biotech focus

to get excited by technologies; it's clinical data that drives our decision making.

Is there a problem or what do you see as the biggest problem with the future development of such aptamer-based drugs? There are no fundamental problems with it, they are relatively expensive but so are antibodies and recombinant proteins, and people are taking steps towards new methods of synthesis which may drive costs down. There's no doubt that these drugs have interesting pharmacokinetics that are not entirely predictable from the small molecule or even the antibody area, but as we gain experience with them, we'll get a better scientific understanding. I think the future for aptamer drugs is very promising, however, it's early days and we have to wait to see.

Glyn Edwards
Antisoma,
West Africa House,
Hanger Lane,
London, W5 3QR, UK

Biotech Focus Editor: Ulrike Knies-Bamforth
ddt@elsevier.com

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Biomanufacturing: a high-growth industry for North Carolina

Boris Hartl, boris_hartl@ncbiotech.org

Somewhere in the United States, in a small meeting room complete with a few chairs, a table and a dry-eraser board, biotechnology entrepreneur Anthony Laughrey outlined the attributes for a suitable location for his new start-up company, KBI BioPharma, a contract process developer and manufacturer of biotechnology drugs.

The KBI BioPharma leaders judged six candidate states on a variety of items: excellent universities and community colleges; supporting infrastructure of government and private agencies; extensive workforce training programs; specialized construction and engineering companies; high quality of life.

All these criteria are important to a successful biomanufacturing operation, and, holding a handful of colored markers, Laughrey checked the boxes over and over again under one state: North Carolina.

'None of the other five states measured up, when all of these factors were considered', he said.

Laughrey's choice has proved a positive one. Since selecting Durham, North Carolina, as the base of his company, and receiving a US$1 million loan from the North Carolina Biotechnology Center in 2003, KBI BioPharma has grown from one employee to 32.

'The fact North Carolina has invested in biotechnology for 25 years was a big reason for coming here compared with the other states', Laughrey said.

The state's investments in biotechnology have come via the North Carolina Biotechnology Center, the world's first government-sponsored organization devoted to biotechnology development. The nonprofit corporation, created in 1984, has formed working partnerships with dozens of public and private organizations and channeled more than US$160 million of state investment into biotechnology research, business and education.

This long-term investment strategy has paid dividends to the state. North Carolina's life science industry has grown to include 173 biotechnology companies, 77 contract research organizations and 51 device and life-science related companies, collectively employing ~40,000 people. In addition, more than 200 companies provide products and services to the industry, accounting for thousands more jobs.

About one-third of the state's biotechnology companies are large, multinational operations such as Biogen Idec, Diosynth, Bayer CropScience, Novozymes, Syngenta and GlaxoSmithKline. The rest are small to mid-sized companies that have either moved to the state or sprung from its universities or larger companies (Box 1).

Outstanding universities drive industry's expansion

Education has fueled the life science industry in North Carolina. The state has more than 50 public and private colleges and universities. More than 45 life science companies in

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BOX 1

North Carolina biomanufacturers

Company	Products	Location	Internet
Ajinomoto USA	Amino Acids	Raleigh	www.ajinomoto-usa.com/
AlphaVax	Vaccines	Durham	www.alphavax.com/
Archer Daniels Midland	Citric acid	Southport	www.admworld.com/
Argos Therapeutics	Therapeutic vaccines	Durham	www.argostherapeutics.com/
Biogen Idec	Multiple sclerosis and psoriasis drugs	Research Triangle Park	www.biogen.com/
Biolex	Therapeutic proteins	Pittsboro	www.biolex.com/
Corn Products International	High-fructose corn syrup and starch	Winston-Salem	www.cornproducts.com/
Diosynth RTP	Contract biopharmaceutical manufacturing	Research Triangle Park	www.diosynthbiotechnology.com/
Embrex	Poultry vaccines	Laurinburg	www.embrex.com/
Greer Laboratories	Allergenic extracts, vaccines	Lenoir	www.greerlabs.com/
KBI BioPharma	Contract biopharmaceutical manufacturing	Durham	www.kbibiopharma.com/
Merck [a]	Vaccines	Durham	www.merck.com/
MWG	Synthetic nucleic acids	High Point	www.mwg-biotech.com/
Novozymes	Industrial enzymes	Franklinton	www.novozymes.com/
Talecris Biotherapeutics	Blood and plasma-related therapeutics	Clayton	www.talecris.com/
Wyeth Vaccines	Vaccines	Sanford	www.wyeth.com/

[a]Merck broke ground in October 2004 with a 2008 completion date.

operation use technologies developed by the state's universities. There are ~150 biotechnology-related patents issued to universities and companies in the state yearly.

The University of North Carolina (UNC) is a multi-campus university composed of 16 constituent institutions, including flagship schools UNC-Chapel Hill and North Carolina State University. With sponsored research grants and contracts of more than US$1 billion, UNC ranks third nationally among university systems.

In addition to the UNC universities, the state has 36 private colleges and universities, including the world renowned Duke and Wake Forest universities. Duke Medical Center is one of the largest biomedical research enterprises in the USA with more than US$431 million in annual sponsored research. Wake Forest University, a US$186-million research community, maintains internationally recognized research centers in cancer, human genomics, investigative neuroscience and other disciplines.

The reputation of Wake Forest and its medical school attracted Anthony Atala, an international authority on tissue engineering, to relocate to Winston-Salem. Atala's work focuses on growing new human tissues and organs to repair those defective at birth or destroyed by disease. Atala moved from Harvard University to Winston-Salem, where he now serves as the Director of the Wake Forest Institute for Regenerative Medicine. A start-up company using the technologies developed by Atala also moved to Winston-Salem. This company could have up to 160 employees within three years.

Atala has created bioengineered urethras, the tube through which urine is excreted from the bladder, which have been successfully implanted in humans. Atala has also successfully created blood vessels, muscle, bladders and wombs, which have been tested in large animals. All of those bioengineered tissues are close to being tested in humans.

Industry's growth brings high-paying jobs

The sustained growth of biotechnology in North Carolina has made the state a worldwide leader in biotechnology (Box 1). Ernst and Young's 2005 report on the industry proclaims North Carolina the third leading biotechnology state in the United States – surpassing Maryland – based on the number of companies, a figure behind California and Massachusetts. Moreover, a 2004 study by the Milken Institute projects that North Carolina will lead the USA in percentage growth of new biopharmaceutical jobs by 2014.

As was envisioned more than two decades ago by the state leaders who created the North Carolina Biotechnology Center, biotechnology is bringing high-paying jobs to the state at a time when many people are losing traditional manufacturing jobs. A constituent asked North Carolina's Governor Mike Easley, 'what is biotechnology, anyway?' His reply: 'Better than US$20 an hour.'

In the fast-growing biomanufacturing sector, which produces drugs, vaccines, enzymes, vitamins and food additives, entry-level bioprocess technicians typically earn between US$25,000 and US$30,000 p.a. and jump to US$50,000 p.a. after five years. According to the North Carolina Employment Security Commission, the average employee at a North Carolina biopharmaceutical manufacturing business currently earns US$70,567 p.a.

To ensure that high-paying biotech jobs keep coming to North Carolina, Governor Easley in 2003 commissioned the Biotechnology Center to craft 'New jobs across North Carolina: a strategic plan for growing the economy statewide through biotechnology'. The plan, developed with the input of 120 leaders across the state, contains 54 strategic recommendations to guide future state investments in biotechnology development, including three immediate priorities:

(i) recruiting and expanding biomanufacturing companies;
(ii) spreading the opportunities and benefits of biotechnology to all areas of the state;

biotech focus

(iii) creating and attracting biotechnology start-up companies.

To accelerate the growth of its biomanufacturing industry, now numbering 16 plants and 30 related plants, North Carolina is focusing on preparing a trained work force. A Biotechnology Center survey indicated up to 3000 new employees will be needed each year.

Golden LEAF, a nonprofit foundation created in 1999 to invest part of North Carolina's federal tobacco litigation settlement money in economic development projects, has committed US$60 million to a new statewide program to train workers for biomanufacturing and pharmaceutical-manufacturing jobs.

North Carolina State University in Raleigh will use its portion of the Golden LEAF money to build a US$36 million Biomanufacturing Training and Education Center, scheduled to open in January 2007. There are plans for a 100,000-square-foot plant to provide hands-on experience for students.

North Carolina Central University in Durham will receive US$19.1 million for the Biomanufacturing Research Institute and Technology Enterprise (BRITE), set to open in January 2007. BRITE will include a 65,000-square-foot laboratory and classroom building for research, teaching and training at all levels in biotechnology and biomanufacturing.

The North Carolina Community College System will receive US$9.4 million for BioNetwork, a statewide initiative placing centers at six community colleges across North Carolina, which will train workers in bioprocessing, pharmaceuticals and bio-agriculture. The BioNetwork initiative aims to place students into the North Carolina State and North Carolina Central university programs for additional training.

The North Carolina Biomanufacturing and Pharmaceutical Training Consortium, a partnership of the University of North Carolina system, the North Carolina Community College System, North Carolina-based biomanufacturing companies and the Biotechnology Center implemented the coordinated training program. The curriculum will address training across all the relevant scientific, technical and engineering disciplines at all levels from certificate or associate degree to PhD. The goal is to train between 2000 and 3000 employees each year.

In addition to these training initiatives, the North Carolina Biotechnology Center has worked with industry and the community colleges to develop BioWork© for training entry-level bioprocess technicians. The 128-h course, taught by the community colleges, covers areas such as good manufacturing practices and manufacturing technology. The course is offered to the public and used by companies for in-house training of new hires and current workers.

'We're determined that North Carolina will have the world's best-trained work force for biomanufacturing', said Leslie Alexandre, the Biotechnology Center's President and CEO.

With a trained workforce being a key part of North Carolina's traveling sales pitch, the Biotechnology Center and the North Carolina Department of Commerce are embarking on a new retention, expansion and attraction plan to bring new biomanufacturing plants to the state and expand the ones already here. The plan's aim is to build on the state's industrial recruitment successes that have netted four biopharmaceutical manufacturers in recent years – Diosynth, Biogen Idec, KBI BioPharma and Merck. Other manufacturers have expanded their operations. For instance, Wyeth Vaccines in Sanford operates one of the world's largest vaccine plants. Talecris Biotherapeutics (formerly Bayer) runs the world's largest blood-fractionation plant in Clayton (Box 1).

State targets biomanfacturing recruitment

Another potent tool for industrial recruitment of biomanufacturing firms is being developed. The General Assembly has set up, but not yet funded, the North Carolina Life Sciences Revenue Bond Authority to provide loan guarantees to help finance the construction of new or expanded biomanufacturing plants, which typically cost tens or hundreds of millions of dollars to build.

A benefit of recruiting biomanufacturing companies is that these plants are more likely to locate in semirural areas of the state compared with research and development-oriented companies. That fits squarely with the Biotechnology Center's strategic goal of developing biotechnology beyond the technology-rich area of Raleigh, Durham, Chapel Hill and the Research Triangle Park.

The North Carolina Biotechnology Center is planning to open three new satellite offices to serve greater Charlotte and Eastern North Carolina. The new offices will join existing satellite offices serving the Piedmont Triad and Western North Carolina, to bring the Biotechnology Center's expertise and programs closer to all areas of the state. Local advisory councils are helping to identify biotechnology opportunities, resources and strategies in the four regions.

'By combining the skills and experience found in both the public and private sectors, we are creating a biotech community for the area', said Rosemary Wander, the Triad committee chairwoman and associate provost for research at UNC-Greensboro.

The community and its support network of academic and business leaders is paying off by nurturing future stars, such as Targacept and TransTech Pharma.

Targacept, which operates in the Piedmont Triad Research Park, grew out of research by its parent company, R.J. Reynolds Tobacco, in the pharmacology, chemistry and toxicity of nicotine.

The 74-person company, who has attracted more than US$120 million in investment capital from venture capital firms from Asia, Europe and North America in about five years, is working on medications focusing on the central nervous system and nicotinic receptors. It is developing compounds that can stimulate the receptors to ease the symptoms of diseases, such as Parkinson's and Alzheimer's. The company's other lead compound is geared toward ulcerative colitis.

Similar work is being done in High Point. TransTech Pharma has developed the anti-thrombotic drug TTP889, which is currently in Phase II clinical trials. The once-daily medication taken orally would help combat thromboembolic disorders. The company is involved in other projects to develop

feature

medications to treat Alzheimer's and cardiovascular diseases. The company aims to become a fully integrated pharmaceutical company with one-stop production and marketing capabilities. The company's work hasn't gone unnoticed by investors, as the company raised about US$65 million since 2004.

To achieve its other strategic goal of helping create and develop companies, the North Carolina Biotechnology Center provides low-interest loans to young companies long on promise and potential but short on cash. The funding comes at a critical time, when the companies struggle to obtain financing. To date, the Biotechnology Center has invested about US$14.5 million in ~90 companies, which have gone on to raise more than US$1 billion in other investments.

For example, Trimeris, a company spun out of Duke University Medical Center, was able to use a US$250,000 Biotechnology Center loan to attract venture capital, which later led to a US$33 million public stock offering. Today the company employs ~135 people and sells Fuzeon, a life-extending drug for the treatment of AIDS. The drug is the first in a new class of anti-HIV drugs known as entry inhibitors that work by blocking HIV from entering T cells.

Tony Laughrey of KBI BioPharma can relate to Trimeris' success story. KBI BioPharma used the Biotechnology Center's US$1 million loan to leverage US$32 million in private funding. That early success has affirmed the company's decision to locate in North Carolina.

'We knew we belonged in North Carolina', Laughrey said. 'And we are glad we are here.'

Boris Hartl
North Carolina Biotechnology Center,
15 T.W. Alexander Drive,
Post Office Box 13547,
Research Triangle Park,
NC 27709-3547, USA

feature

Computing chemistry on the web

Igor V. Tetko, itetko@vcclab.org

Despite the dramatic growth of the internet, the number of practical applications in drug design that are available online, particularly those that predict absorption, distribution, metabolism, excretion and toxicology (ADME–Tox) properties, remains limited. For example, the number of methodological publications about lipophilicity predictions has gradually increased over the past ten years and >25 of these articles are expected to be published in different journals in 2005 [1]. At the same time, the number of programs available for the online prediction of this important property is approximately ten applications [2]. Publicly available tools for predicting many other important physico-chemical and biological properties simply do not exist. Thus, there is a need to develop new web applications to boost drug design and chemoinformatic studies. This article explains why publishing programs on the internet is important and beneficial for authors and users alike, it describes several examples of such sites and, crucially, discusses why this field remains underdeveloped compared with its nearest rival, the field of bioinformatics.

Why develop web services?

The typical research activity of a computational chemist includes data preparation, optimizing molecular structures, calculating indices, selecting the most important indices and deriving property–activity correlations using statistical methods. Then, the calculated models are revised and poorly predicted compounds are analyzed to gain an insight into the new indices that are required to improve the overall model or to detect errors and inconsistency in data preparation. However, if a new method has been developed it might be interesting to compare it with previously existing approaches. This could be difficult if the algorithm is only referenced in a paper but even if the method is available as source or binary code a dedicated computer platform, particular operating system, configuration of system parameters, compiler, libraries, among others, might also be required to perform a study. Problems can arise because the distribution of a binary code can unintentionally propagate viruses or spy software or there could be a conflict of interests (e.g. if the authors plan to commercialize it and substantial efforts are required to support it).

Contrary to this, publishing on the web allows a program to be executed in the same environment where it was developed. This software is easy to maintain, update and every web user can access and use it in their workplace. The web applications also enable much better dissemination of information regarding the algorithm, because of powerful search engines (e.g. Google or Yahoo).

Some examples of web services

An increasing number of diverse tools for performing data analysis in chemistry on the internet is available for users (Table 1), this is also reviewed elsewhere [2–5]. The Virtual Computational Chemistry Laboratory

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