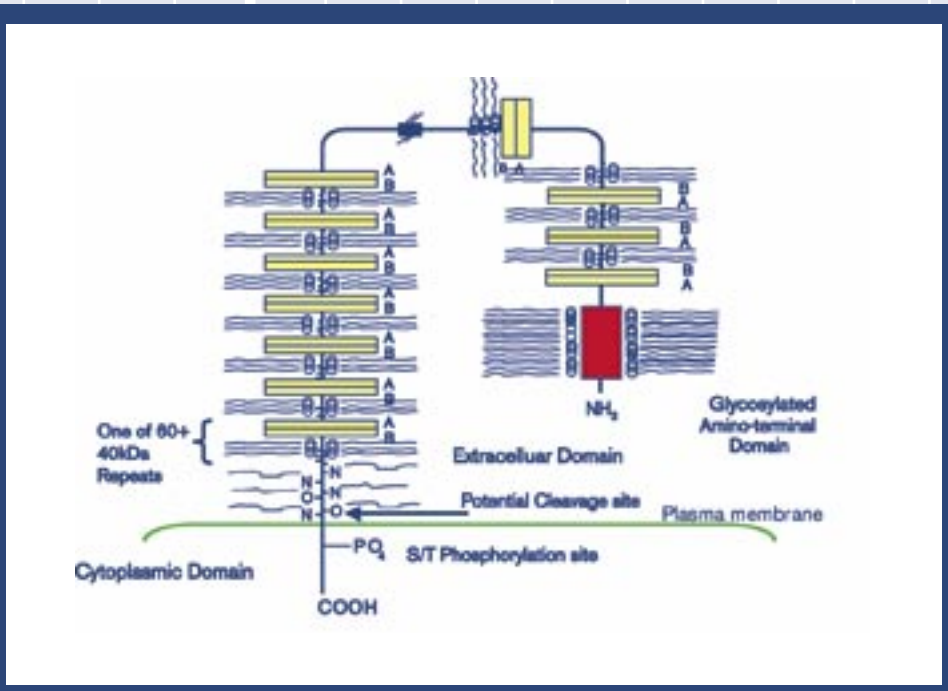

Fig.4: Proposed structure of CA125 (ref.2)

in an acidic environment. It is assumed that the 3-dimensional orientation of the mucin is altered by the acidic pH. This is still hypothetical, but the reactivity at different pH may be used to show differences and similarities in the detailed recognition sites of different Anti S Le^a MAb.

In the workshop, the antibodies were tested for reactivity with different glycoconjugates related to S Le^a, purified antigens and human serum pools as well as performance in sandwich immunoassays.

The researchers found that minor cross reactivity with related saccharide structures was noted in several antibodies; only two antibodies reacted only with SLe^a 1116-NS-19.9 (#246) and C192 MAb (#251)(ref.4).

Conclusions

Today the antigens determined in the CA assays [CA125, CA15-3 and CA19-9] are relatively well-characterised substances with a good correlation between assays when using well characterised MAb. A broad range of well-defined and characterised MAb exists for each of the

CA-analytes.
Overall, the work of ISOBM and its participants have highlighted the fact that CA analytes are no longer mysterious molecules. The research community has not only been able to characterise most molecules to a high degree but can offer more tailored solutions and more specific assays for their determination. This represents an important step forward in cancer diagnosis and tracking of disease.

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Company News

CE Mark for CanAg Diagnostics' Products

The CE-mark indicates that a product complies with the essential requirements of the EU Directive 98/79/EC. Products bearing the CE-mark may be freely marketed in the European Economic Area. CanAg Diagnostics will begin releasing products bearing the CE-mark during May 2003.

Christina Hall, Regulatory Affairs Manager at CanAg Diagnostics explains, "Obtaining the CE-mark involves all aspects of the company from development, to manufacturing, quality control , marketing, and QA/RA". In order to obtain the CE-mark the company has had to go through a number of procedures. It has reviewed, supplemented and organised the technical files for its IVD-kits, it has expanded its quality system to conform to the quality system standard for medical devices specified in ISO 13485, revised all product labelling and established "Declarations of conformity" for its IVD-kits .

"For the majority of products, the CE-mark is obtained through a self-declaration process monitored by the Competent Authority, CA, in the country of origin of the manufacturer," notes Hall. For CanAg Diagnostics it is the CA of Sweden called "Lakemedelsverket" (corresponding to eg. FDA in USA). For products classified as "Annex II, List B", like our PSA EIA and CanAg Free PSA EIA, conformity assessment for the CE-mark will be audited by a designated Notified Body. It is a costly and difficult process says Hall and companies failing to meet the December deadline to gain the CE mark "will be closed out from the European market". Happily, CanAg Diagnostics will not be among them.

CE

Targeting the phage

Hybridoma technology to immortalise antibody secreting B-cells has been the technology platform on which CanAg Diagnostics relied for the development of monoclonal antibodies. Today more powerful and novel techniques based on gene technological methods have been created by the scientific community. Among these methods, display of libraries of antibody fragments on the surface of bacteriophages is of great interest. At CanAg Diagnostics this approach is used as a complement to traditional hybridoma technology in order to increase the capacity to identify antibodies against different target molecules.

Phage display is proving to be a powerful new tool in the search for antibodies that can target antigens associated with tumours and acute and chronic brain disorders. It is a relatively fast and straightforward way of creating and isolating suitable high affinity antibodies that have a specific interaction with a known disease target.

"Phage display technology", explains Christian Fermér, senior R&D scientist at CanAg Diagnostics, "is a considerable step forward in identifying potential new antibodies. It has major advantages when compared to traditional hybridoma technology through the larger diversity of binding repertoire coupled with the possibilities of high throughput screening, possibility to select for "self-antigens" as well as altering the binding properties in the test tube." It is a fast and quick technique to employ based mainly in the test tube.

Phage display is a powerful enabling technology because, in principle, it allows any kind of protein or protein libraries to be displayed on the surface of the phage. This is particularly useful for those being functionally selected. There is an impressive list of ligands that have been displayed on phage including peptides, antibody fragments, enzymes, protease inhibitors, cytokines, transcription factors and cDNA libraries. Researchers have used it as an approach for the engineering of human antibodies, as well as protein ligands, and phage display has a broad range of applications, which include drug and target discovery, protein evolution and rational drug design. Display methods promise to have benefits in the development of therapeutics targeting many different disorders, including cancer, AIDS, autoimmune and other diseases.

At CanAg Diagnostics, the phage display technique has been established to generate scFv phage display libraries from immunised spleen cells, hybridoma cells as well as non-immunised mouse spleens. The technology has been adopted in order to establish antibodies against targets where the traditional hybridoma technology has not been successful and to change properties of established hybridomas by changing isotype. Another important aspect of phage display is to improve the affinity of antibodies with DNA-shuffling and phage display selection. One example relates to anti-proGRP, presented at the ISOBM in Boston 2002, notes Dr. Fermér. The company is now working with scFv antibodies against some cancer antigens that have been difficult to raise antibodies against using traditional techniques. Furthermore, for a repertoire of the company's antibodies, phage display has been used to determine the exact binding site of the antibody on the corresponding antigen.

The essential phage

Phage display is the process by which new genetic material is inserted into a modified phage genome and expressed and displayed on the surface of the phage. From a library of phage displaying different ligands, clones with unique properties can be selected based on a specific function or affinity. This process, called biopanning, allows you to screen a huge number of phage variants simultaneously. The physical link between the proteins displayed (phenotype) and the genetic information inside the phage (genotype) makes it easy to determine the DNA sequence of selected ligands.

When constructing an antibody-phage library you start with cells producing antibodies. At this point, you can choose either to use cells from a non-immunized or immunized source. In principle, very large non-immune libraries can be established so offering the possibility of a selection of antibodies to any desired antigen. However, such libraries must be very large and the construction is fraught with difficulties. By employing cells from an animal already challenged with a particular antigen, the immune system is directed to produce high affinity antibodies with the given specificity. Consequently, the library does not need to be so large and the construction is less complicated. Usually mice are immunized with the antigen of interest. The spleen which has B-cells producing antibodies is used as a source of mRNA, the transcripts of the genes, and this is converted into complementary DNA, cDNA. This results in a mixture of DNA transcripts of all genes expressed in the cells. The conversion of mRNA into cDNA allows the use of PCR to amplify selectively the large repertoire of variable light (VL) and variable heavy (VH) chains. By a second PCR step, the heavy and light chain are joined together in a single chain (VL-VH) that is ligated into the vector in fusion with the gene for the phage protein III that is expressed on the tip of the phage.

The DNA is forced into E. coli bacteria, which start to produce phage that display the antibody fragment on their tips. The displayed antibody fragment, called single-chain Fv (Fragment variable), constitutes the actual segment of the antibody that takes part in antigen binding.

Each phage receives only one single-chain (VL-VH) sequence and this is expressed and displayed on the tip of

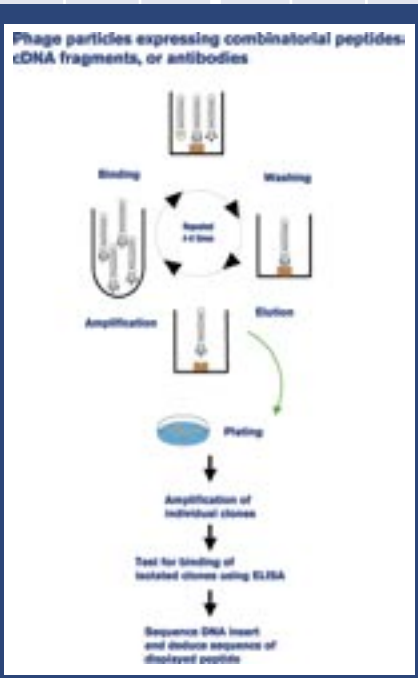
the phage. Collectively, the population of phage can display a huge number of different scFvs, each of which are tied to their own gene. Even though the phage population in an immunized library is biased towards binding the antigen, the majority do not. In order to "fish out" the ones that actually bind the antigen the collection or library is exposed to the antigen, usually immobilised on a plastic surface. This process, called Biopanning is not unlike panning for gold, where the panning process leaves behind the precious and most valuable material. On exposure, some of the phage in the library will bind to the target molecule. After the phage has been given the opportunity to bind to the target, Fermér explains that the "unbound phage is removed by washing." In this way, the promising phage population are captured and this 'edition' in the library can be replicated in bacteria and used for further rounds of biopanning. The procedure is repeated 4-5 times after which the binding properties and nucleotide sequence of individual clones are determined.

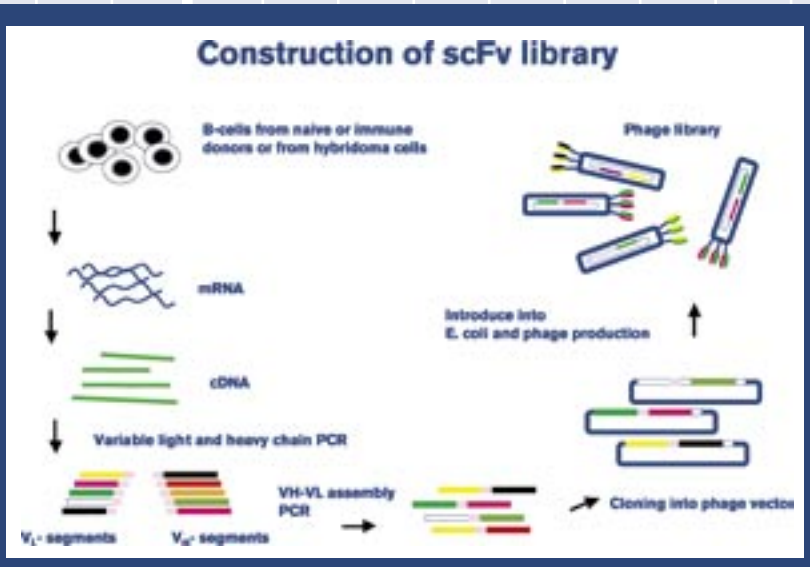
Usually scFvs with the desired properties are selected from immunized libraries. However, occasionally the affinity of the antibody fragment has to be improved. For example, traditional techniques may end up with hybridomas producing antibodies with the right specificity but with poor affinity. If the hybridoma is converted to an scFv, the binding properties may be improved by introducing random mutations into the scFv sequence. The mutations are randomly introduced through DNA shuffling methodology. Briefly, the single-chain DNA (VL-VH) of the clone to be mutated is amplified by PCR. The DNA molecules are randomly fragmented with Dnasel, a DNA digesting enzyme, and the small pieces of DNA are reassembled by a modified PCR step. Random mutations are accumulated during the process. The pool of single-chain DNA molecules with random mutations is ligated into the phage vector, and a new library is constructed. By biopanning, clones with improved affinity are selected and these may be targetted for an additional round of mutagenesis. Sequence analysis will reveal which of the amino acid residues are important for binding. At CanAg Diagnostics, the affinity of an anti-proGRP scFv, was raised by three orders of magnitude by only two rounds of DNA-shuffling. Thus, the procedure proves to be very powerful in engineering antibodies to gain desired properties. Through the introduction of new HTS methods (e.g. Phage display and aptamer selection) for the selection of target binders as a complement to the traditional hybridoma technology, CanAg Diagnostics is well prepared for the future with respect to development of new monoclonal antibodies and ligand binding molecules.

How phage has spread

Though the first report on phage display was published in 1985, it has taken a number of years for the technique to become more widely used. The early problems encountered were associated with the difficulty in using the phage vectors. Today, phage display is an established technique within academia and at commercial companies such as CanAg Diagnostics.

Antibodies are becoming more and more interesting as therapeutic agents, such as the anti-cancer drug, Herceptin. Phage display seen as an important tool when generating new antibodies. Single-chain Fv's can be converted into human antibodies and furthermore may the small size of a single-chain Fv be beneficial since it may penetrate tissue better in order to reach the organ of interest.





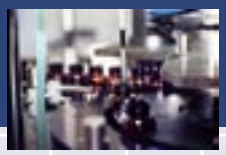
Not Just a Smile

CanAg Diagnostics is participating in a major new European research project related to the detection of stroke using novel monoclonal antibodies and aptamers. 'Rapid Stroke Marker detection via Immunosensors utilising Labeless Electrochemical and Resonant Mass Detection,' or SMILE, for short, is a project aimed at developing generic multi-sensor platforms that can be applied to the detection of any binding event for the detection of a panel of biochemical markers for stroke.

The project fits well with CanAg Diagnostic's desire to collaborate with other organisations to develop innovative diagnostic tools for severe diseases. The company's role is to develop monoclonal antibodies towards biochemical stroke markers that may be used in future immunosensor markers.

The inaugural meeting of the SMILE project took place at the beginning of the year and is supported by EU funding. Ten European research groups and companies are participating including the University of Newcastle-upon-Tyne and Cranfield University in the UK, Universitat Rovira i Virgili in Spain and Ireland's National Microelectronic Research Centre.

Product News



One-Step is the latest offering for both the PSA and Free PSA EIA assays. This adds up to a reduction in incubation time to 90 minutes and offers laboratories the opportunity to make overall cost efficiencies. For the Free PSA assay, the company says that the one step assay can offer increased sensitivity because of the narrowed range (-10 μg/L) in which most of the patient samples are found.

Conferences

CanAg Diagnostics AB will be attending the following major conferences this year.

AACC 2003 in Philadelphia, USA, July 20-24, 2003, Stand no: 2429.

ISOBM 2003, Edinburgh, Scotland, August 30-September 4, 2003.

Medica in Dusseldorf, Germany, November 19-22 2003,

Distributor news

Adding to the global network.

CanAg Diagnostics has gained a new distributor for its network. The company is based in Italy. Beta Diagnostici has been active in Italy since 1990 and concentrates on the in-vitro diagnostics market. Its main headquarters are in Messina, northern Italy, with branch offers spread throughout the company. It is an ISO 9002 certified company, which has grown steadily since its foundation.

CanAg DIAGNOSTICS

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